AN EVALUATION OF RHEOLOGICAL PARAMETERS FOR A MODEL SHEAR-THINNING SYSTEM WITH APPLICATION TO THE DIFFUSION OF HYDROCORTISONE

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A THESIS SUBMITTED IN PARTIAL FULFILMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in the Faculty

of

Pharmaceutical Sciences

Division of Pharmaceutics

We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

December, 1974

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ABSTRACT

Many pharmaceutical systems exhibit shear-thinning flow properties but the expression of these properties in terms of meaningful rheological parameters remains a problem. To be useful, the parameters must be rheometer-independent and either describe the fluid under application, processing and storage conditions, or specify the fluid structure and disposition of the molecules at negligible shear rates. Interlinked with this problem is the correct selection of rheological parameters and systems for applied studies, i.e. the determination of rheological effects on drug diffusion.

The components of the model shear-thinning system, the nonionic cellulose polymer, hydroxyethylcellulose (HEC, Natrosol 250G), and the nonionic surfactant, polyoxyethylene (4) dodecyl ether (Brij 30), were characterized physicochemically. The addition of Brij 30 to HEC dispersions provided a reliable means of obtaining a series of systems showing predictable increments in shear-thinning behaviour at each HEC concentration.

Over a 5 year period, the rheological reproducibility and stability of aqueous HEC dispersions were determined and compared with corresponding data for 2% methylcellulose (MC, 1500 cP) dispersions. For similar consistencies, HEC and MC dispersions showed comparable reproducibility and stability. The power-law consistency index was observed to be related to both storage time and polymer concentration.

Two methods of shear stress calibration were examined for the Rotovisko. The determination of a shear stress calibration constant for each shear rate provided a significant improvement for non-Newtonian shear-thinning fluids over the manufacturer's calibration method when both methods were compared with corresponding data generated with the

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cone-plate Weissenberg rheogoniometer.

The limitations of shear rate equations and two Couette rheometers, Haake Rotovisko and Brookfield Synchro-lectric (with SC-4 spindles), to accurately represent shear stress-shear rate parameters were examined. The Krieger-Maron and the Mooney shear rate equations were found to yield the widest range of rheometer-independent results for the Rotovisko and Brookfield rheometers, respectively, when separately compared with similar data obtained with the rheogoniometer.

Viscometric properties of polyoxyethylene (4) dodecyl ether in HEC dispersions were evaluated over a concentration range of 2.0 – 3.5% HEC and 0 – 16% Brij 30. Three rheological models: the modified Shangraw structure equation, the Steiger-Trippi-Ory equation and the power-law model were fitted to the data and found to describe accurately the flow behaviour of the dispersions at 30.0° C between shear rates of $8.5 - 685 \text{ s}^{-1}$. Variation of model parameters with surfactant concentration was computed for each HEC dispersion. A shear-sensitive interaction between the surfactant and the cellulose polymer was noted.

To determine the disposition of HEC in solution and the nature of the viscous interaction noted for the HEC - Brij 30 systems, low shear rate and dynamic measurements were made. From storage and loss moduli, dynamic viscosities and loss tangents, HEC was determined to be a molecule with intermediate flexibility and the HEC - Brij 30 systems were composed of a loose three dimensional network.

The effect of increased limiting viscosity at low shear rates was measured on the diffusion of hydrocortisone through nylon membrane and human autopsy epidermis. The absence of drug-vehicle interactions

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was demonstrated and the similarity in the results for the two membranes indicated that the observed decrease in steady state flux was due to the alteration of vehicle viscosity. The solubility, partition coefficient and diffusion coefficients were measured for hydrocortisone.

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LIST OF SYMBOLS

a	modified Shangraw equation parameter
a'	Steiger-Trippi-Ory equation parameter
a s	UV absorptivity
Ъ	modified Shangraw equation parameter
c	concentration
C	modified Shangraw equation parameter
C ¹	Steiger-Trippi-Ory equation parameter
d	density (g cm ⁻³)
d	diameter (cm)
d _o	density of the solvent (g cm^{-3})
d _T	density of test dispersion at temperature, T (g $\rm cm^{-3}$)
d _T , sel	density of test solution at temperature, T (g cm ^{-3})
^d 20,w	density of water at 20° C (g cm ⁻³)
^d 20,sol	density of test solution at 20° C (g cm ⁻³)
d w	density of distilled water at temperature, T (g $\rm cm^{-3}$)
f	frequency of oscillation (Hz)
h	height (cm)
h*	effective length or height (cm)
h	physical length of cylindrical portion of the spindle (cm)
k	Mooney shear stress calibration constant
m	power-law consistency index (dyne $cm^{-2} s^{n}$)
n	power-law flow behaviour index
n	percent (w/v) of solute
n'	number of moles of solute
no	number of moles of solvent

radius (cm) r

time t

t r retention time (min)

apparent partial specific volume (cm³ g⁻¹) vapp apparent molar volume (cm³ mole⁻¹). vapp Α

area

С

Cs

Dobs

D

F

G'

G''

Im

J s

a regression constant Α

Rotovisko shear stress calibration constant Α Α' Brookfield shear stress calibration constant amount of HC in the octanol layer $(\mu g)m1$ A₀ total amount of HC in the system $(\mu g)m1$ А_т amount of HC in the aqueous layer (µg)ml) A_w Rotovisko shear rate calibration constant В В an equation parameter

concentration (mole 1^{-1})

concentration difference of a solute across a membrane

 $(\mu g \text{ cm}^{-2}) \text{ or (moles cm}^{-2})$

experimentally observed diffusion constant (cm 2 s $^{-1}$) diffusion constant (cm² s⁻¹) diffusion constant corrected to standard conditions (cm 2 s $^{-1}$) ^D20,w

temperature corrected flow rate (cm 3 min $^{-1}$) storage modulus (dyne cm^{-2}) loss modulus (dyne cm^{-2})

movement of the worm-shaft measured by the oscillation input transducer (µm)

steady state flux of solute ($\mu g \text{ cm}^{-2} \text{ h}^{-1}$) or (moles cm $^{-2} \text{ h}^{-1}$)

77	amenator collibration constant
ĸ	osmometer calibration constant
Km	the membrane-vehicle partition coefficient
ĸ _T	torsion bar constant (dyne cm μm^{-1})
к,	K ₁₀ regression constants
L ₁ ,	L ₁₀ regression coefficients
М	moment of a force or a torque (dyne cm)
Mw	weight-average molecular weight
Mn	number-average molecular weight
P	pressure
R	gas constant (8.314 x 10^7 ergs deg ⁻¹ mole ⁻¹)
R. b	bob radius (cm)
R _c	cup radius (cm)
^R 1,2	gas liquid chromatograph peak resolution
S	scale reading
Sm	maximum movement of the torsion head transducer (μ m)
Sobs	experimentally observed Svedberg constant (s)
^S 20,w	Svedberg constant corrected to standard conditions (s)
Т	temperature
T _i	initial temperature ([°] C)
$^{\mathrm{T}}$ f	final temperature (⁰ C)
U	Rotovisko instrumental gear setting
V	partial molar volume (cm ³ mole ⁻¹)
v	average bridge output (mV)
Vr	retention volume (cm ³)
Wb	gas liquid chromatograph peak width at $\frac{1}{2}$ height
	weight of test dispersion at temperature, T (g)
W,	weight of distilled water at temperature, T (g)

xх

α	cone angle (deg)
Ŷ	shear rate (s ⁻¹)
δδ	membrane thickness (cm)
η	Newtonian viscosity (poise)
ŋ '	dynamic viscosity (poise)
na	apparent or non-Newtonian viscosity (poise)
no	limiting viscosity at low shear rates (poise)
n _{sol}	viscosity of test solution at known temperature, T (poise)
n _T	viscosity of water at temperature of centrifuge run (poise)
ⁿ 20	viscosity of water at 20 ⁰ C (poise)
n w	viscosity of water at temperature, T (poise)
n _{al}	apparent viscosity of the Brij 30-HEC-water system (poise)
ⁿ a2	apparent viscosity of the HEC-water system (poise)
n _{a3}	apparent viscosity of the Brij 30 -water system (poise)
n _{a4}	increased apparent viscosity due to the Brij 30-HEC-water
	system (poise)
λ	thermal conductivity (Cal (g) $h^{-1} cm^{-1} oK^{-1}$)
σ	shear stress (dyne cm ⁻²)
σ _b	shear stress at the bob surface (dyne cm^{-2})
σc	shear stress at the cup surface (dyne cm^{-2})
τ	lag time (h)
ŵ	radian frequency, $2\pi f$ (s ⁻¹)
∆ħ	increase in bob length due to end effects (cm)
${}^{\Delta}\mathbf{T}$	movement of the torsion head transducer (μ m)
θ	cone angle (rad)
ф	displacement of the sinusoidal stress and strain waves (deg)

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Ω angular velocity (rad s⁻¹)Ω_o a low angular velocity (rad s⁻¹)Ω_M maximum angular velocity (rad s⁻¹)

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ACKNOWLEDGEMENTS

To Dr. J.O. Runikis, thesis supervisor.

- To Drs. F.S. Abbott, M.A. Tung, A.G. Mitchell, B. Roufogalis, Prof. J. Lielmezs, committee members.
- To Ellen Ng, Peggy Tom, Gary Sui and Linda Lee, summer students.
- To Dr. F.S. Abbott, for advice and use of the gas chromatograph-mass spectrometer.
- To Dr. S. Nakai, Department of Food Science, for advice and use of the ultracentrifuge.
- To Dr. R.J. Bose, Fisheries Research, for the nuclear magnetic resonance spectrometry work.

To Bill Howald for advice on mass spectrometry.

To the Medical Research Council of Canada, for their generous financial support through the award of a Studentship.

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INTRODUCTION

Rheology, the study of the deformation of materials, including flow (Reiner and Scott Blair, 1967) has intrigued such early philosophers and poets as Heracleitus (500 BC), Aristotle (384 - 322 BC) and Lucretius (96 - 55 BC) but it was not until the 16th Century that the potter Palissy (1510 - 1589) began to write specifically on the science of the flow of matter (Durant, 1939; Durant and Durant, 1961; Scott Blair, 1938). Major advancements were made in the 17th Century by Hooke (1635 \div 1703) and Newton (1647 - 1727). While applying spiral springs to the balance wheel of watches, Hooke observed the action of springs, 'ut tensio sic vis', now known as Hooke's law (Durant and Durant, 1963). Newton, in 1676, defined viscosity for simple or Newtonian liquids, stating that the ratio of stress to rate of shear is constant (Scott Blair, 1969). Rheological equations, based upon experimentation, to describe the rate of flow in relation to fluid viscosity appeared first in the 19th Century, beginning with the Hagen-Poiseuille capillary work (Scott Blair, 1972). The desire for variable shear rates led to the design of the Couette rotational viscometer in 1890 (van Wazer et al., 1963). The discovery of non-Newtonian flow properties soon followed and Wo. Ostwald proposed thatfflow processes consisted of a number of stages as shown in Figure 1 (Scott Blair, 1969; Reiner, 1960). Rheology as a formal branch of science was established with the foundation of the Society of Rheology at the Washington Conference in 1929 (Scott Blair, 1969; 1972). Today, rheology has wide and varied applications, ranging from studies of metal creep and concrete flow to food texture, blood vessel elasticity, the



FIGURE 1. Ostwald's flow curve

consistency of pharmaceuticals and the flow of the earth's mantle (Scott Blair, 1972; Barry, 1970; Post and Griggs, 1973).

As a result of the myriad applications of rheology, many devices have been constructed and numerous mathematical models have been derived for the determination and expression of rheological behaviour (Skelland, 1967; van Wazer <u>et al.</u>, 1963; Oka, 1960; Sherman, 1970). In steady shear rheometry, the conversion of instrumental readings for non-Newtonian systems into absolute units of mass, length and time is still a major problem for the oldest and most commonly used Couette geometry (Krieger, 1968). In non-theoretical literature, a reluctance and an uncertainty persists to the expression of non-Newtonian flow behaviour in terms of rheological model parameters.

Over a period of thirty years, dynamic measuring techniques have been developed to examine fluids at shear rates which do not significantly alter fluid structure. 'Much work is currently being done in the area of polymer molecular modeling based on measurements of viscoelastic behaviour but experimental results are still somewhat sparse (Ferry, 1970).

Recently, pharmaceutical investigators have attempted to correlate vehicle rheology with drug bioavailability (Ashley and Levy, 1973; Braun and Parrott, 1972; Khristov, 1969; Khristov <u>et al.</u>, 1969 and 1970; Davis, 1973). Davis (1973) has noted a tendency to use complex systems where rheological factors cannot be separated from drug-vehicle interactions.

·3

STATEMENT OF PROBLEM

A model shear-thinning system with a wide range of pharmaceutically-interesting consistencies has been characterized both physicochemically and rheologically and then used to examine:

- a) the limitations of two Couette rheometers and shear rate equations to yield rheometer-independent results,
- b) the equivalence of the modified Shangraw, the Steiger-Trippi-Ory and the power-law models to represent non-Newtonian flow properties,
- c) the molecular disposition of the polymer and fluid structure based on dynamic and lowwshear rate measurements, and
- d) the influence of limiting viscosity at low shear rates on vehicle diffusion of hydrocortisone.

Specifically, the problem and thesis has been divided into three sections.

SECTION I. A MODEL SHEAR-THINNING SYSTEM WITH RHEOLOGICAL

FLEXIBILITY: MATERIAL SELECTION AND CHARACTERIZATION

Because of the variability in materials due to commercial synthetic processes, the selected cellulose polymer and nonionic surfactant have been characterized. Weight-average molecular weight and moisture content of the powder as well as densities and apparent molar volumes of aqueous dispersions have been measured for hydroxyethylcellulose (HEC, Natrosol 250G). For polyoxyethylene (4) dodecyl ether (Brij 30), number-average molecular weight, critical micelle concentration, infrared spectrum and the identity of the major gas

chromatographically visible components using mass spectrometry have been determined.

SECTION II. RHEOMETRIC STUDIES OF A MODEL SHEAR-THINNING SYSTEM

The rheometric studies are divided into two: studies of practical importance, and studies of a fundamental nature.

- A. <u>Steady Shear Studies of Practical Importance</u> answering the following questions:
 - What is the rheological reproducibility and stability of aqueous hydroxyethylcellulose dispersions as compared with the standard 2% w/w methylcellulose dispersion?
 - 2. What are the limitations of two popular Couette rheometers, the Haake Rotovisko and Brookfield Synchro-lectric, to represent shear-thinning data? The results from the two Couette viscometers are compared with cone-plate results in which the shear rate is more accurately known.
 - 3. Can shear-thinning behaviour be represented adequately by the parameters of flow models thereby, facilitating total rheogram comparisons and formulation with predicted consistency?
- B. <u>Rheometric Studies of a Fundamental Nature:</u> Low Shear and Dynamic Measurements answering the following questions:
 - Is there a limiting viscosity region at low shear rates for the hydroxyethylcellulose and hydroxyethylcellulose-polyoxyethylene
 (4) dodecyl ether systems?
 - 2. What is the polymer disposition of hydroxyethylcellulose in solution?

3. What is the nature of the shear-sensitive viscous interaction observed for the hydroxyethylcellulose-polyoxyethylene (4) dodecyl ether-water systems?

SECTION III. LIMITING VISCOSITY AT LOW SHEAR RATES AND HYDROCORTISONE DIFFUSION

This section endeavours to apply the results of the low shear rate determinations in Section II to study the effect of viscosity on diffusion in the presence of artificial and biological membranes. The following questions were posed:

What is the lipophilic-hydrophilic character of hydrocortisone?
 Does hydrocortisone (HC) bind with HEC in aqueous solution?
 To what extent does the limiting viscosity at low shear rates of

 a non-Newtonian vehicle influence the rate of diffusion of HC in the presence of artificial and biological membranes?

SECTION I. A MODEL SHEAR-THINNING SYSTEM WITH RHEOLOGICAL FLEXIBILITY:

MATERIAL SELECTION AND CHARACTERIZATION

A. HYDROXYETHYLCELLULOSE

INTRODUCTION AND SELECTION

Hydroxyethylcellulose (HEC) is a nonionic water-soluble cellulose ether derived from the reaction of the three hydroxyl groups (2-, 3- and 6-positions) of the anhydroglucose unit of the cellulose molecule (Figure 2). The etherification of cellulose usually consists of the preparation of alkali cellulose by the interaction of cellulose with dilute sodium hydroxide solution followed by the reaction of the alkali cellulose with the etherifying reagent at an elevated temperature (1).

$$Cell.(OH)_{3} + RCH - CH_{2} \longrightarrow Cell.(OH)_{2} O CH_{2} CHR OH$$
(1)

The etherifying agent, ethylene oxide, reacts initially at the hydroxyls in the cellulose chain and secondly, at previously substituted hydroxyls forming a polymerized side chain (Brown, 1961). The water solubility of the crystalline regions of cellulose is increased through the addition of hydrophilic substitutents which act as spacers reducing the configurational regularity of the parent cellulose molecule. Hydroxyethyl substitutents impart a higher degree of water-solubility than is the case with methyl substitutents (Desmaris and Esser, 1966).

HEC has an optimum molar substitution of 2.5 which renders the aqueous dispersions more stable to addition of salts, changes in pH (Hercules Inc., 1969) and enzymic degradation (Desmaris and Esser, 1966).



FIGURE 2. Idealized two-dimensional structure of HEC (Natrosol 250G)

Of the three, carboxymethyl-, methyl- and hydroxyethyl-cellulose, Brownell and Purves (1957) have shown that HEC is likely to be the most uniformly substituted cellulose. Uniform substitution aids in producing clear dispersions (Desmaris and Esser, 1966).

Because of the industriallimportance of HEC, extensive studies have been done on the physical-chemical properties of fractionated samples. Studies done on very dilute solutions to estimate the unperturbed dimensions of HEC have found the molecule to behave as an extended chain in water (Brown, 1961; Brown <u>et al.</u>, 1963; Brown and Henley, 1964 and 1967). Increased chain flexibility in water was noticed with increased temperature (Brown <u>et al.</u>, 1963). The striking dependence of intrinsic viscosity on the nature of the solvent and the display of large negative temperature coefficients unique to cellulose derivatives (Flory <u>et al.</u>, 1958) has been noted also for HEC by Brown (1961). Recently, Klug <u>et al.</u> (1973) have estimated 6 mole % of unsubstituted anhydroglucose units in HEC (Natrosol 250G) using enzyme hydrolysis.

Dilute solutions of high viscosity HEC (Natrosol 250H) have been used in rheological studies of engineering interest involving the following: flow of high polymer solutions past spheres (Turian, 1967) and in tubes (Meter and Bird, 1964), viscoelastic modeling (Spriggs, 1965), normal stress measurements (Denn and Roisman, 1969; Meister and Biggs, 1969) and drag reduction (Hoyt, 1971 and 1972) but few rheological studies have been done with Natrosol 250G. Cramer (1968) has used dilute solutions of this polymer in modeling studies with engineering applications. The effects of thermal exposure on the viscosity-stability of Natrosol 250G and 250H solutions at concentrations of pharmaceutical interest were studied by Powell <u>et al</u>. (1966).

Although HEC is used in the manufacture of cosmetics and pharmaceuticals, only meagre information concerning the rheological properties of Natrosol 250G is available in the literature. For this reason, plus the apparent stability and ability to form elegant dispersions, HEC was the polymer selected for study.

EXPERIMENTAL

1. Molecular Weight and Moisture Content

Brown (1961) has demonstrated the polydisperse nature of HEC, therefore, the polymer used in the present study was characterized through the determination of molecular weight and moisture content to facilitate further studies.

The determination of the weight-average molecular weight (Mw) of HEC was the most direct method of obtaining polymer size information. The presence of a single approximately symmetrical peak for more than an hour on a preliminary ultracentrifugation run indicated that the HEC solute in a 1% w/w aqueous dispersion was homogeneous in the ultracentrifuge (Figure 3). As a result, the determination of \overline{Mw} for the cellulose polymer was pursued using an ultracentrifugation technique (Chervenka, 1969) involving sedimentation velocity and synthetic boundary runs.

The preliminary sedimentation velocity run with HEC indicated that the standard 1.0% w/w concentration normally employed in ultracentrifugation studies was unsatisfactory due to the slow movement of the


FIGURE 3. Photographs of the HEC peak taken at 1.5 and 2.5 hours during the sedimentation velocity run

meniscus, therefore, a 0.25% w/w dispersion was analyzed. The general run procedure for preparative ultracentrifuges (Beckman, 1968) was used. The sample loading and operation of the schlieren optical accessory was carried out in the prescribed manner (Beckman, 1969). During the sedimentation velocity run (59,000 rpm, 25°C), photographs were taken at 90, 150, 180, 211 and 270 min. A photographic enlarger was used to obtain peak height and magnification factor information. The resultant data from the sedimentation velocity determination (Table I) were analyzed using the common linear least squares fitting routine in a programmable calculator to obtain the Svedberg constant, s_{obs} (s),

$$s_{obs} = \frac{1}{\Omega^2 r} \frac{dr}{dt}$$
, (2)

where <u>r</u> is the radial distance (cm) from the centre of rotation to the meniscus, $\underline{\Omega}$, the angular velocity (rad s⁻¹) and <u>t</u> is time (s) (Chervenka, 1969).

The diffusion coefficient was obtained from the synthetic boundary run. Initially, a sharp boundary was formed in the cell and then the diffusion coefficient was determined from the spreading of the boundary with respect to time at a lower velocity (4000 rpm). A second calculator program analyzed the peak height and area data (Table II) to compute the diffusion coefficient, D_{obs} (cm² s⁻¹),

$$D_{obs} = \frac{A \varepsilon^2}{\left(\frac{dc}{dr}\right)^2_{max}} \frac{1}{4\pi t}, \qquad (3)$$

where \underline{A} is the area under the schlieren peak (cm²), <u>t</u>, time (s) and dc/dr is the concentration gradient represented by the maximum height of the

schlieren peak (cm).

A temperature-controlled, tared specific gravity bottle $(25 \pm 0.5^{\circ}C, \text{Appendix II})$ was used to obtain the solution density, <u>d</u> (g cm⁻³), required for the calculation of the apparent partial specific volume, \overline{v}_{app} (cm³ g⁻¹),

$$\overline{v}_{app} = \frac{\frac{100}{d} - \frac{(100 - n)}{d_{o}}}{n},$$
 (4)

where $\frac{d}{O}$ was the density of the solvent and \underline{n} was the percent (w/v) of solute (Dayhoff <u>et al.</u>, 1952).

The Svedberg constant and the diffusion coefficient were corrected to standard conditions through temperature-controlled viscosity and density determinations for 0.25% w/w HEC (25.0 ± 0.5° C, Appendix II). Following ASTM procedures for transparent liquids (ASTM, 1968), temperaturecontrolled, calibrated capillary viscometers (25.0 ± 0.5° C) were used to obtain the solution viscosity to correct s_{obs} and D_{obs} . The corrected Svedberg constant ($s_{20,w}$, s) was calculated from Equation (5) (Chervenka, 1969),

$$s_{20,w} = s_{obs} \left(\frac{n_T}{n_{20}} \right) \left(\frac{n_{sol}}{n_w} \right) \left(\frac{1 - \overline{v}_{app} d_{20,w}}{1 - v_{app} d_{T,sol}} \right)$$
(5)

where $\underline{n_T}$ was the viscosity of water at the temperature of the centrifuge run (poise), $\underline{n_{20}}$, the viscosity of water at 20° C (poise) (Weast, 1973). $\underline{n_{sol}}$, the viscosity of the sample solution at known temperature, <u>T</u>, (poise), $\underline{n_w}$, the viscosity of water at <u>T</u> (poise) (Weast, 1973), $\underline{d_{20,w}}$, the density of water at 20°C (g cm⁻³, Weast, 1973) and $\underline{d}_{T,sol}$ was the density of the solution at the temperature of the centrifuge run (g cm⁻³). The corrected diffusion coefficient, $D_{20,w}$ (cm² s⁻¹), was calculated from Equation (6),

$$D_{20,w} = D_{obs} \begin{pmatrix} 293.2 \\ T \end{pmatrix} \begin{pmatrix} n_{T} \\ n_{20} \end{pmatrix} \begin{pmatrix} n_{sol} \\ n_{w} \end{pmatrix}$$
(6)

where \underline{T} was the temperature of the centrifuge run (K^o). The weightaverage molecular weight was calculated from Equation (7),

$$\overline{Mw} = \frac{RT s_{20,w}}{D_{20,w} \left(\frac{1}{1 - v_{app}} d_{20,so1} \right)}$$
(7)

where <u>R</u> was the gas constant (8.314 x 10^7 ergs deg⁻¹ mole⁻¹), and $\frac{d_{20,sol}}{d_{20,sol}}$ was the density of the 0.25% w/w.HEC dispersion at 20° C.

Using the general procedure for the Cenco Moisture Balance (Central Scientific Co., 1963), the moisture content of the HEC powder was determined at several time intervals.

2. Density and Apparent Molar Volume of Aqueous Dispersions

Density-temperature relationships were determined and apparent volumes were calculated for the HEC dispersions as supplementary information for polymer characterization and ancillary information required for Section III.

The density of aqueous dispersions of HEC (1.0, 2.0 and 3.0% w/w), prepared according to the general procedure (Appendix I) excluding the preservatives, was determined at 15, 20, 30, 35 and 40° C. Two specific gravity bottles (50 ml) containing thermometers plus six standard

specific gravity bottles (50 ml) were cleaned with chromic acid, rinsed with distilled water and acetone and then dried to constant weight (0.2 mg). The bottles were calibrated at each temperature using boiled distilled water. Three determinations were made and then averaged. Following calibration, the specific gravity bottles were filled with the test liquid using a syringe, immersed in a water bath (Blue M fitted with appropriate trays) and equilibrated for 2-3 h. The experimental temperature was averaged from the two bottles containing thermometers. Prior to weighing, the capillary heights were adjusted with the test liquid equilibrated to the same temperature, wiped carefully and quickly weighed on an analytical balance (0.1 mg). Before changing the test liquid, the bottles were cleaned and dried to the original constant weight. The density of the test dispersion at temperature \underline{T} , $\underline{d}_{\underline{T}}$, was calculated from

$$d_{\rm T} = \frac{W_{\rm T}}{(W_{\rm w}/d_{\rm w})}$$
(8)

where $\frac{W_T}{T}$ was the weight (g) of the test liquid at temperature, \underline{T} , $\frac{W}{W}$, the weight of distilled water at temperature, \underline{T} and \underline{d}_{W} was the density (g cm⁻³) of water at the same temperature (Kell, 1967). The apparent molar volume (v_{app} , cm³mole⁻¹) of the polymer was calculated from

$$app = \frac{M}{d_w} - 1000 \left(\frac{d_T - d_w}{C d_w} \right)_{T,P}$$
(9)

where <u>M</u> was the weight-average molecular weight in this instance, $\underline{d_T}$, the density of the aqueous polymer solution (g/ml) and <u>C</u> was the concentration of solute (moles/1) (Bauer and Lewin, 1959).

RESULTS AND DISCUSSION

1. Characterization Data for Hydroxyethylcellulose

Using the common linear least squares fitting routine, the Svedberg constant, $s_{obs} = 1.81 \times 10^{-13}$ s, was obtained from the sedimentation velocity data for the 0.25% w/w HEC dispersion (Table I). The diffusion coefficient, $D_{obs} = 1.88 \times 10^{-7} \text{ cm}^2 \text{ s}^{-1}$, was obtained from the synthetic boundary determination (Table II). After applying the viscosity correction obtained from capillary measurements, the corrected Svedberg constant, $s_{20,w}$, was 11.4 $\times 10^{-13}$ s and the corrected diffusion coefficient, $D_{20,w}$, was 11.6 $\times 10^{-7} \text{ cm}^2 \text{ s}^{-1}$. The apparent partial specific volume for 0.25% w/w HEC was 0.721 cm³ g⁻¹, the average density at 25.0 \pm 0.5°C was 0.9978 g cm⁻³ and the average viscosity at 25.0 \pm 0.5°C was 0.0632 poise. Using (7), a weight-average molecular weight of 8.6 $\times 10^4$ was calculated. This molecular weight indicated the presence of 314 repeating units with monomeric molecular weight, 272, of the idealized structure of HEC with molar substitution 2.5 (Figure 2).

Using membrane osmometry, Powell <u>et al.</u>((1966) determined the number-average molecular weight of HEC to be 4.73×10^4 (25° C, Natrosol 250G). Although these authors maintained a good correlation existed between the molecular weight averages derived from viscosity and osmotic pressure techniques, they neglected to present a corresponding viscosity-molecular weight value. According to the manufacturer (Hercules Inc.), the approximate molecular weight is 8.0×10^4 (Powell <u>et al.</u>, 1966) which is in agreement with the <u>Mw</u> result obtained in the present study. The lower than expected, <u>Mm</u> of Powell <u>et al.</u> (1966) is probably a result of the permeation of low

	, <u>, , , , , , , , , , , , , , , , , , </u>	
Time (min.)	Peak Height (cm)	Magnification Factor Measurement (cm)
90	5.65	17.20
150	7.35	17.15
180	8.30	17.21
211	9.13	17.25
270	10.85	17.15
	· · · · ·	· .

Sedimentation velocity data for a 0.25% w/w HEC dispersion

Table I

Svedberg Constant, $s_{obs} = 1.81 \times 10^{-13} s$

Table	II

Synthetic boundary data for a 0.25% w/w HEC dispersion

Time (min.)	Peak Area (cm ²)	Peak Height (cm)	Magnification Factor Measurement (cm)
10	8.65	6.75	22.6
20	8.75	6.30	22.6
30	8.69	5.75	22.3
40	8.28	5.55	22.5
50	8.56	5.20	22.2
60	8.51	4.90	22.5
89	8.52	4.40	22.3
120	8.94	4.06	22.2
150	8.35	3.65	22.6
180	9.33	3*65	22.5
			· · · · · · · · · · · · · · · · · · ·

 $D_{obs} = 1.88 \times 10^{-7} \text{ cm}^2/\text{s}$

molecular weight materials through the osmometer membrane because the HEC polymer was used as received from the manufacturer. <u>Mn</u> cannot be determined accurately using unpurified polymers containing reaction products because precision measurements of osmotic pressure are only possible with samples from which all substances which show membrane permeability have been removed (Vink, 1971).

The moisture content was found to be 6 \pm 1% w/w when checked periodically over a 3 year period using a moisture balance. This result for moisture content is in agreement with the 6% by weight estimate of the manufacturer for the equilibrium moisture content if the powder was kept at 50% relative humidity, 73°F (Hercules Inc., 1969).

Density- and Apparent Molar Volume-Temperature Relationships for Aqueous Dispersions

The values for density with respect to changing temperature are presented in Table III for the HEC dispersions. A relatively constant increase in density of 0.0027 g cm⁻³ (± 0.0001 CL_{95%}) was noticeable for each 1.0% w/w increase in HEC concentration over the 15-40°C temperature range. The addition of the first 1.0% w/w HEC to water resulted in an initial density change of 0.0032 g cm⁻³ (± 0.0002 CL_{95%}) at each test temperature.

Equation (10) describes the relationship between temperature $(^{\circ}K)$ and the density of the HEC dispersions and water over the temperature range examined (Figure 4).

$$d = A e^{-BT}$$

(10)

Tal	ble	III

Density and apparent molar volume of aqueous HEC dispersions

		-			
Temperature (^o C ± 0.2)	HEC (%w/w)	Density (g	(± CL _{95%}) /ml)	n	$v_{app} (10^4)$ (cm ³ mole ⁻¹)
15.0	0.0	0.9991 ^a			
· -	1.0	1.0023	0.0001	6	6.08
	2.0	1.0052	0.0002	8	5.98
	3.0	1.0079	0.0000	· .7	5.85
20.0	0.0	0.9982 ^a	· · · ,		
	1.0	1.0014	0.0003	6	6.09
	2.0	1.0042	0.0001	8	6.03
	3.0	1.0070	0.0001	7	5.86
30.0	0.0	0.9957 ^a	:		
	1.0	0.9990	0.0002	6	6.15
	2.0	1.0016	0.0002	7	6.09
:	3.0	1.0044	0.0001	. 6	5.79
35.0	0.0	0.9941 ^a	•		
	1.0	0.9975	0.0004	6	6.16
	2.0	0.9999	0.0001	8	6.12
	3.0	1.0027	0.0001	7	5.67
40.0	0,0	0,9922 ^a		:	
	1.0	0.9953	0.0001	4	6.16
	2.0	0.9981	0.0001	6	6.12
	3.0	1.0009	0.0001	6	5.98

at 15, 20, 30, 35 and $40^{\circ}C$

^a (Kell, 1967)



FIGURE 4. Density-temperature relationship for aqueous HEC dispersions

In this relationship, \underline{A} was required to have units of g cm⁻³ and \underline{B} , units of deg⁻¹. An excellent fit of the equation to the data was found (Table IV).

The tabular values for <u>B</u> were numerically similar to the coefficient of expansion for water at room temperature $(3 \times 10^{-4} \text{ deg}^{-1}, \text{Bauer} \text{ and Lewin, 1959})$. Why the thermal expansion coefficient, which is a function of temperature itself, can be described by a simple exponential equation is not clear at this time. The apparent correspondence between <u>B</u> and the thermal expansion coefficient for water may have been the result of the narrow temperature range $(15-40^{\circ}\text{C})$ and the low polymer concentration used in this experiment.

The apparent molar volume of the HEC dispersions was calculated from (9) (Table III). At each temperature, the apparent molar volume decreased as the HEC concentration increased over the 15-40°C range. The $\frac{v_{app}}{p}$ appeared to increase with increased temperature for only the 1 and 2% w/w HEC dispersions. The fluctuations in $\frac{v_{app}}{p}$ with respect to increasing temperature noticed for the 3% HEC dispersion may have occurred because the density difference, $(d_T^{-d}w)$, in Equation (9) could not be determined with sufficient accuracy using the experimental method.

Using the method outlined by Yalkowsky and Zografii (1972), which was based on the early work of Traube published in 1899 and the later work of Mukerjee (1961), the partial molal volume of HEC was calculated to be 10.3 x 10^4 cm³ mole⁻¹. The partial molal volume (V) and the apparent molar volume (v_{app}) were of the same order of magnitude. The partial molal

Table IV

Density-temperature relationship, $d = A e^{-BT}$, for aqueous HEC

dispersions

HEC Concentration (% w/w)	A (g cm ⁻³)	B (deg, 10 ^{7,4})	r ²
0.0	1.09	2.7	0.986
1.0	1.09	2.7	0.978
2.0	1.10	2.8	0.990
3.0	1.10	2.8	0.988

volume was numerically larger as predicted by

$$v = v_{app} + n' \left(\frac{\partial v_{app}}{\partial n'} \right)_{n_{o}}$$

where <u>n'</u> and <u>n</u> represent the number of moles of solute and solvent respectively. According to theory, v_{appp} should converge with <u>V</u> at infinite dilution (Bauer and Lewin, 1959).

(11)

B. POLYOXYETHYLENE (4) DODECYL ETHER

INTRODUCTION

Polyoxyethylene (4) dodecyl ether (Brij 30) may be represented by the chemical formula,

$$CH_3 (CH_2)_{11} 0 (CH_2 CH_2 0)_4 H,$$

with formula molecular weight, 362.55. The actual surfactant may contain a mixture of repeating ether linkages and unreacted alcohol.

Polyoxyethylene alcohols are prepared commercially by the base-catalyzed addition of ethylene oxide to alcohol (Satkowski <u>et al.</u>, 1967; Equation 12).

$$ROH + n H_2C \xrightarrow{CCH_2} RO (CH_2 CH_2 0)_n H$$
(12)

For commercial purposes, the primary alcohols are prepared from natural sources by the reduction of fatty esters with an alcohol and an alkali metal or from synthetic sources by the Oxo and Ziegler processes (Satkowski <u>et al.</u>, 1967). A mixture of alcohols results from either source.

Although nonionic surfactants are recognized to be heterogeneous systems (Schick, 1967), several workers have used estimates of molecular weight to indicate surfactant polydispersity (Rhodes, 1967; Bloor <u>et al.</u>, 1970). Kalish <u>et al</u>. (1972) have used gas chromatography to demonstrate the complexity of a quaternary ammonium polyoxypropylene alcohol surfactant and nuclear magnetic resonance to identify 3 of the 24 peaks of the aminopolyether acetate derivative. Gas chromatographic analysis of nonionic surfactants following acid cleavage of ether linkages has been done by Tsuji and Konishi (1974). These authors initially removed the numerous ethylene oxide component peaks of several polyoxyethylene alkyl ethers, polyoxyethylene alkyl phenol ethers, polyoxyethylene alkyl amines and polyoxyethylene alkyl thioethers prior to gas chromatography. The chromatography conditions chosen did not give good resolution of the higher boiling components. Faveretto <u>et al</u>. (1972) have proposed thinlayer chromatography followed by spot densitometry for the determination of nonionic polyoxyethylene surfactants in polluted water.

A rising interest has been taken in straight chain polyoxyethylene alcohol surfactants because of their favourable biodegradable properties (Satkowski <u>et al.</u>, 1967) but problems still exist in the methods for component analysis. A gas chromatograph - mass spectrometer has been used in the present study to separate and identify the major components of Brij 30. The conventional number-average molecular weight and critical micelle concentration were determined also for comparative purposes.

EXPERIMENTAL

1. <u>Surfactant Selection</u>

To devise a system with increased rheological flexibility, a number of nonionic surfactants were screened for their ability to thicken HEC dispersions.

Surfactants were added to a 2% w/w HEC dispersion in volume ratios of 1:4, 1:3, 1:2 or 1:1 and combined. The nonionic surfactants

which were in solid form were melted prior to addition. The results of the combinations were evaluated subjectively, immediately and after 2 and 7 days (Table V).

2. Molecular Weight, Critical Micelle Concentration and Infrared Spectrum

The number-average molecular weight was determined using nonaqueous vapour pressure osmometry (Hewlett Packard, 1968). The osmometer was calibrated at $37.00 \pm 0.01^{\circ}$ C using a series of benzil solutions (2.112, 4.223, 8.445 and 16.890 g/l in benzene). The calibration factor, <u>K</u>, was obtained as the least squares intercept of benzil at zero concentration from the relationship

$$\frac{V}{C} = aC + K$$

where \underline{V} is the average bridge output measured in millivolts, <u>C</u>, the concentration (g/l) and <u>a</u> is the slope. The least squares fit of the average bridge output per concentration of the Brij 30 solutions (4.857, 9.713, 19.425 and 38.850 g/l in benzene) was extrapolated to zero concentration and the molecular weight, MW, was calculated from

$$MW = \frac{K}{\left(\frac{V}{C}\right)_{C}}$$

A molecular weight was estimated also from the integrated nuclear magnetic resonance spectrum of Brij 30 in CD Cl₂ (Figure 8).

Direct probe mass spectrometry at two probe temperatures (68 and 120° C) was used to examine Brij 30 for the presence of components

(13)

(14)

with a higher degree of ether substitution than represented by the manufacturer's formula.

The infrared spectrum of Brij 30 was obtained using a thin liquid film technique (Figure 9) (Coutts, 1969).

The critical micelle concentration (cmc) of Brij 30 was determined using surface tension measurements. A series of aqueous Brij 30 solutions were made (0.4, 0.2, 0.04, 0.02, 0.004, 0.002 and 0.001% w/w) and the surface tension measured using the Wilhelmy plate method at $22 \pm 1^{\circ}$ C (Federal Pacific Electric Co., 1968). Five determinations were made. The cmc was calculated from the intersection of the two portions of the surface tension versus Brij 30 concentration (% w/w) graph (Figure 10).

3. Component Analysis

Brij 30 (10 μ g/ μ l in absolute methanol) was gas chromatographed in the temperature programming mode (Ti = 110°C, Tf = 250°C, dT/dt = 6° C/min, Separator Temperature = 275°C, Inlet Temperature = 260°C) and mass spectra were recorded (Scan = 500 mass units at 50 mass units/s, chart speed = 4.8 in/s) for the principal components. Since temperature programming was used and a definite drop in gas flow rate was discerned, the gas flow was measured at convenient intervals during each sample run. A plot of gas flow rate versus temperature revealed a linear relationship over the temperature interval used (Figure 5). By noting the temperatures at which the major peaks were eluted, the correct flow rate for that temperature could be obtained graphically. These values were then used to calculate the retention volume (V_µ) for the major peaks from





where $\frac{F_c}{c}$ is the temperature-corrected flow rate (m1/min) and $\frac{t_r}{r}$ is the retention time (min) determined from the leading edge of the solvent peak (Table VII). Peak resolution, $R_{1,2}$, was determined from

 $V_r = F_c t_r$

$$R_{1,2} = \frac{2(t_{r2} - t_{r1})}{1.669 \left[\left(\frac{W_{b1}}{h_1} \right) + \left(\frac{W_{b2}}{h_2} \right) \right]}$$

where $\underline{t_{r1}}$ and $\underline{t_{r2}}$ are the retention times for peaks 1 and 2 respectively, and $\underline{W_{b1}}$ and $\underline{W_{b2}}$ are the widths of the respective peaks at half-heights h_1 and h_2 (Schupp, 1968).

To remove the possibility that the numerous peaks present in the spectrum were due to impurities or thermal degradation products, a solution of Brij 30 SP (10 μ/μ l in absolute methanol) and a sample of boiled (200^oC) technical Brij 30 (10 μ g/ μ l in absolute methanol) were chromatographed under identical conditions and examined for differences in the number of peaks.

In order to identify the dodecanol contaminant proposed previously (Nakagawa <u>et al.</u>, 1961), a solution of a homologous series of alcohols (octanol, decanol, dodecanol, tetradecanol, hexadecanol and octadecanol, each present at approximately 1.0 μ g/ μ l in absolute methanol Appendix I) was gas chromatographed in the temperature programming mode under conditions identical to those used for Brij 30. The gas flow rates were measured at appropriate intervals while each sample was run. The temperatures at which the alcohol peaks eluted were used to obtain the

30

(15)

(16)

respective flow rates (Figure 6) for retention volume calculations. The solution of homologous alcohols and the Brij 30 solution in 3 separate volume ratios (1:2, 1:3, 1:4 alcohol solution:Brij 30 solution) were combined, chromatographed and examined for a single symmetrical peak at the predicted dodecanol retention time. The retention times and volumes were calculated for the major peaks of the combined surfactant - alcohol series sample (Table VIII). The percent of dodecanol contamination of the surfactant was also estimated. Dodecanol (1.0 μ g/ μ 1 in absolute methanol) was chromatographed in the temperature programming mode under the conditions used for Brij 30, the mass spectrum traced and compared to the mass spectrum of the predicted C-12 alcohol contaminant of Brij 30.

A mass spectrum was recorded for each of the major gas chromatograph peaks of Brij 30. Molecular formulas were proposed and fragment maps developed for each of the major components.

RESULTS AND DISCUSSION

1. Surfactant Selection

Brij 30 was selected from among ten nonionic surfactants found to synergistically increase the apparent viscosity of a 2.0% w/w HEC dispersion and which therefore were relatively stable (Table V). This surfactant was chosen because it had the lowest degree of ethylene oxide polymerization thereby facilitating component identification with gas liquid chromatography - mass spectrometry.

Atlas Chemical Industries Inc. (1965) has indicated several of their nonionic surfactants exhibit atypical thickening behaviour on



FIGURE 6. Typical change in carrier gas flow rate for the solution of homologous alcohols chromatographed in the temperature programming mode

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Surfactant	Composition	HLB	State ^a	Volume ^b Ratio	Viscosity ^C	Stability ^d
Arlatone T ^e	Polyoxyethylene polyol fatty acid ester	9.0	L	1:2	I	Y
Brij 30 ^f	polyoxyethylene (4) dodecyl ether	9.7	L	1:4	I	Y
Brij 76 ^f	POE (10) stearyl ether	12.4	S	1:4	I	Y
Brij 58 ^f	POE (20) cetyl ether	15.7	S	1:3	I	Gel
Brij 96 ^f	POE (10) oleyl ether	12.4	L	1:3	I	Ŷ
Atlas G-1086 ^f	POE sorbitol hexaoleate	10:2	L	1:3	I	Y
Myrj 45 ^g	POE (8) monostearate	11.1	U	1:3	I	Gel
Renex 36 ^f	POE (6) tridecyl ether	[,] 11:4	L ,	1:3	I	Ŷ
Tween 65 ^f	POE sorbitan tristearate	e 10:5	S	1:3	I	Solid
Tween 85 ^g	POE (20) sorbitan tri- oleate	11:0	L.	1:3	I	Ŷ
Arlacel 60 ^f	sorbitan monostearate	4.7	S	1:3	NSC	Y
Arlacel 83 ^f	sorbitan sesquioleate	3.7	L	1:3	NSC	Ŷ

The subjective viscosity and stability of nonionic surfactants in combination with a 2% w/w HEC dispersion

Table V

Continued . .

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Arlacel C ^f	sorbitan sesquioleate	3.7	L	1:3	NSC	Y
Brij 72 ^f	POE (2) stearyl ether	4.9	S	1:3	NSC	Y
Brij 92 ^f	POE (2) oleyl ether	4.9	L	1:3	NSC .	N
Atlas G-1425 ^f	POE sorbitol lanolin derivative	8.0	U	1:3	NSC	Y
Atlas G-1734 ^g	POE sorbitol beeswax derivative	9.0	S	1:2	NSC	Y
Renex 20 ^f	POE esters of mixed fatty and resin acids	13.8	L	1:3	NSC	N
Renex 30 ^f	POE (12) tridecyl ether	14.5	L	1:3	NSC	N
Span 80 ^f	sorbitan monooleate	4.3	L	1:3	NSC	N
Tween 60 ^e	POE sorbitan monostearate	14.9	U	1:3	NSC	N
Tween 80 ^e	POE sorbitan monooleate	15.0	L	1:4	NSC	N
Arlacel 20 ^f	sorbitan monolaurate	8.6	L	1:2	D	N
Arlacel 85 ^f	sorbitan trioleate	1.8	L	1:3	D	N
Atmos 300 ^f	mono- & diglycerides of fat-forming fatty acids	2.8	L	1:2	D	N
Atmul 84 ^f	mono- & diglycerides from the glycerolysis of edible fats	2.8	S	1:3	D	N .
Brij 35 ^e	POE (23) dodecyl ether	16.9	S	1:3	D	N

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Table V contd.

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Brij 52 ^f	POE (2) cetyl ether	5.3	S	1:3	D	N .
Brij 56 ^f	POE (10) cetyl ether	12.9	S	1:4	D	N
Brij 92 ^f	POE (2) oleyl ether	4.9	Ľ	1:3	D	Ν
Atlas G-1441 ^e	POE (40) sorbitol lanolin derivative	14.0	U	1:2	D	N
Atlas G-1471 ^e	POE (75) sorbitol lanolin derivative	16,0	U	1:3	D	Υ
Atlas G-2162 ^e	POE oxypropylene monostearate	16.0	S	1:3	D	Y
Atlas G-2859 ^f	POE sorbitol -4, 5-oleate	3.7	\mathbf{L}_{\perp}	1:3	D	N
Myrj 528 ^e	POE (40) stearate	16.9	S	1:3	D	Ŋ
Myrj 53 ^e	POE (50) stearate	17.9	S	1:3	D	N
Span 85 ^f	sorbitan trioleate	1,8	L	1:3	D	N
Tween 20 ^e	POE sorbitan monolaurate	16.7	L	1:3	D	Y
Tween 40 ^e	POE (20) sorbitan mono- palmitate	15,6	L	1:5	D	N
Tween 61 ^e	POE (4) sorbitan monostearate	9.6	S	1:3	D	Y

Table V contd.

Continued . . .

ω 5 Table V contd.

^a L = liquid, S = solid, U = unctuous

 $^{\rm b}$ volume of surfactant:volume of 2% w/w HEC

^c I = increase, NSC = no significant change, D = decrease

^d after 7 days, Y = yes, N = no

^e Atlas Chemical Industries, 1967b

^f Griffin, 1965

^g Schick, 1967

dilution with aqueous media. Only one of the agents contained in Table V, Brij 58, is included in the Atlas list. The remainder of the surface active agents listed by Atlas did not show appreciable thickening properties in the present study, probably because a 30-50% lower concentration of the agent was used. The addition of HEC, and possibly other cellulose polymers, to the aqueous vehicles used for dilution has the potential for a synergistic increase in viscosity with lower surfactant concentration. HEC addition to diluting solutions has a potential three-fold advantage:

- a) expansion of the number of non-irritating surfactants (Atlas Chemical Industries Inc., 1967a) which may be used for twin-bottle formulations, viz., hair dyes,
- b) reduced incidence of skin irritation because a significantly lower concentration of the surfactant is necessary, and
- c) reduced manufacturing costs.

2. Characterization Data for Polyoxyethylene (4) Dodecyl Ether

Using common linear regression methods, a number-average molecular weight, $\underline{Mn} = 380$, was obtained for the surfactant dissolved in benzene using non-aqueous vapour pressure osmometry and a benzil standard (Table VI and Figure 7). Considering the flatness of the line and the magnitude of the coefficients on the y-axis a coefficient of determination of 0.8533 represented a good fit. Because vapour pressure osmometry is a measurement of colligative properties and deviates from the theoretical to the same extent as the solution behaviour departs from the ideal, a molecular weight was estimated also with nuclear magnetic

Table VI

Vapour pressure osmometer data for Brij 30 and benzil

	Benzil ^a	Brij 30	
Concentration	Average Bridge ^b Output	Concentration	Average Bridge ^C Output
(g/1)	(mV)	(g/1)	(mV)
2.112	179.5 [°]	4.857	229.5
4.223	345.0	9.713	430.0
8.445	674.5 [°]	19.425	831.5
16.890	1301.0	38.850	1586.0

standard dissolved in benzene

^a Linear regression results: Benzil, slope = -0.483, intercept = 84.72, $r^2 = 0.8964$; Brij 30, slope = -0.166, intercept = 46.82, $r^2 = 0.8533$.

^b number of replicates = 4

^c number of replicates = 3





Extrapolation of the vapour pressure osmometer data to zero concentration for the number-average molecular weight determination of Brij 30

resonance. The integrated nuclear magnetic resonance spectrum yielded 383 for the molecular weight (Figure 8) which was in excellent agreement with the colligative properties result.

Because the molecular weight estimate for the surfactant was greater than the formula molecular weight, the presence of polyethers with a higher degree of substitution than indicated by the manufacturer's formula was suspected. Direct probe mass spectrometry was used to explore this possibility and consequent examination of the spectra revealed the presence of a strong peak at 407 which was the P + 1 peak for polyoxyethylene (5) dodecyl ether,

 $CH_3 (CH_2)_{10} CH_2 O(CH_2 CH_2 O)_5 H,$

and a smaller P + 1 peak at 451,

CH₃ (CH₂)₁₀ CH₂ O(CH₂ CH₂ O)₆ H,

polyoxyethylene (6) dodecyl ether. This pair of peaks represented a degree of ether substitution of +1 and +2 higher than the manufacturer's formula for Brij 30,

 $CH_3 (CH_2)_{10} CH_2 O(CH_2 CH_2 0)_4 H.$

The infrared spectrum of Brij 30 (Figure 9) revealed representative bands for alcoholic stretching at 3450 cm⁻¹ (Shriner <u>et al.</u>, 1956), asymmetrical stretching (ν_{as} CH₂) of methylene groups of saturated hydrocarbons at 2925 cm⁻¹, symmetrical stretching (ν_{s} CH₂) of methylene groups of saturated hydrocarbons at 2850 cm⁻¹, and asymmetrical C-O-C stretching of ethers at 1120 cm⁻¹. A smaller peak for a methylene scissoring band (δ_{s} CH₂) occurred at the characteristic 1465 cm⁻¹ position. Methylene









Thin liquid film infrared spectrum of Brij 30

wagging and twisting vibration peaks at 1300 and 1250 cm⁻¹ were typically smaller than the scissoring band at 1465 cm⁻¹. The methylene rocking vibration (ρ CH₂) band in which all of the methylene groups rock in phase appeared at 725 cm⁻¹. The position of this in phase rocking vibration is characteristic for straight chain hydrocarbons of seven or more carbon atoms (Silverstein and Bassler, 1967).

The infrared bands of Brij 30 were identical to those for polyoxyethylene (5) dodecyl ether synthesized and examined by Hummel (1962). This similarity arose because the only difference between the compounds was the degree of polymerization.

A critical micelle concentration of 1.42×10^{-4} moles/1 (22 ± 1° C) ($\overline{\text{Mm}}$ = 380) was calculated for Brij 30 (Figure 10). The cmc has been determined on the unpurified surfactant in this study merely as an identification parameter for future work. The result is predictably higher than the commonly reported literature value, 0.40 x 10^{-4} moles/1 (25° C) (Mukerjee and Mysels, 1971) which was obtained using molecularlydistilled ethylene oxide condensates (Schick, 1962).

3. Polymerization Products Identified

A complex pattern of peaks typical of polyether surfactants (Kalish <u>et al.</u>, 1972) was obtained from the gas chromatogram of Brij 30 but a definite repetitive nature in the peak patterns was noticeable (Figure 11). With increasing retention time, each set of peaks may reflect an increment in the number of ethylene oxide units. The retention times and volumes for the major peaks of Brij 30 are given in Table VII.



FIGURE 10. Relationship of surface tension to concentration of Brij 30 in distilled water at 22 \pm 1^oC



FIGURE 11. Temperature programmed gas chromatogram of Brij 30. $T = 110^{\circ}C$, $T_{f} = 250^{\circ}C$, dT/dt = $6^{\circ}C/min$

Table VII 🕔

Retention time, retention volume and degree of resolution for

the major components of Brij 30

Peak	Program Temperature (°C)	t _r (min.)	V _r (cm ³)	^R 1,2
A	146	5.5	130.2	
В	165	8.9	199.3	24
С	169	9.6	211.8	24.
D	191	13.0	271,5	19/
E	196	14.1	289.1	10:
F,	215	17.1	333.1	6
G	220	17.9	344.4	0.
н	237	20.6	379.5	э
I	243	21.5	388.6	J.
The degree of resolution, (16), is presented also for successive peaks. Resolution of the successive major peaks was good using temperature programming with a 3% SE 30 on Varaport 80/100 mesh 6 ft. x 2 mm i.d. stainless steel column (Table VII).

The retention times and volumes for the solution of a homologous series of straight chain alcohols which was gas chromatographed under conditions identical to those used for Brij 30 are given in Table VIII (Figure 12). This solution when combined with the technical Brij 30 solution in three separate volume ratios (1:2, 1:3, 1:4, alcohol solution: Brij 30 solution) and chromatographed yielded a single intense symmetrical peak for the dodecanol portion of the solution of alcohols and peak A of Brij 30 (Figure 13). For comparison, the retention times and volumes for the technical Brij 30 solution, the solution of the series of homologous alcohols and the Brij 30 – alcohol series combination are shown in

Peak	PrB <u>r</u> ogram Temperature (^O C)	Brij 30 ^a (I) H t _r V _r $\binom{\min}{\min}$ (cm ³)	t _r (min.)	Alcohols ^b (I V _r (cm ³)	I) Combination (I ^t r (min.)) + (II) ^c V _r (cm ³)
Octanol	117	·	1.0	26.8	· 1 . 1	28.0
Decanol	122		2.7	68.3	2.8	68.3
Dodecanol + A - Brij 30	146	5.5 130.2	5.5	129.9	5.6	128.8
Tetradecanol B - Brij 30	165 + 165 139	8.9 199.3	9.0	197.4	9.0	193.7
C - Brij 30	169	9.6 211.8	-	-	9.7	204 .9
Hexadecanol	186	- · -	12.4	254.6	12.5	250.0
D - Brij 30	191	13.0 271.5	. –	-	-	_ ^d
E - Brij 30	196	14.1 289.1	-		14.2	275.3
Octadecanol	207		15.5	298.3	15.6	294.3

Table VIII

Retention times and volumes for Brij 30, the homologous series of alcohols and the Brij 30 -

alcohol series combination

^d poor peak resolution prevents accurate retention time determination (Figure 12)



FIGURE 12. Temperature programmed gas chromatogram of the homologous series of alcohols. T = 110° C, T_f = 220° C, dT/dt = 6° C/min



FIGURE 13. Temperature programmed gas chromatogram of a 1:3 volume ratio of the homologous alcohols solution and Brij 30. $T = 110^{\circ}C$, $T_{f} = 250^{\circ}C$, $dT/dt = 6^{\circ}C/min$

Table VIII. The retention times and volumes for the dodecanol fraction of the homologous alcohol series and peak A of Brij 30 solution were in good agreement and reliably indicated that peak A of Brij 30 was dodecanol. Peak A of the surfactant was estimated to represent a 6% w/w dodecanol contamination.

When gas liquid chromatography was a relatively new technique, Nakagawa <u>et al</u>. (1961) found an 8.9% concentration of dodecanol contaminant in Brij 30. The isothermal conditions and column chosen by these authors resulted in a poorly resolved peak, therefore, the 6% w/w value obtained in the present study is probably a better estimate of the dodecanol content.

The mass spectrum of component peak A of Brij 30 (Figure 11) was identical in fragment pattern and peak ratios to the spectrum for dodecanol, the suspected contaminant (Figure 14). Because dodecanol was a long chain alcohol (C > 6), the parent peak, P = 186, was character-istically absent from the spectrum and the cleavage pattern resembled that of theccorresponding olefin having clusters of peaks at intervals of 14 mass units. In these clusters, the $C_n H_{2n-1}$ (97, 83, 69, 55) and the $C_n H_{2n+1}$ peaks (141, 127, 113, 99, 85, 71, 57). A simplified mass spectral fragment pattern for peak A of Brij 30 and dodecanol is shown in Fragment Map 1.

The mass spectrum of Brij 30 peak C (Figures 11 and 15) was dominated by the repetitive loss of methylene groups. The $C_n H_{2n+1}$ peaks were intense at m/e, 141 and 169, which revealed the presence of the





Principal fragments of Brij 30 - peak A and dodecanol



FIGURE 15.

Mass spectrum of Brij 30 - peak C

complete

fragment in this component. Evidence for the presence of oxygen containing fragments was obtained from the peak, m/e = 199, which represented

and the peak at m/e = 75,

$$+$$
 $\begin{bmatrix} CH_2 & O & CH_2 & CH_2 & OH \end{bmatrix}$

The combined Brij 30 - alcohol series chromatogram (Figure 13) indicated that the molecular weight of this component should be between 214 (tetradecanol) and 242 (hexadecanol) therefore, the plausible parent for Brij 30 - C was

$$CH_3 (CH_2)_{11} O (CH_2 CH_2 O)_1 H,$$

polyoxyethylene (1) dodecyl ether with molecular weight, 230. The mass spectral fragment pattern for this component is presented in Map 2.

The mass spectrum of Brij 30 - peak E (Figures 11 and 16) showed the same repetitive loss of methylene groups as appeared with peak - C. Because the spectrum for component E is very complex, the methylene cleavage pattern has been omitted from Figure 16 so as to clarify the more interesting oxygen-containing fragments. Similar peaks for oxygencontaining fragments were present at m/e 199 and 75 as were present for component C. New oxygen-containing peaks were also present at m/e = 243,

Principal fragments of Brij 30 - peak C, polyoxyethylene (1) dodecyl ether

$$CH_{3} (CH_{2})_{10} CH_{2} O CH_{2} CH_{2} OH M = 230 \text{ parent not discernible}$$

$$m/e = 199 CH_{3} (CH_{2})_{11} O CH_{2} + - + CH_{2} O CH_{2} CH_{2} OH m/e = 75$$

$$m/e = 169 CH_{3} (CH_{2})_{10} CH_{2} + - + CH_{2} CH_{2} OH m/e = 45$$

$$see Map 1 - + CH_{2} OH m/e = 31$$



FIGURE 16.

Mass spectrum of Brij 30 - peak E.

$$CH_3 (CH_2)_{11} \circ CH_2 CH_2 \circ CH_2 +,$$

m/e = 89,

$$+$$
 $\begin{bmatrix} \operatorname{CH}_2 & \operatorname{CH}_2$

and m/e = 119,

$$+ \sim \int CH_2 \circ CH_2 CH_2 \circ CH_2 CH_2 OH.$$

Peaks at m/e 45, 59, 73, 87, and 101 were indicative of successive methylene cleavages from a $C_n H_{2n}$ 0 fragment (Figure 16). The combined Brij 30 - homologous alcohol series chromatogram (Figure 13) indicated that the molecular weight of this component should be approximately 242 -270. Polyoxyethylene (2) dodecyl ether,

 $\texttt{CH}_3 (\texttt{CH}_2)_{11} \circ \texttt{(CH}_2 \texttt{CH}_2 \circ\texttt{o)}_2 \texttt{H},$

with a molecular weight of 274 appeared to fit the mass spectral fragment and gas chromatographic criteria. The mass spectral fragment pattern is shown in Map 3.

The intense methylene cleavage pattern (C H_{2n-1} , C H_{2n} and C H_{2n+1}) characteristic for fragments lighter in mass than m/e 169,

 $CH_3 (CH_2)_{10} CH_2$ +.

has been omitted from Figure 17 in order to clarify the numerous oxygencontaining fragments of Brij 30 - peak G (Figure 11). As noted for peak E, oxygen-containing fragments representing successive methylene fragmentations from a $C_n H_{2n}$ O backbone were visible also at m/e = 45, 59, 73, 87 and 101 for this component. Only one new oxygen-containing peak was apparent at m/e = 133 (Figure 17), to which the following molecular formula may be assigned,

Principal fragments of Brij 30 - peak E, polyoxyethylene (2) dodecyl ether

$$CH_{3} (CH_{2})_{11} \circ (CH_{2} CH_{2} O)_{2} H M = 274 \text{ parent not discernible}$$

$$m/e = 243 CH_{3} (CH_{2})_{11} \circ CH_{2} CH_{2} \circ CH_{2} \right]^{+} - + \left[CH_{2} (\circ CH_{2} CH_{2})_{2} OH m/e = 119 \right]$$

$$m/e = 229 CH_{3} (CH_{2})_{11} \circ CH_{2} CH_{2} O \right]^{+} - + \left[CH_{2} CH_{2} O CH_{2} CH_{2} OH m/e = 89 \right]$$

$$m/e = 199 CH_{3} (CH_{2})_{11} \circ CH_{2} \right]^{+} - - + \left[CH_{2} O CH_{2} CH_{2} OH m/e = 75 \right]$$

$$m/e = 185 CH_{3} (CH_{2})_{11} \circ \right]^{+} - - + \left[CH_{2} CH_{2} OH m/e = 45 \right]$$

$$m/e = 169 CH_{3} (CH_{2})_{10} CH_{2} \right]^{+} - - + \left[CH_{2} OH m/e = 31 \right]$$

$$m/e = 169 CH_{3} (CH_{2})_{10} CH_{2} \right]^{+} - - + \left[CH_{2} OH m/e = 31 \right]$$



$$+ \int CH_2 CH_2 (O CH_2 CH_2)_2 OH.$$

No new peaks with masses greater than 243 were present therefore, combining the fragment, m/e = 133, with the compatible m/e = 185 fragment revealed, polyoxyethylene (3) dodecyl ether,

$$CH_3 (CH_2)_{11} O (CH_2 CH_2 O)_3 H,$$

with formula molecular weight, 318. The mass spectral fragment pattern for this component is shown in Map 4.

Brij 30 peak - I showed an increased amount of tailing (Figure 11) therefore, the mass spectrum may be contaminated but if the pattern emerging is one of increasing ether substitution then this component should have molecular formula,

сн₃ (сн₂)₁₁ о (сн₂ сн₂ о)₄ н,

M = 362. Again, because of the complexity of the spectrum, the repetitive methylene cleavage pattern of fragments lighter in mass than m/e 169,

$$CH_3 (CH_2)_{10} CH_2]^+,$$

has been omitted from Figure 18 for clarity. A series of new oxygen containing peaks were present at m/e = 163, 177, 193, 257 and 273 (Figure 18). The mass spectral fragment pattern is shown in Map 5.

Because of poor peak resolution due to the upper temperature limitations of the column, the mass spectra for the gas chromatograph peaks which indicated the possible presence of polyoxyethylene (n) dodecyl ether substitutions, n = 5 and 6, were not pursued further.

Principal fragments of Brij 30 - peak G, polyoxyethylene (3) dodecyl ether

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Principal fragments of Brij 30 - peak I, polyoxyethylene (4) dodecyl ether

4

Brij 30 peak B (Figure 11) had the same retention time and a similar retention volume as tetradecanol (Table VIII). When the combined alcohol - Brij 30 mixture was chromatographed for identification of the dodecanol peak, a single symmetrical peak was obtained also for tetradecanol and Brij 30 peak B (Figure 13). Examination of the mass spectra for peak B and for tetradecanol revealed similarities in fragmentation of the two components (Figure 19 and Fragment Map 6). From the similarities in retention time and volume, as well as mass spectral fragment pattern, plus a single symmetrical gas chromatographic peak being obtained for both tetradecanol and the Brij 30 peak B, it was concluded that the Brij peak was composed of tetradecanol. The tetradecanol content of Brij 30 was estimated to be 1.0% w/w.

Tsuji and Konishi (1974) analyzed the hydrophobic portions of commercial samples of polyoxyethylene dodecyl ether and demonstrated the presence of C_{10} , C_{12} and C_{14} Oxo and Ziegler alcohols. They found 0.5, 97.0 and 2.5% of the respective alcohols in polyoxyethylene dodecyl ether after acidic cleavage of the ether linkages. The numbers they quote do not separate the free alcohol contaminants from the polymerization products of these alcohols. The 1.0% w/w contamination of Brij 30 by free tetradecanol found in the present study is probably therefore a good estimate.

The mass spectrum of Brij 30 peak D (Figure 11) closely resembled the spectrum for peak C (Figure 15) except for the presence of two extra peaks at m/e = 197,

 $CH_3 (CH_2)_{12}CH_2$,





Principal fragments of Brij 30 - peak B and tetradecanol

$$CH_3 (CH_2)_{13} OH$$
 M = 214 parent not discernible
- H_2O
- $CH_3 (CH_2)_{12} CH_2$ + m/e = 197
- $CH_3 (CH_2)_{10} CH_2$ + m/e = 169
- see Map 1

and at m/e = 227,

 $CH_3 (CH_2)_{13} \circ CH_2$

Another oxygen-containing fragment was present at m/e 75 and had previously been noted for peak C (Figure 15). The combined Brij 30 homologous alcohol series chromatogram (Figure 13) indicated that the molecular weight of this component should be between 242 (hexadecanol) and 270 (octadecanol) therefore, the plausible parent for Brij 30 - Dwas

$$CH_3 (CH_2)_{13} O (CH_2 CH_2 O)_1 H_3$$

polyoxyethylene (1) tetradecyl ether with a molecular weight of 258. The mass spectral fragment pattern for this component is presented in Map 7.

Tetradecanol, a second alcohol contaminant, appeared to have polymerized with ethylene oxide in a manner analagous to dodecanol because the mass spectra of Brij 30 peaks F and H (Figure 11) through the combination of compatible fragments revealed the following plausible parents,

 $CH_3 (CH_2)_{13} O (CH_2 CH_2 O)_2 H,$

(M = 302) polyoxyethylene (2) tetradecyl ether and,

CH₃ (CH₂)₁₃ O (CH₂ CH₂ O)₃ H,

(M = 346) polyoxyethylene (3) tetradecyl ether, respectively. The mass spectral fragment patterns for these two components are shown in Maps 8 and 9, respectively. Principal fragments of Brij 30 - peak D, polyoxyethylene (1) tetradecyl ether

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$$CH_{3} (CH_{2})_{12} CH_{2} O CH_{2} CH_{2} OH M = 258 \text{ parent not discernible}$$

$$m/e = 227 CH_{3} (CH_{2})_{13} O CH_{2} + - + CH_{2} O CH_{2} CH_{2} OH m/e = 75$$

$$m/e = 197 CH_{3} (CH_{2})_{12} CH_{2} + - + CH_{2} CH_{2} OH m/e = 45$$

$$see Map 6 - - + CH_{2} OH m/e = 31$$

Principal fragments of Brij 30 - peak F, polyoxyethylene (2) tetradecyl ether

Principal fragments of Brij. 30 - peak H, polyoxyethylene (3) tetradecyl ether

$$CH_{3} (CH_{2})_{13} (0 CH_{2} CH_{2})_{3} OH \qquad M = 346 \qquad \text{parent not discernible}$$

$$m/e = 271 \quad CH_{3} (CH_{2})_{13} O CH_{2} CH_{2} O CH_{2} \right]^{+} - + \left[(0 CH_{2} CH_{2})_{3} OH \qquad m/e = 149$$

$$m/e = 241 \quad CH_{3} (CH_{2})_{13} O CH_{2} CH_{2} \right]^{+} - + \left[CH_{2} CH_{2} (0 CH_{2} CH_{2})_{2} OH \qquad m/e = 133$$

$$see Map 8 - + \left[CH_{2} (0 CH_{2} CH_{2})_{2} OH \qquad m/e = 119 \right]$$

$$see Map 8 - + \left[CH_{2} (0 CH_{2} CH_{2})_{2} OH \qquad m/e = 119 \right]$$

In summary, Brij 30 is a mixture of polyoxyethylene (n) dodecyl ethers,

where n = 1, 2, 3 and 4 plus dodecanol 6% w/w. It is predicted that the ether substitutions of n = 5 and 6 are also present. Brij 30 also contains 1% tetradecanol and polyoxyethylene (n) tetradecyl ethers,

where n = 1, 2 and 3. It is predicted that an ether substitution of n = 4 is also present in the tetradecyl series.

The polyoxyethylene alkyl ether surfactants are basically unstable under mass spectrometric conditions, breaking immediately into 2 or more segments. Depending upon the chain length, the point of initial cleavage may occur at one or more positions (Table IX). The cleavage of the C - C bond next to the oxygen atom with a stable P - 31 fragment, typical of primary alcohols, occurred with polyoxyethylene (n) alkyl ethers where n = 1 and 2. With higher degrees of ether substitution, the P - 31 fragment was not visible and the cleavages became characteristic of monomeric aliphatic ethers, C - C bond next to an oxygen atom and C - 0 bond cleavage (Table IX; Silverstein and Bassler, 1967).

The parent peaks were characteristically absent from the mass spectra of dodecanol and tetradecanol. The highest molecular weight fragment observed, corresponded to the dehydration of a P + 1 molecule. Fragments corresponding to successive CH_2 or $CH_2 = CH_2$ fragmentations dominated the spectra of both these alcohols (Figures 14 and 19).

Table	IX
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Some positions of initial fragmentation of polyoxyethylene (n) dodecyl and tetradecyl ethers POE^a (1) alkyl ether $\operatorname{CH}_3(\operatorname{CH}_2)_{\mathbf{x}}$ CH_2 o CH_2 CH_2 oh x = 10 or 12 CH_3 $(CH_2)_{x}$ CH_2 O CH_2 CH_2 O CH_2 CH_2 OH_2 CH_2 OH_2 CH_2 OH_2 OH_2 CH_2 OH_2 OH_2 POE (2) alkyl ether x = 10 or 12 $\mathsf{CH}_3 (\mathsf{CH}_2)_{\mathsf{x}} \mathsf{CH}_2 \circ \mathsf{CH}_2 \circ$ POE (3) alkyl ether x = 10 or 12 $\mathsf{CH}_3 (\mathsf{CH}_2)_{\mathbf{x}} \mathsf{CH}_2 \text{ o } \mathsf{CH}_2 \mathsf{CH}_2 \text{ o } \mathsf{CH}_2 \mathsf{CH}_2 \mathsf{O} \mathsf{CH}_2 \mathsf{CH}_2 \mathsf{O} \mathsf{CH}_2 \mathsf{CH}_2 \mathsf{O} \mathsf{H}_2 \mathsf{H$ POE (4) alkyl ether x = 10a polyoxyethylene

In conclusion, the results of the present study have revealed that average molecular weight determinations for surfactants are of limited value because an experimentally determined M_n (380) which is relatively close to the theoretical molecular weight (362) is not indicative of a monodisperse system. Because the commercial synthetic process, etherification by reaction of alcohol and ethylene oxide (Equation (11); Satkowski <u>et al</u>., 1967), may give rise to many polymerization products, there is no reason to suppose that the polyoxyethylene alkyl ether surfactant in this study is unique. The hydrophobic intermediates, obtained from natural or synthetic sources and used commercially, are also not monodisperse (Satkowski <u>et al</u>., 1967). Therefore, it is suggested that micellar thermodynamic studies involving these surfactants should be done with a molecularly-distilled fraction where the purity and identity of the component is assured or with mixtures of known composition.

Without establishing calibration curves for the individual components, Kalish <u>et al</u>. (1972) have proposed integrated gas chromatograph peak areas to describe the molecular weight distribution of the surfactant derivatives they studied. This procedure is in error because the response of the detector is not a constant for all gas chromatographically visible components but it is a function of the composition of each component. For this reason plus the difficulty of isolating pure components, the actual molecular weight distribution for Brij 30 has not been pursued further.

With the advent of gas liquid chromatographic - mass spectrometric methods, it is theoretically possible to identify the components

of commercial surfactants but this approach, at present, is limited to surfactants with a low degree of substitution. In the present study of a polyoxyethylene (n) alkyl ether surfactant, the upper temperature limits of SE 30 columns and the degree of resolution of the large number of polymerization products of two or more alcohols presented restrictions to a complete analysis of Brij 30.

SECTION II. RHEOMETRIC STUDIES OF A MODEL SHEAR-THINNING SYSTEM

Pharmaceutical lotions, thin creams and suspensions commonly exhibit shear-thinning flow properties therefore, a model system with a wide range of consistencies has been used to represent these fluids for the rheometric studies.

The three rheometers employed in the present study were: the Haake Rotovisko (Gebruder Haake, 1969a), reputedly the most versatile concentric-cylinder viscometer (van Wazer <u>et al.</u>, 1963); the Brookfield Synchro-lectric (Brookfield Engineering Laboratories, Inc., 1971), the most economical and widely used rheometer and the Weissenberg rheogoniometer (Sangamo Controls Ltd., 1970), a cone-plate instrument capable of steady and dynamic shear measurements. Instrument descriptions are given by van Wazer <u>et al.</u> (1963).

A. STEADY SHEAR STUDIES OF PRACTICAL IMPORTANCE

Many rotational viscometers have been designed (van Wazer <u>et al</u>., 1963) but few of these are used widely for pharmaceutical measurements. Of these, the commonly used Couette rheometers have not been evaluated statistically to show their limitations to accurately represent flow curves of shear-thinning systems over a pharmaceutically important range of consistencies. Inherent in this evaluation is the examination of shear rate calculation methods and instrument calibration techniques. The expression of shear-thinning properties in terms of flow model parameters and the usefulness of these parameters as an aid to consistency formulation also requires attention. This section of the present study therefore

attempts to examine the above aspects for a model shear-thinning system with a wide range of consistencies.

For economic reasons, the rheological reproducibility and stability of HEC dispersions have also been determined and then compared with the commonly used 2% MC dispersion.

LITERATURE SURVEY

1. Shear Stress/Shear Rate Determination in Rotational Viscometry

a) Coaxial Cylinder Geometry

The coaxial cylinder or Couette rheometer consists of a cylindrical cup of radius $\frac{R}{c}$ and a shorter cylindrical spindle of radius $\frac{R_b}{b}$. Either the cup or the spindle may rotate (Figure 20, van Wazer <u>et al</u>., 1963; Scott Blair, 1969). The material to be measured is sheared between two cylinders, one of which is rotated at a constant speed while the other is attached to a torsion wire or other device for determining the torque (Scott Blair, 1969).

When laminar flow exists or ΣM = 0, the shear stress (σ , dyne cm⁻²) may be represented by

$$\sigma = \frac{M}{2\pi r^2 h}$$

where <u>M</u> is the moment of the forces acting on the cylindrical surface with area, $2\pi rh$, at point <u>r</u> (Figure 20). If <u>r</u> is taken at the rotating surface Equation (17) is valid for non-Newtonian as well as Newtonian fluids (Krieger and Maron, 1951).

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(17)



FIGURE 20.

Laminar flow of an inelastic fluid in the gap between two concentric cylinders. A. the outer cylinder rotates with angular velocity Ω and the inner one is stationary. B. the inner cylinder rotates with angular velocity Ω and the outer one is stationary (adapted from Lielmezs and Runikis, 1967)

For this geometry, the derivation of fundamental equations relating shear rate to viscosity for Newtonian fluids is based on the following seven assumptions (van Wazer et al., 1963).

i. The liquid is incompressible.

ii. The liquid motion is laminar.

iii. No motion exists between the fluid and the cylindrical surfaces.

iv. The liquid motion is two dimensional.

v. The liquid motion is steady.

vi. The system is isothermal.

vii. The fluid velocity is only a function of radius.

Since the design of the original Couette viscometer in 1890, Newtonian flow assumptions have been used for the derivation of shear rate equations by some manufacturers (Gebruder Haake, 1969b; Fryklof, 1961). The equations are predominantly derived from the well known Margules equation,

$$\eta = \left(\frac{M}{4\pi h\Omega}\right) \left(\frac{1}{R_{b}^{2}} - \frac{1}{R_{c}^{2}}\right), \qquad (18)$$

which arose from the basic relation between shear stress and rate of shear in Newtonian fluids,

$$\sigma = \eta \left(\mathbf{r}_{d} \frac{\mathrm{d}\Omega}{\mathrm{d}\mathbf{r}} \right) , \qquad (19)$$

where $d\Omega/dr$ is the rate of rotation at point <u>r</u> (Reiner, 1960). In the Margules equation, <u>n</u> is the Newtonian viscosity (poise), <u>M</u>, the moment of force (dyne cm), <u>h</u>, the cylinder length (cm), <u>Ω</u>, the angular velocity at the rotating surface (rad s⁻¹). Equation (18) may be separated into shear stress (17) (where $r = R_b$) and shear rate ($\hat{\gamma}$, s⁻¹),

$$\dot{\gamma} = 2\Omega \frac{\frac{R_{c}^{2}}{R_{c}^{2} - R_{b}^{2}}$$

Together (17) and (20) form the familiar Newtonian shear stress-shear rate calibration equations for coaxial cylinder rheometers.

The problem of developing an exact shear rate solution for non-Newtonian fluids sheared within the coaxial gap stems from the absence of a set relationship between shear stress and shear rate for these fluids (van Wazer <u>et al.</u>, 1963).

Krieger and co-workers (Krieger and Maron, 1951, 1952 and 1954; Krieger and Elrod, 1953; Maron and Krieger, 1960; Krieger, 1968 and 1969) have worked repeatedly on the shear rate problem for non-Newtonian fluids sheared within the gap of a coaxial rheometer. The applicability of their equations to inner cylinder rotating instruments has been shown by Lielmezs and Runikis (1967).

From Mooney, it was known that the general expression for angular velocity, (21), could be differentiated to give (22) (Krieger, 1968).

$$\Omega = \frac{1}{2} \int_{\sigma_{b}}^{c_{o}c} f(\sigma) \frac{d\sigma}{\sigma}$$
(21)

$$2\sigma_{b}\left(\frac{d\Omega}{d\sigma_{b}}\right) = f(\sigma_{b}) - f(\sigma_{c})$$
(22)

The Euler-Maclaurin formula was used to expand this difference equation (Krieger and Elrod, 1953). The dominant term of the final form of the resultant shear rate equation,

(20)

$$\dot{\gamma} = \frac{2\Omega}{n} \frac{R_c^{2/n}}{R_c^{2/n} - R_b^{2/n}} \left\{ 1 + \frac{2/n}{(2/n)^2} f\left(\frac{2}{n} \ln \frac{R_c}{R_b}\right) \right\}, \quad (23)$$

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(24)

(26)

was identical to the power-law approximation for shear rate (Krieger, 1968) where n was the power-law flow behaviour index.

The correction term in (23) is almost always within 1% of the true rate of shear (Krieger, 1969) therefore, shear rate may be calculated using

$$\dot{\gamma} = \frac{2}{n} \frac{R_c^{2/n}}{R_c^{2/n} - R_b^{2/n}} \Omega$$

according to Krieger (1968). Shear rate approximation using the first term of (23) is valid even for extreme cases of non-power-law fluids and large radius ratios (Krieger, 1969). In (24), the liquid velocity as a function of radius is modified by the flow behaviour index to account for the non-Newtonian character of the fluid.

A finite bob rotating in a cup of infinite radius often approximates the measuring conditions in the Brookfield Synchro-lectric viscometer. Krieger and Maron (1952) proposed a general solution involving graphical differentiation and the relation,

$$\dot{\gamma} = -2 \frac{d\Omega}{d\ln\sigma} .$$
 (25)

Later, Krieger (1968) indicated that the shear rate for non-Newtonian fluids sheared within an infinite gap may be represented by

$$\dot{\gamma} = \frac{2}{n} \Omega$$
 ,

which is the limiting case of (24). From geometric considerations,

Mooney and Ewart (1934) derived shear stress and viscosity relationships for their coni-cylindrical viscometer which may be applicable to the Brookfield SC-4 spindles. Shear stress and shear rate may be computed from

$$\sigma = kS$$
(27)

$$\dot{\gamma} = \frac{R_{c}^{2} - R_{b}^{2}}{R_{c}^{2} + R_{b}^{2}} \Omega$$

where <u>k</u> is a shear stress calibration constant obtained from Newtonian oils and <u>S</u> is the meter reading.

b) Cone-Plate Geometry

Unlike the coaxial-cylinder viscometer, an exact relationship between shear rate and shear stress exists for the cone-plate rheometer if two important assumptions are made (Walters, 1968):

i. the effect of fluid inertia is negligible

ii. the angle between the cone and plate is less than 4° .

This relation is expressed as

$$=\frac{3M\theta}{2\pi r^3 \Omega}$$

where $\underline{\theta}$ is the cone angle in radians and <u>r</u> is the cone radius. Fredrickson (1964) has evaluated the percent difference in shear stress between the cone and plate for several cone angles. These differences were 0.49, 0.12, 0.03 and 0.008% for cone angles, 4, 2, 1 and $\frac{1}{2}^{0}$, respectively. For small cone angles, the assumption that shear stress,

(28)

(29)
and hence shear rate, are uniform throughout the fluid sample independent of radial position, is valid (Fredrickson, 1964; Walters, 1968). Shear rate is calculated from

$$\dot{\gamma} = \frac{\Omega}{\theta}$$
 (30)

The relationship between the measured torque and shear stress is given by

$$\sigma = \frac{3M}{2\pi r^3} \cdot$$

2. Errors in Rotational Viscometry

End-effects, slip and Weissenberg effects comprise the major sources of error in viscometric measurements performed with a Couette rheometer but they may be either mathematically corrected or minimized by design. End-effects are readily corrected by substituting an effective spindle length for the actual physical length in (17) (Lindsley and Fischer, 1947). These effects may assume greater importance with non-Newtonian fluids and require an end correction for each sample at each shear rate (Sherman, 1970). End-effects are minimized by designing coni-cylindrical spindles (Brookfield SC-4 spindles) and open-ended spindles (Ferranti Portable and Haake Rotovisko MV spindles) (van Wazer et al., 1963; Highgate and Whorlow, 1969). Slip may be mathematically corrected (Skelland, 1967). Through the design of ribbed or roughened cylinder surfaces slip may be minimized in dispersed systems (Sherman, 1970). Weissenberg effects are minimized either by repacking the gap or by the presence of a fluid cover but neither is satisfactory (van Wazer et al., 1963).

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(31)

Secondary flows due to fluid inertia, non-uniform shear rate within the gap and sample evaporation comprise the major sources of error in cone-plate determinations. Secondary flows are minimal at shear rates less than 2800 s⁻¹ (Skelland, 1967; Williams, 1965), the presence of non-uniform shear is minimized by small cone angles (Fredrickson, 1964; Walters, 1968) and sample evaporation is reduced by a thin coating of low viscosity oil on the exposed fluid surface (Boger and Murthy, 1969).

Viscous heating is another source of error in rotational viscometry. The maximum temperature rise for coaxial instruments was estimated from

$$T = \frac{\eta_a R_b^2}{4\lambda} (\Omega_o - \Omega_M)^2$$
(32)

where $\Omega_{\underline{o}}$ is a low angular velocity, $\Omega_{\underline{M}}$ is the maximum angular velocity and $\underline{\lambda}$ is the thermal conductivity of the fluid (Fredrickson, 1964). For the cone-plate, an estimate of maximum temperature rise as a result of viscous heating may be calculated from

$$\Delta T = \frac{3M\Omega_M \theta}{16\pi\lambda r}$$
(33)

as derived by Bird and Turian (1962). Using the thermal conductivity value for water (Weast, 1973), the maximum change in temperature due to viscous heating, in the present study, was 0.2° and $0.6^{\circ}C$ for the Couette and cone-plate rheometers, respectively.

3. Flow Model Selection

The expression of shear-thinning flow properties in terms of flow model parameters would facilitate total rheogram comparisons and thereby aid in product development and quality control. Hence, three models, the modified Shangraw structure equation, the Steiger-Trippi-Ory model and the power-law equation, were selected for evaluation.

Yakatan and Araujo (1968) proposed that the Shangraw structure equation (Shangraw <u>et al.</u>, 1961) can be modified to a three parameter model for the shear-thinning flow region,

$$a = a\gamma + b(1 - e^{-c\gamma}).$$
 (34)

<u>a</u>, <u>b</u> and <u>c</u> are empirical parameters describing the system. They used an analogue computer to simulate the rheograms of carboxymethylcellulose mucilages.

The second model,

$$= a'\sigma^3 + c'\sigma, \qquad (35)$$

was proposed by Steiger-Trippi and Ory (1961) for shear-thinning pharmaceutical systems. <u>a'</u> is the liquéfaction factor and <u>c'</u> is the reciprocal of the limiting viscosity at low shear rates. Originally, Eisenschitz (1933) had used this equation to describe the rheology of concentration cellulose dispersions. Kassam and Mattha (1970a, b, c, d; 1971a, b) have used (35) in their work with guaran, methylhydroxyethylcellulose and polyvinylpyrrolidone dispersions.

The well-known power-law or Ostwald-de Waele equation,

(Reiner, 1960; Scott Blair, 1970) has been widely used to describe the shear-thinning behaviour of non-Newtonian systems (Bird, 1965; Cramer, 1968; Tung <u>et al.</u>, 1971). <u>m</u> is known as the consistency index and <u>n</u>, as the flow behaviour index (Skelland, 1967).

EXPERIMENTAL

1. Rheometers and Methods

Haake Rotovisko, Model RV1 (van Wazer <u>et al.</u>, 1963). An MVI spindle with a gap width of 0.91 mm was used over a range of shear rates from $8.5 - 1370 \text{ s}^{-1}$. The sample temperature was maintained by a thermostated water jacket surrounding the measuring head. Each sample was subjected to a stepwise shear rate increase and then a decrease with the shear stress signal either being read directly from the meter or traced onto a strip chart. The manufacturer's equations, used to obtain shear stress and shear rate respectively, were as follows

$$\sigma = AS \tag{37}$$

and

 $\dot{\mathbf{y}} = \mathbf{B}/\mathbf{U}^*, \tag{38}$

<u>S</u> was the meter reading, <u>U</u>, the gear setting and <u>A</u> and <u>B</u> were calibration constants. <u>A</u> incorporated a correction for end-effects.

<u>Brockfield Synchro-lectric</u> (van Wazer <u>et al.</u>, 1963). The SC-4 coni-cylindrical spindle series was used over a shear rate range of $0.37 - 20 \text{ s}^{-1}$. The sample temperature (25.0 ± 0.5° C) in the SC-4 cup was controlled by a circulating water bath. Each sample was subjected

(36)

to a stepwise shear rate increase and then a decrease with the shear stress signal being read directly from the meter. At each shear rate, one minute was allowed for speed equilibration followed by three consecutive readings taken at 30 second intervals. Calibration constants were obtained for the spindles using oil viscosity standards (Cannon Instrument Co., Appendix I) as suggested by the manufacturer (Brookfield Engineering Laboratories Inc., 1971). Shear stress and shear rate were calculated from (39) and (20), respectively, where <u>A'</u> is a shear stress calibration constant.

$$\sigma = A'S \tag{39}$$

The geometrical shape of the spindles was accounted for through the shear stress calibration constant, $\underline{A'}$, obtained from Newtonian oils and the relation

$$A' = \frac{\eta \dot{\gamma}}{S} , \qquad (40)$$

where <u>n</u> was the Newtonian viscosity (poise) of an oil at a constant temperature. The influence of the conical ends of the cylindrical spindle was included in the effective length, (h*),

 $h^* = h_0 + \Delta h, \qquad (41)$

where $h_{\underline{o}}$ was the length of the cylindrical portion (cm) and $\underline{\Delta h}$, the extended length due to the submerged surface area of the spindle ends.

Weissenberg Rheogoniometer (van Wazer <u>et al.</u>, 1963). Several platen diameters, 5.0, 7.5 and 10.0 cm, with varying cone angles, 2.0, 1.0, 0.5, 0.25 deg, were used in combination with selected torsion bars to accommodate several decades of shear rate. In each instance, the cone was mounted on the top and the plate on the bottom. The sample temperature was maintained by an air bath surrounding the measuring head and a thermocouplemmounted in the upper platen recorded the sample temperature. Sample symmetry was checked prior to subjection to a stepwise shear rate increase and then a decrease in forward and reverse directions with the sheargstress signal recorded on a strip chart.

The manufacturer's equations (Sangamo Controls Ltd., 1971) were used to calculate shear rate,

$$= \frac{180\Omega}{\pi\alpha}, \qquad (42)$$

and shear stress,

Ŷ

$$T = \frac{3\Delta_T^{K}T}{2\pi r^3}.$$
 (43)

 $\underline{\Omega}$ was the angular rotation of the platen (rad s⁻¹), $\underline{\alpha}$, the cone angle (deg), $\underline{\Delta}_{\underline{T}}$, the movement of the torsion head transducer (μ m), \underline{r} , the platen radius (cm) and $\underline{K}_{\underline{T}}$ was the torsion bar constant (dyne cm μ m⁻¹).

2. <u>Rheological Properties</u>, <u>Reproducibility and Stability of</u> Hydroxyethylcellulose and Methylcellulose Dispersions

Ten replicate dispersions of HEC were prepared at concentrations of 1.5, 2.0, 2.5, 3.0 and 3.5% w/w following the general procedure outlined in Appendix I. After aging 0.13, 1 and 5 years at room temperature, rheograms for each dispersion were obtained using the Haake Rotovisko viscometer ($\dot{\gamma} = 8.5 - 1370 \text{ sec}^{-1}$). The shear stress signal was read directly from the meter. All tests were made at a sample temperature of 30.0 ± 0.5°C. Calibration constants were obtained for the spindle/ cup combination using oil viscosity standards (Cannon Instrument Co.) as suggested by the manufacturer (Gebruder Haake, 1969a). A fresh sample was used for each viscometric measurement. Between rheometric determinations, all sample containers were sealed with paraffin and stored at room temperature in the absence of light. For comparison, a set of ten replicate 2% w/w methylcellulose (MC, 1500 cP) dispersions wass treated in a similar manner.

The data were put on punch cards to facilitate calculations and statistical analyses using an IBM 360/67 computer. Shear stress and shear rate were calculated using (37) and (38) respectively.

The rheograms were compared for preparation reproducibility using a logarithmic transform of the power-law model (36) in a co-variance program (Appendix III, Program 1) to test for differences in slope (flow behaviour index) and level (consistency index) (Snedecor, 1965). At each polymer concentration, confidence limits (95%) and coefficients of variation, CV (44), were calculated for the power-law parameters at measuring times, 0.13, 1 and 5 years (Tables X and XI).

$$CV = \frac{SD}{\bar{x}} \times 100\%$$
 (44)

<u>SD</u> was the standard deviation and \overline{X} was the average power-law flow behaviour index or consistency index.

To acquire stability information, the apparent viscosity of the HEC and MC polymers was examined with respect to time (Figures 25 to 27). The power-law consistency index was taken as a dependent variable to calculate linear, quadratic, logarithmic and hyperbolic functions with respect to time. These functions were then compared for accuracy of fit

to the data (47, Figure 24).

<u>Rheological Properties of Hydroxyethylcellulose - Polyoxyethylene</u> <u>(4) Dodecyl Ether Systems</u>

Four replicate dispersions of HEC were prepared at concentrations of 2.0, 2.5, 3.0 and 3.5% w/w following the general procedure outlined in Appendix I. After aging for 1 day, flow curves for each of the four replicate HEC dispersions at each concentration were measured with the Haake Rotovisko viscometer. The three dispersions with the closest rheograms were selected for further evaluation. At each of the HEC concentrations, triplicate sets of Brij 30 - HEC dispersions were made containing 0.0, 4.0, 8.0, 12.0 and 16.0% w/w of the surfactant (Appendix I).

Rheological properties of the HEC - Brij 30 systems were determined with a Rotovisko after 1 and 7 days storage. All tests were made at a sample temperature of $30.0 \pm 0.5^{\circ}$ C over a shear rate range of $8.5 - 685 \text{ s}^{-1}$. Shear rate and shear stress were calculated from (38) and (37), respectively.

4. Comparison of Rotovisko Shear Stress Calibration Methods

The manufacturer suggests that two shear stress calibration constants, <u>A</u> (37), are sufficient for the ten shear rates associated with the two dynamometer settings of the Rotovisko. Because this procedure ignores the possibility of changed flow=effects at high shear rates, an attempt has been made to examine whether a single value for the shear stress factor is adequate for all ten shear rates associated with each dynamometer setting or whether there should be a shear stress constant for each shear rate.

A series of Newtonian oils (Appendix I) was measured under constant temperature conditions and a shear stress constant was calculated from

$$A = \frac{\eta \dot{\gamma}}{S}$$
(45)

for each of the ten gear setting associated with the two ranges of dynamometer sensitivity (Table XII). The manufacturer's method was also used to evaluate the shear stress calibration constant (Gebruder Haake, 1969a); Table XII). A selection of shear-thinning fluids with a powerlaw flow behaviour index range of 0.48 to 0.69 was then measured and the shear stress results calculated using both the proposed method and the manufacturer's method.

To determine which calibration method yielded the best representation of the shear stress-shear rate parameters, the data calculated with both methods were separately compared with shear stressshear rate data obtained for the same dispersions using the Weissenberg rheogoniometer (Appendix III, Program 1; Table XIII).

5. <u>Evaluation of Non-Newtonian Rheograms Derived from Two Different</u> Types of Rheometers

The choice of viscometers for the rheological evaluation of pharmaceuticals poses an interesting problem because comparisons among instruments of different geometry are lacking for a range of non-Newtonian fluids. Constant shear throughout the sample is theoretically

possible with the cone-plate viscometer (Fredrickson, 1964) however, the commonly used instruments have a Couette geometry in which the sheer rate varies across the sample gap. The Haake Rotovisko is a versatile Couette instrument with well defined geometry and minimal end-effects therefore, a comparison of this instrument with the coneplate Weissenberg rheogoniometer would be valuable. Also a Couette attachment with temperature control is currently available for the Brookfield Synchro-lectric viscometer. The evaluation of this instrument would have practical significance because it has the potential of providing the manufacturer with a Couette rheometer at nominal cost.

Dispersions of 2.0 and 2.5% w/w HEC were prepared following the general procedure outlined in Appendix I and aged for 1 day. Sets of Brij 30 in HEC dispersions were made containing 0.0, 4.0, 8.0, 12.0 and 16.0% w/w of the surfactant in both of the HEC dispersionsconcentrations (Appendix I). Rheological properties of the HEC - Brij 30 systems were determined after 1 day of storage using the Haake Rotovisko ($\dot{\gamma} = 8.5 - 685 \text{ s}^{-1}$, σ calculated using the proposed calibration method Section II. 4.), the Brookfield (SC-4 - 27 and 29 spindles, $\gamma\dot{\gamma} = 0.4 - 20 \text{ s}^{-1}$) and the Weissenberg rheogoniometer (platen diameter = 7.5 cm, angle = 0.9842°, $\dot{\gamma} = 0.11 - 690 \text{ s}^{-1}$) instruments. The sample temperature was 25.0 ± 0.5°C. The Rotovisko and rheogoniometer shear stress signals were recorded. An undisturbed sample was used for each viscometric measurement and all tests were done in triplicate.

Briefly, several methods for shear rate calculation were selected for the Rotovisko and Brookfield rheometers. The rheograms

obtained using the selected calculation methods were compared separately with data generated with the Weissenberg rheogoniometer (Appendix III, Program 1).

In detail, two separate shear rate equations were used with data from the Rotovisko and Brookfield rheometers. The first equation, designated as the calibration equation was (20). The second shear rate equation evaluated for both rheometers was a theoretical equation proposed by Krieger and Maron (Krieger, 1968)((24). An additional pair of shear rate equations were examined with the Brookfield data. The first of these was the Mooney and Ewart equation, (28), for conicylindrical spindles and the second was the Krieger infinite gap equation, (26). In all instances, shear stress was calculated from (17) except for the Mooney and Ewart equation where (27) was used.

The manufacturer's method was used for shear rate-shear stress determination with the data generated using the rheogoniometer in steady shear (Equations 42 and 43, respectively).

Prior to pooling the data for the instrument comparisons, a preliminary screen of the triplicate data sets for each rheometer was performed to reject any members of the sets which differed at P < 0.01. The pooled shear rate and shear stress values calculated by the methods being tested for the Rotovisko and Brookfield instruments were read directly into the co-variance program for comparison with the rheogoniometer results (Appendix III, Program 1; Tables XVI and XIX).

6. Evaluation of Rheological Models for Shear-Thinning Systems

Brij 30 in HEC dispersions were prepared and measured as described previously in Section II. 3. The data were put on punch cards to facilitate calculations and statistical analysis by computer. Shear stress and shear rate were calculated from (37) and (38), respectively.

A non-linear least squares fitting routine was then applied to obtain the best fit to the data by the modified Shangraw, the Steiger-Trippi-Ory and the power-law models, (34), (35) and (36), respectively (Appendix III, Program 2). Calculations were made in double precision and the iterative procedures were continued until successive estimates of the parameters differed by less than 0.0001. The program printed the model parameters along with the root mean square total error of estimate for each. The parameters were also punched on cards to facilitate plotting and further programming. A file containing the actual and fitted shear stress-shear rate values was created and used to calculate coefficients of determination for each rheological model.

As a test of dispersion stability, flow curves obtained after 1 and 7 days storage were compared for each HEC - Brij 30 combination (Appendix III, Program 1). When the pairs of flow curves differed significantly (P < 0.01), the 7 day values were discarded from the following analysis to determine the effect of varying HEC and Brij 30 concentrations on the flow model parameters. For each HEC concentration, the parameters <u>a</u>, <u>b</u>, <u>c</u>, <u>a'</u>, <u>c'</u>, <u>m</u> and <u>n</u> were taken as dependent variables and

the Brij 30 concentration as the independent variable to calculate linear, quadratic, logarithmic and hyperbolic functions. The highest coefficient of determination denoted the best fit (Figures 33 to 39 and Equations 52 to 58).

Dispersions containing 16% w/w Brij 30 in distilled water were also prepared and measured under identical conditions to those used for the Brij 30 - HEC systems. At each shear rate, the increase in apparent viscosity, n_{a4} , due to the combination of Brij 30 - HEC water was calculated from

$$\eta_{a4} = \eta_{a1} - (\eta_{a2} + \eta_{a3})$$
 (46)

where n_{a1} was the viscosity of the Brij 30 - HEC - water system, n_{a2} , the viscosity of the HEC - water dispersion and n_{a3} , the viscosity of the Brij 30 - water system.

RESULTS AND DISCUSSION

1. <u>Rheological Properties</u>, <u>Reproducibility and Stability of</u> Hydroxyethylcellulose and Methylcellulose Dispersions

a) Rheological Properties

The HEC dispersions exhibited shear-thinning flow properties within the concentration range of 1.5 - 3.5% w/w when measured with the Rotovisko. Figure 21 presents a typical rheogram for each HEC concentration. At a constant shear rate, a distinct shift to higher shear stress is noticeable for each 0.5% w/w increment in polymer concentration.



FIGURE 21. Rheograms for aqueous HEC dispersions (age = 0.13 yr) measured with the Rotovisko rheometer ($\mathring{\gamma}$ = 8.5 - 1370 s⁻¹, T = 30.0 ± 0.5°C)

With each addition of HEC, a substantial increase in the apparent viscosity is revealed by the increased slope of the rheograms at low shear rates. Variation in shear stress with changing polymer concentration (age = 0.13 years) is shown in Figure 22 for a selected range of shear rates.

The shear-thinning flow properties of a typical 2.0% w/w MC (1500 cps) dispersion are compared with those for HEC 3.0 and 3.5% w/w in Figure 23. From their rheograms, 2.0% w/w MC and 3.0% w/w HEC exhibited identical flow properties at shear rates less than 100 sec⁻¹. Above 100 sec⁻¹, 2.0% MC was more viscous than 3.0% HEC (250G) but less viscous than 3.5% w/w HEC. The rheological properties exhibited by MC and HEC were a function of both polymer grade and concentration.

b) Reproducibility

The reproducibility of rheological properties from batch to batch is an industrial concern because of consumer requirements for a consistent product. A statistical estimation of preparation and storage effects on rheological reproducibility through examination of flow⁴ curves is lacking in the literature for HEC and MC.

The variability in sample preparation was examined for the 1.5, 2.0, 2.5, 3.0 and 3.5% w/w HEC and 2.0% w/w MC dispersions and summarized in Table X. A comparison of the replicate flow curves (Appendix III, Program 1) resulted in 1/10 of the 1.5%, 1/10 of the 2.0%, 0/10 of the 2.5%, 0/10 of the 3.0% and 0/10 of the 3.5% w/w HEC dispersions being significantly different (P < 0.05) in power-law flow behaviour index or



FIGURE 22. Shear stress - HEC concentration relationship for a selected range of shear rates



FIGURE 23. Rheograms for 2.0% w/w MC in comparison with two HEC dispersions measured with the Rotovisko rheometer $(\ddot{\gamma} = 8.5 - 1370 \text{ s}^{-1}, \text{ T} = 30.0 \pm 0.5^{\circ}\text{C}, \text{ age} = 0.13 \text{ yr})$

consistency index (36). At the same probability level, none of the ten 2.0% w/w MC dispersions was significantly different. For the dispersions that were not significantly different, the power-law parameters, <u>m</u> and <u>n</u>, were averaged and $CL_{95\%}$ and CV were calculated to indicate the reproducibility of rheological properties with repetitive sample preparation (Table X). The small range in the confidence limit intervals, 2.0 - 5.2% for <u>mave</u> and 0.6 - 1.6% for <u>nave</u>, shows that the reported sample preparation method and HEC polymer were sufficiently reliable rheologically to be used as the basis for a system to examine shear rate equations, rheometers and flow models for shear-thinning systems.

The effect of aging on the rheological reproducibility of HEC and MC dispersions is summarized in Table XI. At HEC dispersion age of 1 year, the range in the confidence limit intervals about the mean consistency index was 2.4 - 5.1% and the corresponding range for the mean flow behaviour index was 0.8 - 177%. These ranges in the confidence limit intervals were the same as found for the dispersions at age, 0.13 years. After 5 years of storage, a 4.1 - 14.6% range in the confidence limit intervals about the mean consistency index and a corresponding range of 0.6 - 1.7% for the mean flow behaviour index was noted for the HEC dispersions. The confidence limit interval for the 2% w/w MC dispersions remained at 5\% of the mean consistency index over the 5 year period whereas, the size of the corresponding confidence interval for the flow behaviour index appeared to decrease slightly with increasing storage time (Tables X and XI).

Tab:	le X	
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Rheological reproducibility data for HEC and MC dispersions after 0.13 yr. storage^a

oncentration		Average Powe	r-law Param	neters, ^b m an	d n	
(% w/w)	m	CL _{95%}	CV (%)	n	^{CL} 95%	CV (%)
1.5 HEC ^C	2.4606	0.0807	4.3	0.7631	0.0053	0.9
2.0 HEC ^C	6.7507	0.3501	6.7	0.7051	0.0076	1.4
2.5 HEC ^d	14.9798	0.3212	2.8	0.6474	0.0037	0.8
3.0 HEC ^d	29.9016	0.6016	2.6	0.5980	0.0042	0.9
3.5 HEC ^d	52.6414	2.5670	6.3	0.5478	0.0085	2.0
2.0 MC ^d	23.1781	1.1316	6.4	0.6520	0.0098	2.0

^a T = 30.0 ± 0.5^oC, Rotovisko rheometer equipped with the MVI spindle/cup combination ^b $\sigma = m \chi^n$ (Equation 36)

^C 9 replicates

d 10 replicates

Table XI

Rheological reproducibility data for HEC and MC dispersions after 1 and 5 years storage^a

Time	Conce	ntration	Ave	rage Power-law P	arameters, ^b m and	. n	
(years)	(%	w/w)	ന്നു m	CL _{95%} CL _{95%}	n	CL _{95%}	•
1	1.5	HEC	2.3214	0.0947	0.7693	0.0090	-
	2.0	HEC	5.6380	0.4575	0.7335	0.0127	•
	2.5	HEC	13.1684	0.5663	0.6729	0.0052	
	3.0	HEC	28.3076	0.6878	0.6157	0.0095	
	3.5	HEC	50.0584	2.5667	0.5810	0.0083	
	2.0	MC	21.8539	0.8399	0.6708	0.0066	
5	1.5	HEC	2.2086	0.1346	0.7439	0.0130	
	2.0	HEC	4.3958	0.1791	0.7492	0.0047	
	2.5	HEC	8.8610	1.2982	0.7269	0.0148	
	3.0	HEC	19.0388	1.7432	0.6848	0.0099	
	3.5	HEC	33.8490	3.0685	0.6561	0.0071	
	2.0	MC	12.4315	0.7727	0.7599	0.0054	

^a $T_{meas.} = 30.0 \pm 0.5^{\circ}C$, Rotovisko Rheometer equipped with an MVI spindle/cup combination ^b $\sigma = m\chi^n$ (Equation 36))

c) Stability

A polymer included in the formulation of a fluid product to enhance vehicle viscosity must be stable during its shelf life. No stability information at 25° C has been published for HEC therefore, the effect of storage time on the apparent viscosity of aqueous dispersions has been determined over a 8.5 - 1370 s⁻¹ shear rate range.

Except for the 2.0% HEC dispersions, the power-law consistency and flow behaviour indices altered minimally over the first year of storage (Tables X and XI). Within this time period, it is improbable that the measured decrease in polymer vehicle viscosity would be detected subjectively. A distinct decrease in the consistency index was observed after 5 years of dispersion storage (Tables X and XI; Figure 24). A mathematical examination of the change in consistency index with respect to time revealed that a linear function,

$$m = K_1 - L_1 (t),$$
 (47)

described the relationship best for the 2.0, 2.5, 3.0 and 3.5% w/w HEC and 2.0% w/w MC dispersions. $\underline{K_1}$ and $\underline{L_1}$ were empirical equation parameters. None of the functions tested described the relationship well for the 1.5% w/w HEC dispersion. $\underline{L_1}$ which described the change in consistency index with respect to time was also closely related to HEC concentration as follows

$$L_1 = 0.01 (HEC)^{4.94},$$
 (48)

 $r^2 = 0.9670$. For the 2.0 - 3.5% w/w dispersions, the consistency index was related to both time and HEC polymer concentration as described by



FIGURE 24. Relationship of the power-law consistency index to storage time for aqueous MC and HEC dispersions $(m \pm CL_{95\%})$

$$m = K_1 - 0.01 (t) (HEC)^{4.94}$$
 (49)

where t is time in years.

The apparent viscosity of the HEC dispersions increased from day 1 to day 47 (Figures 25 and 26). Whether a further increase in viscosity occurred after day 47 is not known. The increase in apparent viscosity was shear sensitive and decreased in magnitude as the shear rate increased. At shear rates greater than 152 s⁻¹, the increase was not noticeable. The magnitude of the increase appeared to be a function of polymer concentration.

At shear rates over 25 s⁻¹, the apparent viscosity of the 2.0% w/w MC (1500 cP) dispersions appeared to increase slightly when remeasured after aging 1 year (Figure 27). Previously, a 10 to 15% increase in the viscosity of a medium grade of MC after a year of storage had been noted by Davies and Rowson (1958). Why the apparent viscosity of the MC dispersions did not appear to increase at shear rates below 25 s^{-1} in the present study is not known at this time.

Cellulose is a linear, crystalline high molecular-weight polymer insoluble in water even though there are three hydrophilic hydroxyl groups per anhydroglucose unit. The high degree of crystallinity (60 - 70%) prevents sufficient cellulose hydroxyl-water interaction necessary for hydration. Substitutents such as methyl and hydroxyethyl groups function as spacers, reducing the configurational regularity and crystallinity. Therefore, the type, size, amount and distribution of the substitutent will significantly affect the degree of solubility in water (Desmarais and Esser, 1966). It follows therefore, that bulky hydrophilic hydroxyethyl







FIGURE 26.

Effect of storage time on the apparent viscosity of 3.0% w/w HEC dispersions measured with a Rotovisko over a shear rate range of 8.5 - 685 s⁻¹ (T = 30.0 ± 0.5°C; age = 1 day, $\overline{n}_a \pm$ range; age = 47 and 365 days, $\overline{n}_a \pm CL_{95\%}$)



FIGURE 27.

Effect of storage time on the apparent viscosity of 2.0% w/w MC (1500 cP) dispersions measured with a Rotovisko rheometer over a shear rate range of 8.5 - 1370 s⁻¹ ($\overline{n}_a \pm CL_{95\%}$, n = 9)

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substitutents would impart a greater degree of water-solubility to the cellulose molecule than methyl substitutents. The observed shorter time required for the increase in the apparent viscosity of HEC as compared with that for MC would appear to be related to the degree of hydrophilic character and spacer efficiency of this substitutent.

The exact reason for the decrease in viscosity of the HEC and MC dispersions over the 5 year storage period is not known at this time. Marriott and John (1973) have related the decrease in viscosity of MC dispersions on storage in the absence of microbial contamination to polymer dehydration. This would explain a portion of the observed HEC viscosity decrease in this study.

<u>Rheological Features of Hydroxyethylcellulose - Polyoxyethylene</u> <u>(4) Dodecyl Ether Systems</u>

HEC exhibited shear-thinning flow properties within the concentration range of 2.0 - 3.5% w/w. With 0.5% w/w increments in HEC concentration in the absence of Brij 30, the flow curves shifted to higher shear stresses at each shear rate (Figure 28). Each flow curve was fitted to the pooled data (51 in total) from the tests of the dispersions prepared in triplicate.

With the addition of 4.0% w/w Brij 30, a distinct shift of the rheograms to higher shear stresses occurred showing an increase in n_a for all HEC concentrations (Figure 28). For 2.5% w/w HEC plus increasing concentrations of Brij 30, there was a pronounced shift in the flow curves to higher shear stress with successive additions of the



FIGURE 28.



surfactant (Figure 29). Also, the increase in the non-Newtonian character with increasing Brij 30 concentrations was discernible as an increase in the slope of the flow curve at low shear rates.

The addition of Brij 30, a nonionic surfactant, to the HEC dispersions provided a reliable means of obtaining a series of systems showing predictable increments in shear-thinning properties at each polymer concentration. Simply stated, the surfactant gave rheological flexibility to the HEC dispersions without changing the type of flow properties exhibited in steady shear.

3. An Improved Rotovisko Shear Stress Calibration Method

Although the shear stress constant (A) determined for each shear rate fluctuated with increasing shear rate, a trend was apparent with respect to the two dynamometer settings (Table XII). The <u>A</u> values appear to increase and then to decrease with increasing shear rates.

Because the shear stress constant is calculated from Equation (45) where the viscosity of the Newtonian oil and the shear rate are both constant, the trend noticed must be the result of greater or lesser changes in <u>S</u>, the scale reading. A higher scale reading and, therefore, a lower shear stress constant reflect an increased resistance of the oil to flow at that shear rate. This increased resistance may be due to increased end-effects. It should be noted that the manufacturer recommends the determination of shear stress constants at the mid-shear rate region where the oils were found to exhibit less resistance to flow (Table XII).







Tab:	le X	II

Shear stress calibration data for the Rotovisko rheometer

Shear Rate			A ^a	
(s ⁻¹)	50 ^b	n ^c	500 ^b	n
· · · · · · · · · · · · · · · · · · ·			<u> </u>	
8.46	3.09	7	29.00	2
16.91	3.12	. 5	29.52	. 5
25.37	3.06	5	30.08	7
50.74	3.12	9	30.61	7
76,11	3.14	10	30.30	.8
152.22	3.18	10	30.51	6
228.33	3.16	7	29.19	3
456.67	3.16	2	29.77	10
685.00	3.14	2	29.89	• 9
1370.00	3.13 ^d		29.52	6
Manufacturer's Method	3.08	· · ·	30.78	

fitted with an MV1 spindle

^a σ = AS (Equation 37)

^b dynamometer setting

^c number of replicates

 $^{\rm d}$ average of the above values

Shear stress was calculated using both calibration methods and the results compared to corresponding sets of data generated with the Weissenberg rheogoniometer over a similar range of shear rates. The results from the proposed method were not significantly different (P > 0.05) in power-law flow behaviour index (n) and consistency index (m), (36), for the shear 0 thinning fluids with $n \ge 0.55$ (Table XIII). A further increase in non-Newtonian character (n < 0.55) resulted in the Rotovisko data calculated using the proposed method deviating from those of the cone-plate Weissenberg rheogoniometer. Using the manufacturer's method for calculation, all the fluids tested were significantly different (P < 0.05) in <u>n</u> or <u>m</u>.

From the noted improvement in the Rotovisko shear stressshear rate data correspondence to similar data from the Weissenberg rheogoniometer, a shear stress calibration constant should be determined for each Rotovisko shear rate for non-Newtonian shear-thinning fluids with power-law parameters, $m \leq 41.5$ and $n \geq 0.55$. Shear stress calibration using Newtonian oils may be inadequate or Weissenberg effects may be significant for the fluids with a higher degree of non-Newtonian shearthinning character (n < 0.55).

4. Limitations of the Couette Rheometers in Shear Stress/Shear Rate Determination of Non-Newtonian Shear-Thinning Systems

A uniform shear rate within the sample was obtained using the cone-plate, Weissenberg rheogoniometer, because of the following imposed conditions:

i) the highest shear rate (1095 s^{-1}) employed was considerably less

Table XIII

Comparison of the two Rotovisko shear stress calibration methods to data generated using the

	Rotovisko (Calibration Methods) - Rheogoniometer Comparison							
Consistency	Flow Behaviour	Proposed Method 1		Manufacturer's	Method	D _f b	D _f	
ma	n ^a	m	n	m	n	m	n	
12.0	0.69	Nc	N	N	s ^d	1/138	1/139	
22.0	0.62	N	N	S	S	1/127	1/128	
41.5	0.55	N	N	S .	S	1/165	1/166	
56.9	0.52	S	S	S	S	1/170	1/171	
84.6	0.48	S	S	S	S	1/172	1/173	
$\sigma = m_{\chi}^{n}$ degrees of N = not S = sign	(Equation 36; sho of freedom significantly different	ear rate r erent at P t at P < 0	ange, 10 > 0.05	.9 - 690. s ⁻¹)		· · ·		

Weissenberg rheogoniometer

than the shear rate region (2800 s^{-1}) requiring inertial corrections (Skelland, 1967; Williams, 1965),

ii) cone angles $\leq 2^{\circ}$ were used, and

iii) the maximum sample temperature rise due to viscous heating was 0.6° , (33).

Therefore, the shear stress/shear rate data obtained with this instrument were considered accurate and were used to evaluate the accuracy and limitations of the two Couette rheometers and several shear rate equations for a series of shear-thinning systems.

a) Haake Rotovisko - Weissenberg rheogoniometer comparison

Measured with the Rotovisko over a $8.5 - 685 \text{ s}^{-1}$ shear rate range, the HEC - Brij 30 systems spanned a 0.76 - 0.48 range in flow behaviour index, <u>n</u>, (Table XV) andshowed shear-thinning flow properties (Figure 28). As an indication of dispersion variability, a range has been presented for each of the power-law parameters (Table XIV). The power-law model parameters for data generated with the rheogoniometer which overlap the shear rate range of the Rotovisko are given in Table XV.

The power-law flow behaviour indices for both the Rotovisko calibration and Krieger-Maron shear rate calculation methods (Equations 220anand4)24) corresponded well with those for the rheogoniometer for $n \ge 0.55$ (Tables XIV and XVI). The consistency index, <u>m</u>, was more sensitive to rheological changes and revealed a slight difference between the two shear rate calculation methods when they were separately compared with data from the rheogoniometer (Table XVI).

Dispersion	Composition	. <u></u>	Calibration Equation ^b				Krigger-Maron Equation ^C			
HEC (%	w/w) Brij 30	n	t R ^d	m	ŧ	R	n		R m	R
2.0	0.0	0.757	0.002	4.85		00088	0,757	0.00	2 4.80	0.08
2.0	4.0	0.678	0.006	10.35	ł	0.8929	0.678	0.00	6 10.21	0•42
2.0	8,0	0.584	0.020	21.31		2.17.17	0.598	0.00	4 20.92	1.05
2.0	12.0	0.515	0.004	42.42	•	1.53	0.515	0.00	4 41.48	1.49
2.0	16.0	0.453	0.010	73.26		7.50	0.453	0.01	0 71.48	7.24
2.5	0.0	0.703	0.002	11.07	I	0.15	0.703	0.00	2 10,93	0.14
2.5	4.0	0.616	0.001	22.51	. 1	0.41	0.616	0.00	1 22.15	0.41
2.5	8.0	0.544	0.008	41.61		1.47	0.544	0.00	8 40,85	1.43
2.5	12.0	0.470	0.007	76.07		2.92	0.470	0.00	7 74.34	3.42
2.5	16.0	0.409	0.008	125.79	-	5.80	0.409	0.00	8 122.45	5.60

Power-law^a parameters for HEC - Brij 30 systems measured with the Haake Rotovisko at 25° C

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:

 $\sigma = m \tilde{\gamma}^n$ (Equation 36)

b Equation 20

^c Equation 24, Rc/Rb = 1.04

^d Range, 3 replicates

Table XIV

Dispersi	ion Composition		Sh	ear Rate Ran	ge_Overlag	p
	(% w/w)	Rote	Rotovisko ^b		kfield	
HEC	Brij 30	n ^C	m	n	m	Shear Rate Range (s ⁻¹)
2.0	0.0	0.758	4.85	ď	d	(0 7 [°]
2.0	4.0	0.678	9.89	0.872	5.90	0.7 - 10.95
2.0	8.0	0.599	20.09	0.715	14.45	0.4 - 17.3
2.0	12.0	0.544	33.19	0.620	27.61	0.7 - 27.5
2,0	16.0	0.490	55.59			* . : .
2.5	0.0	0.691	11.97	0.922	6.44	0.7 - 10.95
2.5	4.0	0.622	21.98	0.807	13.30	0.3 - 17.3
2.5	8.0	0,546	41.50	0.689	28.64	0.4 - 17.3
2.5	12.0	0.521	56.88	0.563	53.33	0.6 - 10.95
2.5	16.0	0.477	84.53			1

Table XV

Power-law^a parameters for the HEC - Brij 30 systems measured with the Weissenberg rheogonio-

meter at 25°C

^a $\sigma = m \chi^{5,n}$ (Equation 36) ^b $\gamma = 10.95 - 690 \text{ s}^{-1}$

^c from pooled Weissenberg rheogoniometer data

d system viscosity too low to be measured accurately at these shear rates with the chosen instrumental conditions
Table XVI

Comparison of two shear rate calculation equations for the Rotovisko with results from the

Dispersion	n Composition					
(% w/w)		Calibr	ation Method	Krieg	er-Maron Method	D _e b
HEC	Brij 30	, n ^a	m	n	m	' (m)
2.0	0.0	N ^C	N	N	N	1/116
2.0	4.0	N	S	N	N	1/136
2.0	8.0	N	S	N	N	1/151
2.0	12.0	S	S	S	S	1/182
2.0	16.0	S ·	S	S	S	1/180
-					· ·	
2.5	0.0	Ν	N	N	N .	1/139
2.5	4.0	N	N	N .	N	1/128
2.5	8.0	N	N	N	N	1/166
2.5	12.0	S	S	S	S	1/135
2.5	16.0	S	S	S	S	1/173

Weissenberg	rheogoniometer	for a	shear-thinning	systems
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 $a_{\sigma} = m_{\gamma}^{(n)}$ (Equation 36)

^b degrees of freedom for <u>m</u>, D_f for <u>n</u> is one less, i.e. 1/115 instead of 1/116

^c N = not significantly different (P > 0.05); S = significantly different (P < 0.05)

The Krieger-Maron method for shear rate calculation, (24), for the Rotovisko was more reliable and gave a better indication of the true shear rate for shear-thinning fluids with a flow behaviour index, $n \ge 0.55$, than the calibration method, (20) (Table XVI). Both methods failed to represent Couette shear rate adequately for fluids with n < 0.55 measured with the Rotovisko rheometer (Rc/Rb = 1.04). Reexamination of Tables XIV and XV showed that the Rotovisko values for <u>m</u> and <u>n</u> were markedly higher and lower, respectively, than those for the. rheogoniometer for HEC dispersions containing 12 and 16% Brij 30. The changed power-law parameters for these concentrations of Brij indicated that the Rotovisko was sensing a higher degree of non-Newtonian character than was actually present. This phenomenon could be due to two reasons:

- (1) the use of Newtonian oils to obtain calibration constants for each shear rate is no longer adequate or
- ii) true laminar flow no longer exists within the sample gap because of Weissenberg effects.
 - b) Brookfield Synchro-lectric Weissenberg rheogoniometer .
 comparison

Measured with the Brookfield rheometer over a shear rate range of 0.4 to 20.0 s⁻¹, the HEC - Brij 30 systems spanned a 0.95 - 0.52 range in flow behaviour index, <u>n</u> (Tables XVII and XVIII). A range has been given for the power-law parameters describing the data from the four shear rate calculation methods, Equations (20), (24), (26) and (28). The power-law parameters for the rheogoniometer for the shear rate range corresponding to that of the Brookfield are given in Table XV.

Table XVII

Power-law^a parameters for the HEC - Brij 30 systems measured with the Brookfield rheometer at 25°C. Calibration and Krieger-Maron shear rate equations.

Dispersio	n Composition	Radius		Calibrat	ion Equa	tion ^b	Kriege	r-Maron	Equati	.on ^C
HEC	(% w/w) Brij 30	Ratio Rc/Rb	n	b R ^d	m III	j £j £ − R	n (;	E R	m	R R
2.0	0.0	1.64	0.954	0.001	2.68	00005	0.951	0.002	2.68	0.05
2.0	4.0	1.64	0.827	0Ç040	6.80	0.07	0.822	0.001	6.40	0.07
2.0	8.0	2.50	0.682	0.020	17.17	0.81	0.682	0.020	14.19	0.55
2.0	12.0	2.50	0.553	0.040	43.17	5.25	0.553	0.040	33.55	2.91
2.5	0.0	1.64	0.932	0.001	6.40	0.21	0.926	0.001	6.22	0.20
2.5	4.0	2.50	0.804	0.005	14.54	0.50	0.801	0.003	12.86	0.44
2.5	8.0	2.50	0.672	0.010	32.16	1.51	0.672	0.010	26.46	1.15
2.5	12.0 ^e	2.50	0.523	0.005	72,61	0.34	0.523	0.005	55.72	0.16
$a_{\sigma} = m$	γn (Equation 3	16)			· · · ·					<u> </u>

^b Equation 20

^C Equation 24

^d Range, 3 replicates

^e 2 replicates

Table XVIII

Power-law^a parameters for the HEC - Brij 30 systems measured with the Brookfield rheometer at 25° C. Krieger and Mooney shear rate equations.

Dispersi	on Composition	Radius		Krie	ger Equa	tion ^b		Moone	y Equat	ion ^C
HEC	(% w/w) Brij 30	Ratio Rc/Rb	n	± R ^d	'n.	± R	n	z R	m	< R
2.0	0.0	1.64	0.951	0.002	2.68	0.01	0.951	0.002	4.12	0.14
2.0	4.0	1.64	0.822	0.002	6.43	0.13	0.822	0.002	8.68	<i>,</i> 0 . 16
2.0	8.0	2.50	0.682	0.016	14,43	2.11	0.682	0.016	14.89	1.04
2.0	12.0	2.50	0.553	0.039	33.80	5.49	0.554	0.039	34.27	5.53
2.5	0.0	1.64	0.926	0.002	6.22	0.40	0.926	0.002	9.30	0.56
2.5	4.0	2.50	0.801	0,004	13.05	0.89	0.801	0.004	14.01	0.97
2.5	8.0	2.50	0.672	0.011	26.91	2.33	0.672	0.011	27.70	2.31
2.5	12.0 ^e	2.50	0.523	0.005	55.86	0.22	0.523	0.005	56.63	0.24

a $\sigma_{\sigma} = m_{\gamma}^{\sqrt{n}}$ (Equation 36)

^b Equation 26

^C Equation 28

^d 3 replicates

^e 2 replicates

Examination of Tables XVIII and XIX showed that the Brookfield results calculated using the Mooney shear rate equation, (28), were not significantly different (P > 0.01) from those generated with the rheogoniometer for a power-law flow behaviour index greater than or equal to 0.81. For the Krieger-Maron and the calibration equations (.24 and 20, respectively), flow behaviour indices greater than or equal to 0.87 and 0.92, respectively, are required for data correspondence with the rheogoniometer (Tables XVII and XIX). The shear rate results calculated using the Krieger equation for an infinite gap, (26), were not significantly different (P > 0.01) from those of the rheogoniometer for only the most non-Newtonian dispersion measured (Table XIX). This result was expected because the coaxial geometry, Rc/Rb = 2.50, may behave as an infinite gap with high viscosity shear-thinning fluids at the low shear rate range of the Brookfield.

It is distinctly possible that the degree of Brookfield rheogoniometer data correspondence could have been improved by generating a shear stress calibration constant for each shear rate as was done with the Rotovisko (Tables XII and XIII).

At this point, the accuracy of the rheogoniometer shear stress/ shear rate data may be emphasized. A semilogarithmic equation described the relationship between the power-law consistency and flow behaviour indices for the HEC - Brij 30 dispersions measured with the rheogoniometer over a 10.95 - 690 s⁻¹ range in shear rate (Figure 30, Equation 50).

 $\log m = K_2 + L_2 n$ (50)

Dispersion	Composition		•	Sig	gnifica					
(%	w/w)	Calibr	ation	Krieg	er-Maron	Моо	ney	Krie	ger	Df
HEC	Brij 30	n	m	n	m	n	m	n	m	
2.0	4.0	NC	S	N	N	N	Ŋ.	NN N	S	1/73
2.0	8.0	S	S	S	S	. S	S	S	S	1/126
2.0	12.0	S	S	S	S	S	S	S	S	1/130
2.5	0.0	N	N	N	N	NN	N	N	S	1/80
2.5	4.0	N	S	N	S	N	N .	N	S	1/95
2.5	8.0	N	S ·	N	S	N	S	N	S	1/129
2.5	12.0	N	S	N	S	S	N	N	N	1/49

Table XIX

Comparison of several shear rate equations for the Brookfield Synchro-lectric with results from the Weissenberg rheogoniometer for shear-thinning systems

 $a_{\sigma} = m_{\chi}^{n}$ (Equation 36)

^b degrees of freedom for \underline{m} , D_f for \underline{n} is one less, i.e. 1/72 instead of 1/73

 $^{\rm C}$ N = not significantly different (P > 0.01); S = significantly different (P < 0.01)



FIGURE 30. Consistency index - flow behaviour index relationship for the HEC - Brij 30 systems measured with the rheogoniometer at 25° C over a 10.95 - 690 s⁻¹ range in shear rate

 $\underline{K_2}$ and $\underline{L_2}$ were equation parameters. The <u>m</u> and <u>n</u> values obtained from the Rotovisko rheometer deviated from the linear relationship noted for the rheogoniometer at n < 0.55 and showed a greater degree of non-Newtonian character than was ascertained with the cone-plate instrument (Tables XIV and XV). Figure 31 shows a similar relationship between <u>m</u> and <u>n</u> for the HEC - Brij 30 systems measured with the rheogoniometer over a low shear rate range ($\dot{\gamma} = 0.3 - 17.3 \text{ s}^{-1}$). The <u>m</u> and <u>n</u> values generated with the Brookfield showed minimal correspondence to those obtained with the rheogoniometer in this region (Tables XV, XVII and XVIII). In a linear power-law region described by

$$\log \sigma = \log m + n \log \dot{\gamma}, \qquad (51)$$

a linear relationship between \underline{m} and \underline{n} as shown by (50) and Figures 30 and 31 provided additional evidence that the rheogoniometer measurements are correct for the range of shear-thinning fluids measured.

With an increase in the concentration of HEC, the consistency index changed by a constant amount for each system but the slope, \underline{L}_2 , (50) which may reflect or describe the interaction between the Brij 30 -HEC components did not change. If the interaction between the HEC -Brij 30 - water components had changed with an increase in HEC concentration in the linear log σ - log $\hat{\gamma}$ region then the slope of (50) would also have changed.

5. Rheological Models for Shear-Thinning Systems

The modified Shangraw, Steiger-Trippi Ory and power-law models accurately fitted the flow data for the HEC - Brij 30 dispersions as



FIGURE 31. Consistency index - flow behaviour index relationship for the HEC - Brij 30 systems measured with the rheogoniometer at 25° C over a 0.3 - 17. s⁻¹ range in shear rate

indicated by respective average coefficients of determination of 0.989, 0.990 and 0.993 (Equations 34, 35 and 36). A t-test of the three sets of r^2 values showed no significant difference among the means (P > 0.05). Thus, all three models fitted the data equally well for the dispersions studied.

At most concentrations of HEC, the power-law fitted the data best at low shear rates whereas the Steiger-Trippi-Ory model fitted the data more accurately at higher shear rates (Figure 32). The modified Shangraw equation appeared to oscillate around the experimental data.

Functions that suitably described the variation of flow parameters with Brij 30 concentration (B) were:

Modified Shangraw model

$$a = K_3 + L_3 B$$
 (52)

$$b = K_4 + L_4 B^2$$
(53)

$$c = K_{r} + L_{r} \log B$$
 (54)

Steiger-Trippi-Ory model

 $a' = K_6 + L_6 \log B$ (55)

$$c' = K_7 + L_7 \log B$$
 (56)

Power-law model

$$m = K_o + L_o \log B$$
 (57)

$$n = K_0 + L_0 \log B \tag{58}$$

where \underline{K} and \underline{L} are regression constants and coefficients, respectively. The functional relationship chosen in each instance had coefficients of



FIGURE 32. Flow behaviour of 2.5% HEC dispersions containing 16% Brij 30. The modified Shangraw, Steiger-Trippi-Ory and power-law models are shown fitted to the data

determination with the highest magnitude and frequency.

The modified Shangraw structure equation parameters, a, b and c, were dependent upon both HEC and Brij 30 concentration (Figures 33, 34 and 35). With 2.0% w/w HEC and increasing Brij 30 levels, the values for the parameter a increased in a linear fashion. Increasing HEC concentrations resulted in an upward shift of the curve while the slopes remained approximately constant. There was an exception to the above generalization with 3.5% w/w HEC and Brij 30 concentrations over 8.0% w/w for which the parameter appeared to plateau and then decrease. Values of b increased in a curvilinear manner with increasing Brij 30 and showed upward shifts of the curves for increasing HEC concentrations. Parameter c varied as the logarithm of dispersion composition (Figure 35). These values were not as sensitive to changes in HEC concentration as were those for a and b. On the other hand, c was more sensitive to increasing surfactant concentrations. Deviations of b and c from the selected functional relationships ((Equations 52, 53 and 54) were noted for 3.5% w/w HEC containing over 8.0% Brij 30. Curves in Figures 33, 34 and 35 for 3.5% HEC are truncated at 8.0% Brij 30 because the function does not apply at higher surfactant concentrations.

The Steiger-Trippi-Ory parameters, <u>a'</u> and <u>c'</u>, decreased in a logarithmic manner with increased Brij 30 and HEC concentrations (Figures 36 and 37). The sensitivity to alterations in HEC concentration decreased exponentially with increasing cellulose polymer concentration. At 2.0% w/w HEC, a large decrease in the values of the two parameters was noticeable with increasing surfactant concentration, whereas at 3.5% HEC little change was discernible. Deviations of these parameters from the fitted



FIGURE 33. Variation of the modified Shangraw parameter, \underline{a} , with HEC and Brij 30 concentration



FIGURE 34. Variation of the modified Shangraw parameter, \underline{b} , with HEC and Brij 30 concentration



FIGURE 35.

Variation of the modified Shangraw parameter, \underline{c} , with HEC and Brij 30 concentration



FIGURE 36.





FIGURE 37. Variation of the Steiger-Trippi-Ory model parameter, <u>c'</u>, with HEC and Brij 30 concentration

functions at higher polymer and surfactant concentrations are relatively small in comparison with those of the other two rheological models.

The power-law parameters were sensitive to both surfactant and cellulose polymer concentrations (Figures 38 and 39). The consistency index, <u>m</u>, increased as a curvilinear function of polymer and surfactant concentrations. Curves for the flow behaviour index, <u>n</u>, showed a decrease with increasing HEC and Brij 30, i.e., the dispersions became more shear-thinning as the two solute species increased in concentration (Figure 39). Deviations of parameter values from the selected functions (Equations 57 and 58) were evident for 3.5% HEC dispersions containing over 8.0% Brij 30. These discrepancies may arise from concentration-dependent interactions among the dispersion components or from significant Weissenberg effects occurring during rheometric measurement in a co-axial viscometer.

Although the equations evaluated were empirical models, use of flow model parameters to describe rheograms in the shear-thinning flow region and determination of parameter-viscosity inducing agent(s) concentration relationships can aid in formulating with desired consistency and flow properties. Construction of figures, such as 38 and 39 for the power-law model in the shear-thinning flow region, would enable rapid determination of the effect of alterations in processing conditions or formulation components. The areas of acceptable consistency and flow characteristics as obtained from rheometric measurements of panelselected formulations may also be blocked in and used as an adjuvant to



FIGURE 38. Variation of the power-law model parameter, \underline{m} , with HEC and Brij 30 concentration



FIGURE 39. Variation of the power-law model parameter, \underline{n} , with HEC and Brij 30 concentration

quality control and storage information.

The magnitude of apparent viscosity reflected an interaction between the components of the HEC - Brij - water system at low shear rates (Figure 40). A possible explanation for this increase in apparent viscosity was an interaction of HEC molecules with Brij 30 micelles (cmc = 0.0055% w/w, Figure 10) to form large bulky aggregates. The postulated aggregate was thought to be shear-sensitive as indicated by a very large decrease in apparent viscosity with initial increments of shear rate (Table XX). This form of shear-sensitive, viscosityincreasing interaction with Brij 30 additions at low shear rates was noted for all HEC concentrations tested. This interaction will be discussed further in Section II. B. 3.





Apparent viscosity of 2.5% HEC dispersions containing 0, 4, 8, 12 and 16% Brij 30. The power-law model is shown

Table XX

Viscous interaction at low shear rates in a 2.5% HEC dispersion containing 16% Brij 30

ι.

		Apparent vi	scosity ^a (Poise)	. 1
Shear rate (sec ⁻¹)	2.5% HEC +	0.5% NEC	16 0% D-4+ 20	· · ·
- 	ni al	2.5% HEC	n _a 3	b n _{a4}
8.5	32.79	6.10	4.69	22.00
16.9	21.65	4.98	3.52	13.15
25.4	16.97	4.43	2.97	9.57
50.7	11.20	3.62	2.23	5.35
76.1	8.78	3.21	1.88	3.69
152.2	5.79	2.62	1.41	1.06
228.3	4.54	2.33	1.19	1.02
456.7	3.00	1.90	0.89	0.21
685.0	2.35	1.69	0.76	-0.10

^a Calculated from the power-law fitted to the data

^b $n_{a4} = n_{a1} - (n_{a2} + n_{a3})$, Equation 46

B. RHEOMETRIC STUDIES OF A FUNDAMENTAL NATURE: LOW SHEAR AND DYNAMIC MEASUREMENTS

Cellulose derivatives have been noted to have unique properties in water exhibiting higher intrinsic viscosities and lower sedimentation coefficients than other polymers with the same molecular weight (Flory <u>et al.</u>, 1958). The intrinsic viscosity in water shows a strong solvent dependence and invariably displays large negative temperature coefficients (Flory <u>et al.</u>, 1958; Brown and Henley, 1964 and 1967). Brown and Henley (1967), in studying the unperturbed dimensions of cellulose derivatives, have stated that HEC is considerably more extended in a good solvent such as water. The determination of viscoelastic properties in conjunction with low shear rate measurements should confirm these findings concerning the deposition of HEC in aqueous media. The nature of a shear-sensitive HEC - Brij 30 - water interaction noted previously (Section II. A. 5), may be clarified also through low shear rate and dynamic measurements.

INTRODUCTION

1. Limiting Viscosity at Low Shear Rates

Shear-thinning fluids theoretically have two Newtonian regions, one at very low shear rates and the second at very high shear rates (van Wazer <u>et al.</u>, 1963; Scott Blair, 1969). Between these two regions, the fluid shear-thins or the viscosity is no longer constant but rather is a function of shear rate (Figure 1).

The limiting viscosity at low shear rates is an extremely

important parameter in characterizing the properties of systems with a structure which is unaffected by external influences (Dreval <u>et al.</u>, 1973). The Newtonian viscosity in this shear rate region is sensitive to changes in polymer molecular weight distribution and molecular structure, polymer concentration and "goodness" of the solvent.

Mendelson <u>et al</u>. (1970) examined the melt rheological properties of linear and branched polyethylenes at low shear rates. The degree of polymer branching was found to lower the characteristic shear rate required for the onset of the lower Newtonian region (Figure 1). The magnitude of the Newtonian viscosity of a branched polyethylene in this low shear region was observed to be greater than $\frac{1}{2}$ that for a linear molecule of the same molecular volume.

The zero-shear viscosity - concentration dependence for a series of polymers of different chain flexibilities in various solvents was examined by Dreval <u>et al</u>. (1973). Their results showed that the parameters characterizing the individual macromolecular chain, viz., the dimensions of the polymer coil and the rheological effectiveness of solvent-polymer interactions, were significant in determining the viscosity of polymer solutions from very dilute to highly concentrated. The nature of the solvent was observed to affect the magnitude of the limiting viscosity at low shear rates of concentrated polymer solutions in a manner dependent upon the flexibility of the polymer chains (Tager and Dreval, 1970). It was shown that the nature of the solvent had a greater effect on the viscosity of polar polymer solutions with very strong specific interactions than on the viscosity of non-polar solutions.

2. Viscoelastic Moduli

Although it is well recognized that the addition of small amounts of polymer to a solvent may increase the viscosity, it is less well known that dilute polymer solutions may also possess elastic properties (Ferry, 1973). The determination of the elastic and viscous components of such a polymer solution comprises an estimate of the energy stored and lost as the result of short range deformations. The characteristic shapes of the viscoelastic functions can be associated qualitatively with different types of molecular responses (Ferry, 1970).

<u>The Storage Modulus</u> This modulus is a measure of the energy stored and recovered per cycle in simple linear sinusoidal shear deformation. The storage modulus (G'(ω), dyne cm⁻²) is defined as the stress in phase with the strain divided by the strain (Ferry, 1970) therefore, as the phase angle approaches 90°, only negligible energy is recovered and the fluid is predominantly viscous.

<u>The Loss Modulus</u> The loss modulus (G"(ω), dyne cm⁻²) is a measure of the energy dissipated as heat per cycle and is defined as the stress out of phase with the strain divided by the strain in sinusoidal shear deformation (Ferry, 1970). As the phase angle approaches 0[°] only negligible energy is lost as heat and the material is predominantly elastic in nature.

The Loss Tangent This viscoelastic function is a dimensionless ratio and is a measure of the energy lost to the energy stored in a cyclic deformation,

$$\tan \phi = G''/G'$$
.

The loss tangent is of considerable practical interest (Ferry, 1970). Davis (1971a) has referred to the loss tangent as a consistency spectrum and has indicated its potential usefulness to follow rheological changes in formulation, quality control and storage stability.

<u>Dynamic Viscosity</u> Dynamic viscosity (n', poise) is the real part of complex viscosity and describes the dissipative effects of alternating stress,

$$= \frac{G''}{\omega}.$$
 (60)

This parameter is useful in discussing uncross-linked polymers because at low frequencies, <u>n</u>' approaches the steady shear viscosity. The value the dynamic shear - steady shear correspondence assumes for uncrosslinked polymers at low frequencies and shear rates is a function of temperature, molecular weight and polymer concentration (Ferry, 1970).

3. Dynamic Testing

n'

The complex rheological properties of pharmaceutical semisolids may be elucidated by dynamic testing where the method of test does not significantly alter the fluid structure (Barry, 1971). Davis (1969a, 1969b, 1971a and 1971b) used creep response and oscillatory testing (destructive and non-destructive) for ointment bases and creams and has interpreted the observed rheological behaviour with mechanical models. In the 1969 papers, Davis clearly showed the limitations of steady shear viscometry to detect the limiting viscosity at low shear rates of pharmaceutical semisolids. A comparison of long time creep and short

(59)

time non-destructive oscillatory testing was made for pharmaceutical semisolids in the 1971 papers. Davis proposed a log G"/G' (loss tangent) versus log ω plot or consistency spectrum for the character-ization of these materials. Destructive oscillatory testing was proposed as a means of assessing consumer acceptance of topical preparations.

Although not a new idea, the problem of correlating sensory assessment with rheological measurement (reviewed by Scott Blair, 1969), has remained unsolved. Barry and co-workers (Barry and Grace, 1971 and 1972; Barry and Meyer, 1973) have studied the rheological assessment of texture profile and of sensory testing of spreadability. They, like others, have used ranking methods to evaluate subjective sensory assessment, a procedure which does not separate viscosity, elasticity and ductility. In addition, they have combined continuous shear and viscoelastic measurements to construct master curves of the rheological conditions operative during spreading. The master curves showing the acceptable ranges of viscosity for topical application were different for lipophilic and hydrophilic gels as well as for the O/W emulsion studied (Barry and Meyer, 1973). The master curve concept, when later used to evaluate the consumer acceptability of a topical vehicle, appeared to correlate with subjective-assessment conclusions (Barry, 1973).

Barry and Eccleston (Barry and Eccleston, 1973a and 1973b; Eccleston <u>et al.</u>, 1973) have studied the linear viscoelastic behaviour of O/W emulsions stabilized with mixed emulsifiers of the self-bodying type. They have correlated increased viscoelastic functions (G' and <u>m</u>) with the formation of emulsion networks resulting from increased concentration and chain length of the mixed emulsifier. These authors have used

oscillatory and creep testing over a wide frequency range as the basis for the conclusion of network formation.

EXPERIMENTAL

Low Shear Rate Studies of Hydroxyethylcellulose and Hydroxyethylcellulose - Polyoxyethylene (4) Dodecyl Ether Systems

Low shear rate measurements were performed because polymer information about the disposition and interaction of macromolecules can be acquired from these measurements in conjunction with dynamic determinations.

Hydroxyethylcellulose dispersions were prepared at concentrations of 1, 2, 3 and 4% w/w following the general procedure outlined in Appendix I. Flow curves were measured at 23.0 \pm 0.5^oC using the Weissenberg rheogoniometer in the steady shear mode. Several decades of shear rate were covered with special attention given to the low shear rate region ($\dot{\gamma} < 1.0 \text{ s}^{-1}$). The shear stress signal was recorded. The equilibrium shear stress signal at each shear rate wasetaken as the true reading. Calculations were done using Equations (42) and (43).

The procedure was repeated with Brij 30 (8, 12 and 16% w/w) in HEC dispersions (2, 3 and 4% w/w) to obtain information about a shear sensitive interaction noted with these dispersions in Section II. A. 5.

2. Viscoelastic Studies: Rheometer and Methods

Viscoelastic behaviour was studied using the Weissenberg rheogoniometer in small amplitude oscillatory shear (van Wazer et al., 1963). The sample was subjected to a sinusoidal strain with both the input strain and the resultant stress signals recorded simultaneously. The dynamic response was measured in terms of an amplitude ratio (Sm/Im) and the displacement of the two curve traces (ϕ).

Using two different platen combinations (both the radius and angle were changed), the linear viscoelastic region was determined initially at a fixed frequency through variation of the strain wave amplitude. An amplitude was selected in the linear viscoelastic region and then dynamic measurements were made progressing from low to high oscillatory frequencies. The strain and stress sine waves were traced by a potentiometric strip chart recorder at lowffrequencies and an oscillograph at high frequencies. The wave amplitudes and displacements were measured as suggested by the manufacturer (Sangamo Controls Ltd., 1971).

Dynamic shear storage (G', dyne cm^{-2}) and loss (G", dyne cm^{-2}) moduli were computed using the manufacturer's equations (Equations 60 and 61, respectively, Sangamo Controls Ltd., 1971).

$$G' = \frac{\frac{2160 \alpha K_{T}}{d^{3}}}{\frac{3}{10}} \frac{Sm}{1m} \cos \phi$$
(61)

$$G G'' = \frac{2160 \alpha K_T}{d^3} \frac{Sm}{Im} \sin \phi$$
 (62)

<u>Sm</u> was the maximum movement of the torsion head transducer (μ m), <u>Im</u>, the maximum movement of the worm-shaft measured by the oscillation input transducer (μ m), <u>d</u>, the platen diameter (cm) and <u> ϕ </u> was the phase difference between the recorded strain and stress waves (deg). Dynamic viscosity (poise) was determined from the loss modulus,

$$n' = \frac{G''}{2\pi f}$$
(63)

where <u>f</u> was the frequency of oscillation (Hz) and $2\pi f$ was the radian frequency (ω , s⁻¹).

3. <u>Viscoelastic Features of Hydroxyethylcellulose and Hydroxyethyl-</u> cellulose - Polyoxyethylene (4) Dodecyl Ether Systems

Aqueous dispersions of HEC were prepared at concentrations of 1.0, 2.0, 3.0 and 4.0% w/w following the general procedure (Appendix I). A second set of 2.0, 3.0 and 4.0% w/w HEC dispersions were prepared and allowed to age one day. After aging, Brij 30 (8.0, 12.0 and 16.0% w/w) was added to each of the three HEC dispersions (Appendix I). All dispersions were measured using the oscillatory mode of the rheogoniometer.

For the HEC dispersions, the linear viscoelastic region was determined at a constant frequency using the following conditions:

- 1 and 2% w/w HEC platen diameters, 7.5 and 10.0 cm; cone angles, 0.9842 and 0.2522 deg; torsion bar constant 94 dyne cm μm^{-1}
- 3 and 4% w/w HEC platen diameters, 5.0 and 7.5 cm; cone angles, 2.0242 and 0.9842 deg; torsion bar constants 94 and 875 dyne cm μm^{-1} .

The linear viscoelastic region was determined for only the most non-Newtonian of the Brij 30 in HEC dispersions (4.0% HEC + 16.0% Brij 30). Significant conditions in the frequency curve generation for each of the dispersions using the rheogoniometer are given in Table XXI. The storage and loss moduli, dynamic viscosity and loss tangent were calculated and examined over the frequency interval for both sets of dispersions (Equations 61, 62, 63 and 59).

RESULTS AND DISCUSSION

Flow Characteristics of Hydroxyethylcellulose and Hydroxyethylcellulose - Polyoxyethylene (4) Dodecyl Ether Systems at Low Shear Rates

A theoretical Newtonian flow region at low shear rates (Figure 1) was detected for each of the 1, 2, 3 and 4% w/w HEC dispersions (Figure 41). The shear rates at which Newtonian flow initially occurred appeared to decrease with increasing polymer concentration. For example, this region initially began at 75 s⁻¹ for the 1% dispersion and at 0.18 s⁻¹ for the 4% HEC dispersion (Figure 41). The limiting viscosity at low shear rates (η_0) was found to be a logarithmic function of HEC concentration (% w/w),

$$\log n_{2} = \log K_{10} + L_{10} \log C(HEC)$$

where $\frac{K_{10}}{M_{10}}$ and $\frac{L_{10}}{M_{10}}$ are regression constants and coefficients, respectively (Figure 42).

The discussion of the disposition of HEC polymers in aqueous solution will follow the viscoelastic studies (Section II. B. 2.). The detection of a Newtonian region for the HEC dispersions yields systems

(64)

Dispers	sion Composition	P1; d	aten a	Torsion Bar Constant K	Maximum Strain	Frequency 1	Range
HEC	Brij 30	(cm)	(deg)	$(dyne cm/m^{-1})$	(µm)	(Hz)	
1.0	0.0	10.0	0.2522	94	2.6	0.38 -	7.54
2.0	. 0.0	10.0	0.2522	94	1.9	0.06 - 3	3.77
2.0	0.0	7.5	0.9842	94	0.5	0.06 - 3	3.77
2.0	. 8.0	7.5	0.9842	94	0.3	0.06 - 3	3.77
2.0	12.0	7.5	0.9842	94	0.3	0.04 - 2	2.99
2.0	16.0	7.5	0.9842	875	0.3	0.06 - 3	3.77
3.0	0.0	7.5	0.9842	94	0.4	0.04 - 4	+.75
3.0	8.0	7.5	0.9842	875	0.3	0.05 - 3	3.77
3.0	12.0	7.5	0.9842	875	0.3	0.075 – 🔅	3.77
3.0	16.0	7.5	0.9842	875	0.3	00.04 - 2	2.99
4.0	0.0	7.5	0.9842	94	0.4	0.04 -	5.96
4.0	8.0	7.5	0.9842	875	0.3	0.05 - 3	3.77
4.0	12.0	7.5	0 .9 842	875	0.3	0.04 - 3	3.77
4.0	16.0	7.5	0.9842	985	0.3	0.04 - 2	2.99
<u> </u>			. <u></u>		. <u> </u>		

Table XXI

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Significant instrumental conditions in HEC - Brij 30 dispersion frequency curve generation



FIGURE 41. Viscosity-shear rate relationship for the HEC dispersions showing the limiting viscosity region at low shear rates. Measured with the rheogoniometer at 23.0 \pm 0.5 ^oC



FIGURE 42. Low shear rate limiting viscosity - HEC concentration relationship

with predictable viscosity at zero shear rates for the investigation of viscosity effects on the diffusion of hydrocortisone (Section III).

Steady shear measurement of the 2, 3 and 4% HEC dispersions containing Brij 30 (8, 12 and 16%) did not reveal a Newtonian region at low shear rates (Figure 43). These dispersions exhibited shearthinning flow properties over 4 to 5 decades in shear rate. At low shear rates, the flow properties showed a marked dependence on surfactant concentration whereas, at high shear rates the HEC - Brij 30 rheograms appeared to converge with the HEC flow curve reflecting minimal surfactant contribution (Figure 43).

It was not conclusively determined whether or not a Newtonian region existed at low shear rates because these fluids still showed shear-thinning flow properties at the shear stress signal sensitivity-limits of the rheogoniometer. These measurements will be discussed further under Section II. B. 3.

2. Viscoelastic Properties of Hydroxyethylcellulose Dispersions

The storage moduli for the HEC dispersions formed a slightly curvilinear relationship with radian frequency (Figure 44). With an increase in $\underline{\omega}$ there was a pronounced increase in the storage modulus at each of the cellulose polymer concentrations. A substantial increase in the storage modulus at each radian frequency was evident also with an increase in cellulose concentration.

The HEC dispersion loss moduli were typical of a viscoelastic liquid at low frequencies (Figure 45). $\underline{G''}$ was directly proportional to


FIGURE 43. Viscosity - shear rate relationship for the 3% HEC plus 0, 8, 12 and 16\% Brij 30 dispersions showing the absence of a limiting viscosity region at low shear rates. Measured with the rheogoniometer at 23.0 ± 0.5° C



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the radian frequency as described by Equation (65) for a simple Newtonian liquid.

$$G'' = \eta \omega \tag{65}$$

The calculated values of <u>n</u>' in this flow frequency region were 0.31, 3.5, 18 and 57 poise for the 1, 2, 3 and 4% w/w HEC dispersions, respectively. These values agreed well with the corresponding <u>n</u> values (0.4, 3.5, 17 and 60 poise) obtained from steady shear measurements at low shear rates (Section II. B. 1., Figure 41).

The shape of the storage and loss moduli (Figures 44 and 45) wwere characteristic of a dilute polymer solution in which the viscoelasticity was a relatively minor perturbation of the Newtonian behaviour of the solvent (Ferry, 1970). The relationship of the storage moduli to the loss moduli (Figure 46) resembled the springy wormlike model of Harris and Hearst (Hearst et al., 1966). This molecular model represented a degree of stiffness between the perfectly flexible beadspring model and the rigid rod model of Kirkwood and Auer (Ferry, 1970). This result was in agreement with Brown's conclusions from intrinsic viscosity studies that the HEC molecule was considerably more extended or less flexible in a good solvent such as water (Brown, 1961; Brown and Henley, 1967). These workers cited specific effects of the solvent on the chain rather than conventional short range polymer-solvent interactions to be the cause of decreased flexibility. Flory et al. (1958) reached a similar conclusion in their intrinsic viscosity studies on cellulose derivatives. Solvents, particularly water, were visualized to interact with cellulose chains so as to restrict rotation about the ether linkages thereby decreasing molecular flexibility.



FIGURE 46. Storage - loss moduli relationship for the 3 and 4% HEC dispersions

Dynamic viscosity or the real component of complex viscosity was another means of describing the dissipative effects of alternating stress. From Figure 47, it was evident that dynamic viscosity approached the steady shear apparent viscosity of the HEC dispersion at low shear rates. The agreement between the <u>n'</u> and <u>n</u> values at low frequencies and shear rates was indicative of an uncross-linked polymer (Figure 47). The similarity in the two types of viscosity in this region implied that the dynamic viscosity values were also related logarithmically to the HEC polymer concentrations as depicted by Figure 42. The small differences (011 poise) observed between <u>n'</u> and <u>n</u> for the 1% HEC dispersion, were considered negligible.

The viscoelastic properties of the aqueous HEC dispersions (1, 2, 3 and 4% w/w) were a relatively minor perturbation of the Newtonian fluid properties of the solvent. The HEC molecules were found to be uncross-linked and to have intermediate stiffness as described by the Harris and Hearst springy wormlike model.

3. Viscoelastic Features of Hydroxyethylcellulose - Polyoxyethylene

(4) Dodecyl Ether Systems

The storage moduli for the most non-Newtonian HEC - Brij 30 systems are shown in Figure 48. With the addition of 8% Brij 30 to the cellulose polymer dispersion, the storage moduli increased dramatically to higher values at corresponding radian frequencies. The pronounced shift plus a flattening of the curves at radian frequencies less than 0.5 s⁻¹ indicated the presence of an increased elastic component. This elastic component disappeared at higher frequencies





FIGURE 48.

Storage modulus as a function of oscillatory frequency for 4% HEC plus 0, 8, 12 and 16% Brij 30 (T = 23.0 \pm 0.5^oC)

because the HEC and HEC - Brij 30 storage moduli assumed similar shapes and appeared to approach each other. Similar changes in viscoelastic properties were noted when Brij 30 (8, 12 and 16%) was added to the 2.0 and 3.0% w/w HEC dispersions.

At low fadian frequencies, the loss moduli of the 4% HEC -Brij 30 dispersions were not longer directly proportional to the radian frequency as described by Equation (65) (Figure 49). This proportionality region, characteristic of viscoelastic liquids and evident for the HEC dispersions without Brij 30 (Figure 45), now theoretically would occur at lower frequencies than were measured. The flattening of the HEC - Brij 30 loss moduli curves showed the presence of an increased elastic component due to the addition of Brij 30.

At the low frequencies and shear rates measured, the dynamic and steady shear viscosities still coincided for 4% HEC + 8% Brij 30 and 3% HEC + 12% Brij 30. This correspondence indicated that the systems were not cross-linked. There was a progressive divergence in the dynamic and steady shear results for 3% HEC + 16% Brij 30, 4% HEC + 12 and 16%Brij 30 over the same frequency and shear rate range (Figure 50). The large divergence noted for 4% HEC + 16% Brij 30 may be due in part to experimental errors. It is expected that the two viscosity parameters of the 3% HEC + 16% Brij 30 and the 4% HEC + 12% Brij 30 systems would also converge at lower frequencies and shear rates than were measured. This prediction was made because the general shape of the storage and loss moduli parameters was similar to uncross-linked viscoelastic polymers (Ferry, 1970).



FIGURE 49. Loss modulus as a function of oscillatory frequency for 4% HEC plus 0, 8, 12 and 16\% Brij 30 (T = 23.0 ± 0.5°C)





The loss tangent or consistency spectrum (Davis, 1971a) was also examined for the HEC and HEC - Brij 30 systems (Figure 51). The logarithmic tan ϕ - radian frequency relationship for the 4% HEC -Brij 30 dispersions coincided for all three Brij 30 concentrations therefore, the energy lost and stored for each cycle of deformation can be assumed to be independent of the surfactant concentration after the first addition. Comparison of the loss tangent curves for 4% HEC and 4% HEC + Brij 30 revealed pronounced elastic behaviour in the presence of Brij at radian frequencies less than 0.3 s⁻¹. Increasing the HEC concentration from 3 to 4% w/w in the presence of the surfactant caused a radian-frequency-sensitive increase in the loss tangent (Figure 51).

Examination of the loss tangent over a range of frequencies is of interest because it has the potential of providing information on the destructive, non-destructive or viscosity-inducing effects of various formulation additives upon macroscopic rheological properties.

The introduction of a pronounced elastic component, evident at low radian frequencies, into the HEC dispersions when Brij 30 was added indicated that the hydrated HEC molecules were interacting with Brij 30 or its micelles (cmc = 0.0055% w/w) to form a loose threedimensional network. The presence of a loosely bonded network rather than cross-linking would explain the shear-sensitive viscous interaction observed in Section II. A. 5.



FIGURE 51. Consistency spectrum or loss tangent of selected HEC and HEC - Brij 30 systems

SECTION III. LIMITING VISCOSITY AT LOW SHEAR RATES AND HYDROCORTISONE

DIFFUSION

INTRODUCTION

Davis (1971) noted a scarcity of data relating rheological properties to drug bioavailability. Khristov (1969) observed a strong correlation between the rheological parameters of a complex ointment base and the rate of liberation of incorporated drugs. Relationships between decreasing viscosity and an increase in drug release rate were also described for complex calcium soap-liquid paraffin-hydroxypropylmethylcellulose-water and polyethylene glycol-hydroxypropylmethylcellulosewater systems (Khristov <u>et al</u>., 1969 and 1970) Linear relationships,

$$\log \eta_a = 0.22 \, (\%PPE) + 0.23,$$
 (66)

were observed between the release of salicylic acid and the reciprocal of apparent viscosity for a Plastibase system containing varying amounts of polyethylene (PPE) (Davis and Khanderia, 1972). The plastibase system did not exhibit a limiting Newtonian viscosity region at low shear rates therefore, the viscosity at the shear rates of diffusion is not known.

Generally, experimental diffusion studies involving membranes ignore the role of vehicle viscosity at very low shear rates even though the study may be examining the effect of surfactants on drug diffusion (Short and Rhodes, 1972). Therefore, a portion of the present work has attempted to identify the effect of a change in limiting vehicle viscosity at low shear rates on the diffusion of hydrocortisone (HC) through artificial and biological membranes.

EXPERIMENTAL

1. Determination of Solubility and Partition Coefficient for

Hydrocortisone

The solubility of hydrocortisone at 25.0 \pm 0.5^oC was determined using an equilibrium solubility technique. An excess of hydrocortisone was tumbled mechanically with 100 ml of distilled water (pH = 6.5) in a water bath. Samples were withdrawn at 1, 3 and 4 days, filtered through a 0.22 µm Millipore filter and diluted appropriately for analysis at 249 nm. FFrom the absorbance, the concentration of steroid in solution was calculated using Beer's law (Pernarowski, 1969). The absorptivity valueswas obtained from the regression slope of the standard curve for HC in distilled water (Figure 52). Triplicate samples were done.

Preliminary experiments had shown that HC reached distribution equilibrium in the two phase octanol/water system within five days. Therefore, duplicate HC samples of 10 ml (20.4 mg/50 ml in water saturated octanol) were tumbled with 20 ml of distilled water (pH = 6.5) for 5 days in amberbglassabottles. After five days, the octanol and aqueous phases were allowed to separate, samples were withdrawn from both layers and centrifuged (1 h) to remove any suspended droplets of the alternate phase (Leo <u>et al.</u>, 1971). Absorbance of the aqueous samples at 249 nm was read directly. Octanol samples were diluted (1:50) for analysis at 245 nm. (The standard curve is shown in Figure 53).) Partition:coefficients were calculated from the ratio of octanol to aqueous concentration of HC.

A second series of partition samples was done to explore the accuracy of analyzing the aqueous layer only thereby determining the



FIGURE 52. UV spectrophotometric standard curve for hydrocortisone



FIGURE 53. UV spectrophotometric standard curve for hydrocortisone in octanol

amount of drug in the octanol layer indirectly. Triplicate samples of two separate volume ratios (10 and 15 ml) of HC in water saturated octanol (44 mg/100 ml) were tumbled with 50 ml of deionized-distilled water (pH = 6.5) for five days in amber glass bottles. The aqueous layer was separated, removed, centrifuged and analyzed directly at 249 nm. Theramount dneithe octanolelayerlwasacalculated indirectly,

$$A_{o} = A_{AT} - A_{w}$$
(67)

where $\underline{A}_{\underline{o}}$ was the amount of steroid in the octanol layer $(\mu g)' \mu A_{\underline{t}}$, the total amount of HC in the system and $\underline{A}_{\underline{W}}$ was the amount of HC in the aqueous layer. The partition coefficients obtained from the direct and indirect methods were compared.

2. The Interaction of Hydrocortisone with Hydroxyethylcellulose

To isolate the effects of viscosity on diffusion from possible retardation of molecular movement due to extensive HC - HEC binding, interaction studies were done using an equilibrium dialysis technique (Kazmi, 1971).

a) Membrane Preparation and Selection

Three artificial membranes commonly used in equilibrium dialysis studies were prepared in the following manner.

<u>Cellophane dialyzer tubing</u> was soaked in distilled water, cut flat and then washed with several changes of distilled water.

Nylon membrane was soaked (24 h) and washed with several changes of distilled water.

Dimethylpolysiloxane membrane was washed thoroughly with a soap solution,

washed with several changes of distilled water and soaked in distilled water (24 h).

All membranes were pressed between absorbent paper to remove excess moisture.

The prepared cellophane membrane was placed between the compartments of a two chambered dialysis cell (Appendix II). Ten ml of a 0.25% w/w HEC solution (no preservatives) was pipetted into one compartment of two cells and 10 ml of distilled water was pipetted into the other compartment. The cells were tumbled in a water bath (23.0 \pm 0.5°C) and after 24 h, equal volumes of the solutions were pipetted from both sides of each cell. qThe samples were diluted (1:4) for analysis at 206 nm (blank = distilled water). The absorptivity value was obtained from the regression slope of the standard curve for HEC in distilled water (Figure 54).

The prepared nylon membrane was placed between the compartments of a pair of dialysis cells. Ten ml of distilled water was added to one compartment of each cell. Ten ml of a 82.2 mcg/ml HC solution was added to the second compartment of one cell and 10 ml of a 25.4 mcg/ml HC in 0.25% w/w HEC solution (no preservatives) was added to the second cell. The cells were tumbled in a water bath $(25.0 \pm 0.5^{\circ}C)$ and at intervals (44, 68, 135, 183h), equal volumes of the solutions were pipetted from both sides of each cell. The absorbance was noted at 249 nm for the HC species (blank = distilled water and 0.25% w/w HEC in distilled water respectively). This procedure was repeated with dimethylpolysiloxane membrane.



FIGURE 54. UV spectrophotometric standard curve for hydroxyethylcellulose

b) Binding of Hydrocortisone with Nylon Membrane

Hydrocortisone solutions of varying concentration were made in distilled water. Twenty ml of HC solution was pipetted into one compartment of the dialysis cell and 20 ml of distilled water was pipetted into the other compartment. Three glass beads were added to each compartment to ensure continuous stirring during dialysis. The cells were tumbled inaa water bath (23.0 \pm 0.5^oC) for 4 days. Aliquots were taken from both compartments and, after proper dilution, the HC concentrations were determined using UV spectrophotometry. The percentage recovery was calculated to estimate membrane binding.

c) Interaction of Hydrocortisone with Hydroxyethylcellulose

Hydrocortisone solutions of various concentrations were prepared aseptically in 0.25% w/w HEC (Stock solutions: 200.6 μ g/ml HC in 0.25% w/w HEC and 0.25% w/w HEC). The HEC dispersions were not preserved. Twenty ml of the HC in HEC solution was pipetted into one compartment of a two-chambered dialysis cell (rinsed with 70% EtOH and sterile distilled water) and 20 ml of sterile distilled water was placed in the second chamber. The cells were tumbled in a water bath (23.0 ± 0.5^oC) until the concentration of HC in the receptor chamber was the same on two consecutive days (35 days). Aliquots were withdrawn from the receptor compartment, diluted appropriately with distilled water for analysis at 249 nm. Nylon membrane was used in this study and was prepared as previously described previously described.

Hydrocortisone - Hydroxyethylcellulose Diffusion Studies in the Presence of a Membrane

Two membranes were used in this study, nylon membrane (prepared as previously described, Section III. 2.) and human autopsy epidermis (prepared as described by Scheuplein, 1965). The integrity of the skin samples was determined by measuring the electrical resistance after it was mounted in the diffusion cell (Table XXII).

The prepared membranes were sandwiched between the Teflon discs of the diffusion cell (Appendix II) and clamped tightly in place atop the ground glass surface of the receptor chamber. 8 ml of 0.9% w/v sodium chloride solution was pipetted into the lower chamber. The cells were carefully inverted to dispel any air bubbles below the skin surface. 0.3 g of the test dispersion (113 µg/ml HC in 1% w/w HEC or 11 µg/ml HC in 4% w/w HEC or 10.8μ g/ml HC in distilled water) was added to the donor chamber and 0.1 ml of tritiated HC solution (2.17 x 10⁸ dmp/ml) was layered on to the surface of the upper reservoir. Samples were occluded with a grease-edged cover slip and the side arm stoppered to prevent evaporation $(T = 23 \pm 1^{\circ}C)$. 0.5 ml samples were withdrawn at convenient time intervals and added to 14 ml of Bray's scintillation cocktail and counted in the Nuclear Chicago Isocap 300 using the tritium program for low quench samples as supplied by the manufacturer. The amount of HC present in the sample was calculated using a channels ratio technique in conjunction with a quench correction curve (Figure 55). The receptor volume was renewed by the addition of 0.5 ml of normal saline. Diffusion curves were constructed for all samples and the rate of penetration (Js, $\mu g \text{ cm}^{-2} \text{ h}^{-1}$) was



🗯 4% HEC and • distilled water

calculated from the steady slope of the cumulative diffusion - time plot (Figure 56). Diffusion constants (D, cm² h⁻¹) were computed from

$$Js = \frac{Km D Cs}{\delta}$$
(68)

where <u>Km</u> was the membrane-vehicle partition coefficient, <u>Cs</u>, concentration difference of solute across the membrane, δ was the membrane thickness (cm). Km was assumed to be 5 (Scheuplien and Blank, 1971).

To check the identity of the radioactively labelled diffusing species, samples of receptor fluid were subjected to thin layer chromatography in two solvent systems (chloroform/absolute ethanol (90:10) and chloroform/acetone/acetic acid (10:8:1). At least 80% of the radioactivity was recovered from an area corresponding to the R_f value for 'cold' HC : 0.63 - 0.72 for chloroform/absolute ethanol and 0.75 - 0.79 for chloroform/acetone/acetic acid. Although some tritium exchange may occur during the period of the diffusion process, the radioactive compound penetrating the membranes was primarily HC.

RESULTS AND DISCUSSION

1. Hydrocortisone Solubility and Partition Coefficient

In the present work, 301 μ g/ml (± 5 SD) was obtained for the aqueous solubility of HC at 25.0 ± 0.5°C. This result was in excellent agreement with the 302 μ g/ml result of Short <u>et al.</u> (1972) and also falls within the limits of 285 μ g/ml (± 10% CV) found by Kabasakalian (1966). Macek <u>et al</u>. (1952) obtained a solubility value of 280 μ g/ml for HC from shaking an excess of HC one hour prior to analysis. This is the commonly quoted value but it is improbable that HC can achieve equilibrium solubility within one hour.

An average partition coefficient of 33.65 was determined from measurement of the HC concentration in both the aqueous and octanol layers and $33.28 \stackrel{+}{-} 0.60 \text{ CL}_{95\%}$ from the indirect method (Equation 67). These values agreed well with each other therefore, it was sufficient to determined the octanol concentration indirectly. The experimental results were also in excellent agreement with Flynn's partition coefficient in diethyl ether (Flynn, 1971) which had been converted by Leo <u>et al.(1971)</u> to a corresponding octanol value of 33.88.

2. Hydrocortisone - Hydroxyethylcellulose Interactions

Cellophane membrane was rejected as a suitable dialysis membrane for studying the interaction of HC with HEC because the 0.25% w/w HEC dispersion showed 90% equilibration on both sides of the dialysis cell within 24mh. Although dimethylpolysiloxane membrane (DMPS) did not permit the transfer of HEC, it was rejected also because of the extremely slow passage rate of HC. The passage rate of HC through nylon membrane was better than through DMPS and also nylon membrane did not allow the transfer of HEC.

HC did not bind with nylon membrane. Within the errors of the experimental technique and analytical emthod, HC did not interact with HEC therefore, this was a good system to study the effects of viscosity upon the diffusion of HC.

3. Influence of Limiting Viscosity at Low Shear Rates on the Diffusion of Hydrocortisone in Hydroxyethylcellulose Dispersions

The following factors permit the identification of vehicle viscosity effects on the release or diffusion rate of HC:

- a) HC and HEC are both nonionic solutes
- b) HC does not bind with nylon membrane (Section III. 2)

c) HC and HEC do not interact (Section III. 2)

- d) the HCcconcentration gradient is constant
- e) two different types of membranes are used
- f) the vehicles are aqueous solutions of uncross-linked polymers
 (Section II. B. 2) and have a known viscosity at the shear rates of diffusion (Section II. B. 1).

An increase in the limiting viscosity at low shear rates from 0.4 to 60 poise (Section II. B. 1) resulted in a 22% decrease in the steady state penetration rate of HC (J_s) through artificial nylon membrane and a corresponding 19% decrease in the passage rate through human autopsy epidermis at 23 ± 1°C (Table XXII). The similarity in the results using two membranes indicated that the decrease in J_s was due to the increase in vehicle viscosity.

The effect of increasing vehicle viscosity on the diffusion of HC through an artificial nylon membrane is shown in Figure 56. The decrease in slope with an increase in vehicle viscosity indicated that the flux or the amount of drug transferred per unit time at steady state had decreased. With human autopsy epidermis for a membrane, the cumulative

Table XXII

Comparison of vehicle viscosity effects on the diffusion of HC through nylon membrane and

								·
	Vehicle	Viscosity	J ± Range		(' t)' -	r ²	Electrical Resistance	D
		(P)	(µg cm	· ² h ⁻¹)	(h)	- -	(ohms)	$(cm^2 sec^{-1})$
nylon	water	0.01	0.320	0.020 ^a	7.7	0.984	_	_
	1% HEC	0.40	0.258	0.001	6.3	0.998	-	
	4% HEC	60.	0.200	0.020	7.0	0.994	-	_ . :
human autopsy epidermis	water	0.01	0.059		26.	0.995	90,000	1.4×10^{-11}
	1% HEC	0.40	0.037		30.	0.997	110,000	1.0×10^{-11}
	4% HEC	60.	0.030		28.	0.994	90,000	0.8×10^{-11}

human autopsy epidermis

^a 2 replicates



FIGURE 56. Cumulative diffusion of HC through nylon membrane from a 11 μ g/ml solution in 1.0 and 4.0% w/w HEC dispersions and distilled water

diffusion curves were in the same order as noted for the nylon membrane (Figure 57).

The lag times remained unaffected by the increase in viscosity but were influenced by the nature of the membrane. The lag time for the diffusion of HC through the epidermis was four times longer than that for the nylon membrane. Also, the HC flux, $J_{\underline{s}}$, through nylon membrane was approximately six times faster than through epidermis (Table XXII). Since the thickness of both membranes was comparable, these two results may be due to differences in the polarity of the membranes. The octanol/water partition coefficient (Section III. 1) and the <u>Km</u> (Equation 68) showed that the relatively polar HC molecule was not sufficiently lipid soluble to penetrate the epidermis rapidly (Scheupleingand Blank, 1971) but should show an increased penetration through the more hydrophilic nylon membrane.

The diffusion coefficient for HC dissolved in water and penetrating hyman epidermis as calculated from Equation (68) was 100 times greater (Table XXII) than the corresponding literature values, 3×10^{-13} cm² s⁻¹ noted by Scheuplein and Blank (1971), 0.68 x 10^{-13} cm² s⁻¹ calculated from partition data by Lien and Tong (1973) and 4.8 x 10^{-13} cm² s⁻¹ determined by Yotsuyangi and Higuchi (1972). The experimental temperatures for the above were not stated. The higher value determined in this study was explained by one, or a combination of, the following:

i. a higher concentration gradient (Scheuplein and Ross, 1974), or,
ii. insufficiently intact epidermal sheets, or,
iii. aahhigher experimental temperature.





Cumulative diffusion of HC through human autopsy epidermis from a 11 $\mu g/m1$ solution in 1.0 and 4.0% w/w HEC dispersions and distilled water

Although the calculated diffusion coefficient was significantly higher, this does not invalidate the results because relative changes rather than absolute changes were examined.

A portion of the noted decrease in steady state flux with increasing vehicle viscosity may be explained by an estimated 1.8% decrease in apparent molar volume with an increase in HEC concentration from 1.0 to 4.0% w/w (Section I. A. 2). This decrease in apparent molar volume is indicative of a corresponding decrease in free volume or the number of available positions for the diffusing molecule in the fluid. The amount of free volume is a factor in the diffusion process whether the mechanism of diffusion involves a potential energy barrier (Eyring, 1936) or thermal motion (Alder and Hildebrand, 1973).

It is expected that the magnitude of the viscosity effects on HC diffusion noted in the presence of a membrane which is rate limiting to the transport process would be larger in the absence of such a membrane. Theoretical studies involving determination of the influence of vehicle components on drug diffusion should separate drug-component absorption or adsorption effects from any increase in vehicle viscosity due to the addition of the component, i.e. a surfactant.

SECTION IV. SUMMARY AND CONCLUSIONS

A. RHEOMETRIC STUDIES OF A MODEL SHEAR-THINNING SYSTEM

1. Material Characterization

Because of the variability in materials due to commercial synthetic processes, HEC and Brij 30 were characterized physicochemically. The \overline{Mw} of the HEC sample (Natrosol 250G) was 86,000. Between 15 - 40°C, the density-temperature relationship for 1 - 3% HEC dispersions was described adequately by Equation (10),

$$d = A e^{-BT}$$
,

where \underline{B} was numerically similar to the thermal expansion coefficient of water. The apparent molar volumes of these dispersions decreased with increasing cellulose concentration.

The \overline{Mn} of Brij 30 was determined to be 380 from vapour pressure measurements and 383 from nuclear magnetic resonance determinations. The critical micelle concentration was 1.42×10^{-4} moles/1 (Mn = 380, 23 ± 1°C). The surfactant was well resolved using gas liquid chromato-

graphy and the major polymerization products identified were

i. dodecanol 6%

ii. polyoxyethylene (n) dodecyl ether, where n = 1, 2, 3 and 4 iii. tetradecanol 1%

iv. polyoxyethylene (n) tetradecyl ether, where n = 1, 2 and 3.

2. Steady Shear Studies of Practical Importance

These studies were concerned with the rheological properties of HEC and HEC - Brij 30 systems, the determination of rheometerindependent shear rate-shear stress parameters and the equivalence of rheological models.

a) Reproducibility and Stability of HEC and MC Dispersions

For similar consistencies, the preparation of HEC and MC dispersions was equally reproducible rheologically. The decrease in apparent viscosity on prolonged storage was comparable. Both HEC and MC dispersions exhibited increases in apparent viscosity during the initial storage period. The time required for the maximum increase was ascribed to the spacer efficiency of the substitutent or the degree of hydrophilic character of the substitutent. The power-law consistency index was related to both storage time and HEC concentration (Equation 49).

$$m = K_1 - 0.01 t (HEC)^{4.94}$$
.

b) HEC - Brij 30, A System with Rheological Flexibility

The addition of Brij 30, a nonionic surfactant, to the HEC dispersions provided a reliable means of obtaining a series of systems showing predictable increments in shear-thinning behaviour at each polymer concentration. Simply stated, the surfactant gave rheological flexibility to the HEC dispersions without changing the type of steady shear flow properties ($\gamma = 8.5 - 685 \text{ s}^{-1}$).

c) An Improved Rotovisko Shear Stress Calibration Method

The manufacturer's method and a method involving the determination of shear stress calibration constants for each shear rate were compared for a series of shear-thinning fluids. The latter method allowed determination of rheometer-independent shear stress and shear rate parameters to a significant degree of non-Newtonian character.

d) Limitations of Couette Rheometers in Shear Stress/Shear Rate Determination of non-Newtonian Shear-Thinning Systems

The determination of a shear stress calibration constant for each Rotovisko shear rate yielded shear rate-shear stress parameters which were rheometer-independent for shear-thinning fluids with power-law parameters $n \ge 0.55$ and $m \le 41.5$. The Krieger-Maron shear rate equation (24) was more reliable than the calibration equation (20) for this rheometer.

The results were rheometer independent for the Brookfield fitted with the SC-4 spindles when $n \ge 0.81$ and $m \le 14.0$. The Mooney shear stress and shear rate equations (Equations 27 and 28) were the most reliable. The non-Newtonian region for shear rate-shear stress rheometerindependent results may be extended by the determination of shear stress calibration constants for each shear rate.

e) Flow Models for Shear-Thinning Systems

The modified Shangraw, Steiger-Trippi-Ory and power-law models were not significantly different and all accurately fit the shear-thinning systems measured ($\gamma = 8.5 - 685 \text{ s}^{-1}$). For a constant concentration, parameters of the flow models varied with the surfactant concentration. The modified Shangraw parameters <u>a</u> and <u>b</u> followed linear and squared functions of Brij 30 concentration respectively, whereas the Shangraw parameter <u>c</u>, the Steiger-Trippi-Ory parameters <u>a'</u> and <u>c'</u> and the power-law parameters <u>m</u> and <u>n</u> varied as the logarithm of Brij 30 content. These curves may be used to obtain the flow parameters for HEC - Brij 30 dispersions of composition within the range used in this experiment.

3. <u>Rheometric Studies of a Fundaméntal Nature: Low Shear and Dynamic</u>

Measurements

a) Low Shear Rate Studies

The 1 - 4% w/w HEC dispersions exhibited a theoretical limiting viscosity at low shear rates. This viscosity was a function of polymer concentration (Equation 64),

$$\log \eta_0 = \log K_{10} + L_{10} \log (\text{HEC}).$$

The Brij 30 in HEC dispersions did not show a limiting viscosity region over the shear rate range measured.

b) Molecular Disposition of HEC

The storage and loss moduli, dynamic viscosity and loss tangent were computed from dynamic measurements for the 1 - 4% w/w HEC dispersions. The loss moduli were directly proportional to radian frequency as described by Equation (65). The shape of the storage and loss moduli plots were characteristic of a dilute polymer solution in which the viscoelasticity was a relatively minor perturbation of the Newtonian behaviour of the solvent. The convergence of the dynamic and steady shear viscosities at low radian frequencies and shear rates showed the absence of cross-linking. In aqueous solution, HEC resembles the springy-wormlike model of Harris and Hearst. This model represents a degree of stiffness between the perfectly flexible bead-spring model and the rigid-rod model of Kirkwood and Auer.

c) Viscoelastic Features of HEC - Brij 30 Dispersions

The storage and loss moduli, dynamic viscosity and loss tangent were computed for the 0 - 16% Brij 30 in 2 - 4% w/w HEC dispersion. At low frequencies, the storage and loss moduli for the HEC - Brij 30 systems were not as sensitive to changes in radian frequency as were the HEC dispersions. This decrease in sensitivity revealed the presence of a pronounced elastic component with the addition of Brij 30 to the HEC dispersions. The general shape of the storage and loss moduli curves were similar to uncross-linked polymers. The dynamic and steady shear viscosities showed increased divergence with the three most non-Newtonian dispersions but it was expected that these parameters would converge at lower frequencies and shear rates than were measured in this study.

B. EFFECT OF LIMITING VISCOSITY AT LOW SHEAR RATES ON HC DIFFUSION

The aqueous solubility and octanol/water partition coefficient of hydrocortisone were determined to be 301 μ g/ml (25.0 $\stackrel{+}{-}$ 0.5°C) and 33.65, respectively. HC did not bind with HEC within the limitations of the equilibrium dialysis technique and UV analytical method.

In the absence of drug-vehicle interactions, and increase in the limiting viscosity at low shear rates of an uncross-linked nonionic polymer from 014 to 60 poise resulted in a 22% decrease in the steady state flux of HC through artificial nylon membrane and a corresponding
19% decrease in the passage rate through human autopsy epidermis at 23 $\frac{+}{-}$ 1°C. The similarity in the results using the two membranes indicated that the observed decrease in J was due to the alteration of vehicle viscosity.

CONCLUSIONS

- The region of rheometer-independent shear rate-shear stress results for a range of shear-thinning fluids was less for the Brookfield Synchro-lectric (SC-4 spindles) than for the Haake Rotovisko (MV1 spindle). This result for the Brookfield may be improved through the determination of a shear stress constant at each shear rate.
- 2. The use of flow model parameters to describe a non-Newtonian flow curve and the construction of parameter - viscosity inducing agent(s) concentrations graphs was advocated to facilitate product development, literature comparisons, quality control measurements and consumer acceptability assessments through objective measurements.
- 3. Dynamic and low shear rate parameters provided a method of determining molecular disposition and fluid structure. HEC was observed to be a molecule with intermediate flexibility in aqueous solution and HEC – Brij 30 systems has a pronounced elastic component at low frequencies which was indicative of a loose three-dimensional shear-sensitive structure.
- 4. In the absence of drug-vehicle interactions, increased limiting vehicle viscosity at low shear rates of an uncross-linked nonionic polymer decreased the steady state flux of hydrocortisone by similar amounts through nylon membrane an human autopsy epidermis.

APPENDIX I

MATERIALS

- NATROSOL 250G, hydroxyethylcellulose (lot # 22201, Hercules Incorporated, Wilimington, Delaware).
- METHYLCELLULOSE, 1500 cps (lot # 17316, British Drug Houses, Toronto, Ontario).
- 3. BRIJ 30, polyoxyethylene (4) dodecyl ether, technical grade (lot # 5165B, I.C.I. America Inc., Wilimington, Delaware).
- BRIJ 30 SP, polyoxyethylene (4) dodecyl ether, pharmaceutical grade (lot # 7078B, I.C.I. America Inc., Wilimington, Delaware).
- METHYL p-HYDROXYBENZOATE, reagent grade (lot # 38809, British Drug Houses, Laboratory Chemicals Division, Poole, England).
- n-PROPYL p-HYDROXYBENZOATE, reagent grade (lot # 26922, British Drug Houses).
- HYDROCORTISONE, 11β, 17α, 21-trihydroxy-4-pregnene-3, 20-dione, micronized free alcohol (lot # 45909, British Drug Houses, Toronto, Ontario).
- 8. CORTISOL (1, 2 ³H) 5.5 mCi/mg, 98 + % pure radiochemically, supplied in benzene/ethanol (9:1 v/v) sealed under vacuum (The Radiochemical Centre, Amersham, Bucks, England). A portion of the newly opened, tritium labelled cortisol was chromatographed on activated silica gel using two solvent systems: chloroform/absolute ethanol (90:10 v/v) and chloroform/acetone/acetic acid (12:8:1 v/v) to check for radioactive degradation or reaction products. Two of the developed strips from each solvent system were

sectioned and counted (Dioxane scintillation solvent, Comish and and Juhlin, 1969). Also a strip from each solvent system was autoradiographed.

Although some tailing was apparent in both solvent systems (Figures 58 and 59), the Rf values for the labelled HC were comparable to those for 'cold' HC: 0.63 - 0.72 for chloroform/absolute ethanol and 0.75 - 0.79 for chloroform/acetone/ acetic acid.

 POPOP, 1,4-bis [2-(5-phenyloxazolyl)] -benzene (Sigma Chemical Company, 3500 de Kalb Street, St. Louis, Missouri).

10. PPO, 2,5-diphenyloxazole (Sigma Chemical Company).

- NAPHTHALENE, scintillation grade (Kent Laboratories, 1292 Franklin Street, Vancouver, British Columbia).
- 12. GAS CHROMATOGRAPHY STANDARDS
 - a) Octan-1-ol, specially pure (lot # 1345810, British Drug Houses Chemicals Ltd. Poole, England).
 - b) Decan-1-ol, specially pure (lot # 1218340, British Drug Houses Chemicals Ltd.).
 - c) Dodecan-1-ol, specially pure (lot # 1197800, British Drug Houses Chemicals Ltd.).
 - d) Tetradecan-1-ol, Baker grade (lot # 1-8238, J.T. Baker Chemical Co., Phillipsburg, New Jersey).
 - e) Hexadecan-1-ol, reagent grade (lot B2A, Eastman Kodak Co., Rochester, New York).
 - f) Octadecan-1-ol, specially pure (lot # 1062770, British Drug Houses Chemicals Ltd.).



Thin layer chromatogram of (1, 2 ³H) Cortisol.
 Solvent system, chloroform/absolute ethanol (90:10 v/v)



Thin layer chromatogram of (1, 2^{33} H) Cortisol. FIGURE 59. Solvent system, chloroform/acetone/acetic acid (12:8:1 v/v)

13. MEMBRANES FOR EQUILIBRIUM DIALYSIS STUDIES

- a) Fisher cellophane membrane (1 47/64 in. flat width, Dialyzer tubing, Fisher Scientific Co., Fair Lawn, New Jersey).
- b) Nylon membrane (0.0005 in. thick, Capran 77, Allied Chemical Corp., Morristown, New Jersey).
- c) Dimethylpolysiloxane membrane (0.005 in. thick, Silastic Sheeting, non-reinforced, 500-1, Dow Corning Corp., Medical Products Division, Midland, Michigan).

14. VISCOSITY STANDARDS

Newtonian oils used in rheometer calibration are listed in Table XXIII, (Cannon Instrument Co., Boalsburg, Pennsylvania).

Table XXIII

oil designation °	temp ([°] C)	viscosity (Póżše)
. s - 20	20.0	0.410
s – 200	25.0	3.936
S – 200	37.78	1.747
s - 60	20.0	1.467
S - 60	25.0	1.059
s – 600	20.0	20.66
s – 600	25.0	13.50
*		

Viscosity Standards Used in Rheometer Calibration

15. GENERAL PROCEDURE FOR THE PREPARATION OF HYDROXYETHYLCELLULOSE AND METHYLCELLULOSE DISPERSIONS

Four hundred and fifty ml of distilled water $(65 - 70^{\circ}C)$ preserved with methyl and propylparahydroxybenzoates (Hoover, 1970) were transferred to a Waring blendor. The weighed HEC was added slowly into the vortex with the blendor on low speed and agitated for a total time that depended upon the concentration of HEC (Table XXIV). The dispersion was quantitatively transferred to a 1000 ml tared beaker and brought to 500 g total weight with $70^{\circ}C$ preserved water. It was then placed in an ice bath and stirred until it cooled to below $20^{\circ}C$. The cold dispersion was refrigerated $(3^{\circ}C)$ for 2 - 4 h prior to bottling. This procedure yielded clear, stable dispersions.

Table XXIV

Concentration (% w/w)	Time Blended (sec)
1.0	105
1.5	120
2.0	135
2.5	150
3.0	165
3.5	180
4.0	195

Blending time for HEC and MC dispersions

16. GENERAL PROCEDURE FOR THE PREPARATION OF BRIJ 30 IN HYDROXYETHYL-CELLULOSE DISPERSIONS

HEC dispersions were prepared as described under item 15 and aged for 1 day. Using a balance with a sensitivity of 10 mg, the Brij 30 and HEC dispersions were weighed, combined and mixed until homogeneous. The resulting 70 or 120 g samples were bottled in amber glass ointment jars because the effect of light on the dispersions was unknown.

SOLVENTS AND REAGENTS

1.	Octan-1-ol (Fisher Scientific Company, Fair Lawn, New Jersey).
2.	p-Dioxane, scintillation quality (Mallinckrodt Chemical Works,
	St. Louis, Missouri).
3.	Dioxane scintillation solvent (Bray's Solution, Bray, 1960):
	Naphthalene
	PP0
	POPOP0.2 gm
	Methanol (absolute)100.0 ml
	Ethylene Glycol20.0 ml
	p-Dioxaneqs 1000.0 ml
4.	Dioxane scintillation solvent (Comish and Juhlin, 1969):
×	PP0
	POPOP0.3 gm
	Naphthalene
	p-Dioxaneqs 1000.0 ml
	solvent for the (1, 2 3 H) cortisol thin layer chromatography
	studies.
5.	Receptor solution for the diffusion cells:
	Methyl p-hydroxybenzoate0.18 % w/v
	n-Propyl p-hydroxybenzoate0.02 % w/v
	Sodium Chloride
	Distilled Waterqs 100.0 % w/v
6.	Thin Layer Chromatography solvents
	a) Chloroform

	Ethanol (absolute)10
b)	Chloroform12
	Acetone
	Acetic Acid1

7. Saturated preserved water

Accarboy of distilled water was heated to 80° C and the weighed preservatives (methyl p-hydroxybenzoate (0.26% w/v) and n-propyl p-hydroxybenzoate (0.04 % w/v)) were added gradually while stirring. The stirring and heating were continued until all the preservative had melted. The preserved water was then allowed to cool. The excess parabens formed a hard white cake on the bottom leaving the solution clear. As the water was withdrawn, it was filtered through eight layers of cotton gauze. All fittings used on the carboy were glass to decrease the possibility of microbial growth. The preserved water was diluted 1 in 2 prior to use.

- 8. Water saturated octanol and octanol saturated water were prepared by gently shaking water and octanol in a 1 litre separatory funnel. The two phases were separated after standing 24 h.
- 9. Ethylene Glycol, analytical reagent (Mallinckrodt Chemical Works).
 10. Solution of a Homologous Series of Alcohols for Gas Chromatography

Octan-1-010.0467	g
Decan-1-ol0.0497	g
Dodecan-1-010.0495	g
Tetradecan-1-010.0531	g
Hexadecan-1-o10.0504	g
Octadecan-1-010.0470	g
Methanol (absolute) gs	m1

APPENDIX II

APPARATUS

A. Analytical Equipment

- BECKMAN DB-GT SPECTROPHOTOMETER and 10 inch linear recorder equipped with 1P28A photomultiplier, deuterium and tungsten sources (Beckman Instruments, Inc., Fullerton, California).
- BECKMAN IR-10 SPECTROPHOTOMETER recording spectra linear in wave number in the 4000 - 300 cm⁻¹ range (Beckman Instruments Inc., Fullerton, California).
- BECKMAN PREPARATIVE ULTRACENTRIFUGE, Model L2-65B, equipped with the Schlieren optics attachment (Spinco Division, Beckman Instruments Inc., Palo Alto, California).
- 4. CENTRIFUGE, Model SVB, (International Equipment Co., Boston, Massachusetts) for separation of lipid droplets suspended in the aqueous layer during the octanol/water partition coefficient determination.
- 5. NUCLEAR CHICAGO ISOCAP/300, ambient temperature, automatic programming liquid scintillation counter with ¹³³Ba external standard (Nuclear Chicago, Des Plaines, Illinois).
- 6. ROSANO SURFACE TENSIOMETER, Roller Smith Precision Balances (Federal Pacific Electric Co., Newark, New Jersey).
- SKIN DIFFUSION CELL designed by Coldman <u>et al</u>. (1969) and used for the viscosity - steroid diffusion studies.
- SPECIFIC GRAVITY BOTTLES, 50 ml adjusted at 20°C, # 10655-50 and with thermometer, # 10669-50 (CENCO, Central Scientific Co. of Canada Ltd., Mississauga, Ontario).

- 9. TWO CHAMBERED PLEXIGLASS DIALYSIS CELLS, as described by Patel and Foss (1964), for the steroid polymer binding determination.
- 10. THIN LAYER CHROMATOGRAPHY was done using the Eastman Chromagram Developing Apparatus with sheets # 6061 and # 6060 which were activated at 100°C for 20 min. immediately prior to spotting and developing (Eastman Kodak Co., Rochester, New York).
- 11. VAPOUR PRESSURE OSMOMETER, Model 302B equipped with variable temperature controller (18575A) (Hewlett Packard, Avondale, Pennsylvania).
- 12. VARIAN GAS CHROMATOGRAPH/MASS SPECTROMETER SYSTEM, MAT 111, 70 ev, equipped 3% SE 30 on Varaport 80/100 mesh 6 ft. x 2 mm i.d. stainless steel column, electron ionization detector and Kompensograph and Oscillofil L recorders (Varian MAT, 28 Bremen 10, Postfach, Germany).
- 13. VARIAN NUCLEAR MAGNETIC RESONANCE SPECTROMETER, Model HA 100, high resolution, 100 Megahertz instrument (Varian Associates', Palo Alto, California).

B. Balances

- CENCO MOISTURE BALANCE, # 26675, for the determination of the moisture content of hydroxyethylcellulose (Central Scientific Co., Chicago, Illinois).
- METTLER TOP LOADING, Model P(k) 1200, in the preparation of the cellulose and hydroxyethylcellulose - surfactant dispersions (Mettler Instruments AG, Zurich, Switzerland).
- SARTORIUS, Model 2743, analytical balance (Sartorius Werke AG, Gottingen, Germany).

C. Constant Temperature Baths

- CANNON, Model M1, circulating water bath for the capillary viscometers (Cannon Instrument Co., Boalsburg, Pennsylvania).
- 2. HAAKE, Model FE, circulating water bath for the Brookfield rheometer small sample adaptor (Gebruder Haake K.G., Berlin, Germany).
- HAAKE, Model E-51, circulating water pump for temperature controlled solubility and partition coefficient measurements (Gebruder Haake K.G., Berlin, Germany).
- MAGNI-WHIRL^R constant temperature bath for density measurements (Blue M Electric Co., Blue Island, Illinois).
- ULTRA-KRYOMAT, Model TK-30D, circulating water bath for the Weissenberg rheogoniometer and the Haake Rotovisko rheometer (Lauda Instruments, Westbury, New Jersey).
- D. Mixing Equipment
- POWER STIR, Model 58, stirrer for the preparation of preserved water (Eberbach Corp., Ann Arbor, Michigan).
- 2. WARING BLENDOR^R, Model PB-5, in the preparation of the cellulose dispersions (Waring Products Corp., New York, New York).

E. Recorders

- MOSELEY AUTOGRAF, Model 7100A, two channel, 10 inch strip chart recorder for tracing the Haake Rotovisko shear stress signal (F.L. Moseley Co., Pasadena, California).
- 2. RECORDING OSCILLOGRAPH, Model 5-127, for recording the Weissenberg ... rheogoniometer oscillatory output (Bell & Howell Ltd., Consolidated

Electrodynamics, Basingstoke, England).

3. RIKEN, Model SP-H3, 10 inch strip chart recorder for the Weissenberg rheogoniometer steady shear traces (Riken Design Co. Ltd., Tokyo, Japan).

F. Viscometers

- BROOKFIELD SYNCHRO-LECTRIC, Model LVT, powered by a general electric synchronous induction type motor. The instrument was equipped with a water-jacketed small sample adaptor and the SC-4 spindle series (D.W. Brookfield Ltd., Cooksville, Mississauga, Ontario).
- 2. CANNON-FENSKE ROUTINE VISCOMETER FOR TRANSPARENT LIQUIDS, Size 50, capillary viscometers calibrated at four temperatures (ASTM, 1968a and 1968b) (Cannon Instrument Co., Boalsburg, Pennsylvania).
- 3. HAAKE ROTOVISKO, Model M1, powered by a synchronous electric motor operating at 3000 rpm (Gebruder Haake K.G., Berlin, Germany).
- 4. WEISSENBERG RHEOGONIOMETER, Model R-18, equipped with steady and dynamic shear facilities and an air bath for sample temperature control (Sangamo Controls Ltd., North Bersted, Bognor Regis, Sussex, England).

APPENDIX III

COMPUTER PROGRAMS

- 1. General Co-variance Program
- 2. Modified Shangraw, Steiger-Trippi-Ory and Power-law Model

Program

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	1 3 1 1 1 3 1									
,	0001		CALL PLOTS							
	0002		DOUBLE PRECI	SION SX, SY	, SXY, SXX, SXXC OR	,SYYCOR,SXYCOR,	SYY,AI,BI,CI			
	0003		DOUBLE PRECIS	SION XBAR,	YBAR, A, B, KEUZ, B	COL COK COL CO	A, GUB, GUL, GUE			}
	0004		DIMENSION X(2001.Y/200	U. AT(2), BT(2), C	1(2).N(2).RESS(2).REDS(2).			
			1DFRS(2) +NAME	(10),T(200),YB(2),YE(2),X	B(2),XE(2),YS(2),YT(2)			
	0005		YS(1)=10.07					· · · ·		
	0007		YS(2)=7.77							
	0008		YT(1)=10.							
	0009		YT(2) = 9, 7		,			·····		
	0010		RM1 = M1							
•	0011	C ≄*	* INSERT FORM	AT CARD AN	D NP=NUMBER OF	PAIRS OF DATA	TESTED ***			
	0012	1	FORMAT(F5.2,	F5.4)						
	0013		NP = 40							
	0014	2	FORMAT(//IX,	<u>13,1044)</u>					······································	
	JU15	3	- FURMAI(15,10	441 D						
	0017		WRITE(6.11)	r			•			
	0013	11	FURMAT(1H1)							
	0019		NA=1							
	0020		DJ 100 J=1,N	L						
	0021		READ(5,3,END	=89) N(J),	{NAME(1);I=1,10) }				
	0022		PRIMI Zythtj RN=N(1)	/ , (NAME (17	,1-1,10//					
	0024	,	NT = NA + N(J) - 1					•	· · · · · · · · · · · · · · · · · · ·	
·	3025		N10=J							
	0026		<u>SX = 0.0</u>							
	0027		$SY_{i} = 0.0$							
	0023		SXX = 0.0		•					
	0030	· ·	SXXCOR = 0.0		-					
	0031		$SYYCOR = C_{\bullet}O$							-
	0.032		SYY = 0.0	÷ .						\
	0033		READ(5.1) V(÷		
	0035		SX = SX + X(I)					•	
	0036		SY = SY + Y(I) .						· · ·
	0037		SXY = SXY +	$X(I) \neq Y(I)$)	•				
	0038	2.0	$\frac{5XX = 5XX +}{5YY = 5YY +}$	$\frac{X(1) + X(1)}{Y(1) + V(1)}$	<u>}</u>	••••••••		······		V
	0039	. 20	112 = 511	7 (17 ~ 7 (1 RN			4		*	-
	0041		YPAP = SY /	PN						<u> </u>
	J04 2		SXYCOR = SXY	- (SX * S	Y) / F.N					
	0043		DO 30 I=N4,N	T						
	0)44	2.3	SXXCOR = SXX	$\frac{1}{100} + \frac{1}{100}$	1-XBAR 1**2		,			· ·
	0045	5 J.	B = SXYCOR /	SXXCOR	. / TUAN / ""4					
	0047		A = YPAR - P	* XBAR						<u> </u>
	0048		R=SXYCOR/DSQ	RT(SXXCOR*	SYYCORI					
	0049		SEY=DSQRT((S	YYCOR-B*SX	(YCOR)/(RN-2.))					
	0050		DF=RN-1.	VCOP						
	0051		SECC(1)=CAAC	TCOK DR-BEDS (1)	•				• •	7
	0053	•	DFRS(J) = FN+2	• 0						
		······								
	0054		PRIMI 42, (NI	0,A,B,SEY,	R + DF)					

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0056		$\Delta I(1) = SXXCOR$					
0057		BI(J) = SXYCOR					
0053		CI(J) = SYYCOR					
0059		NZ=N1 DO 108 T=NA-N7					
0080	1.03	T(I)=X(I)	· ·				
00.5.2		NNA=NA+1					
0063	· ·	NNZ = NZ - 1					
0054		IE(T(NA).LE.T(I)) GO TO 109			· · · · · · · · · · · · · · · · · · ·		
3056		TEMP=T(NA)					
0057		T(NA) = T(I)				•	
	1.00						
0059	109	00 110 I=NNA, NNZ		•			
0071		IF(T(NZ).GE.T(1)) GO TO 110		·	· · · · · · · · · · · · · · · · · · ·		
007?		TEMPET(NZ)			,		
0073							
0074	11)	CONTINUE					
0076		XB(J) = T(NA)					•
007-7		$\frac{XE(J) = T(NZ)}{XE(J) = A + B \# XE(J)}$					
0079		YF(J) = A + B + XE(J)					
0030		CALL SYMBOL (. 5, YS(J) 14, J.0., -1)				
0031	•	CALL SYMBOL (1., YT(J), 14, NAME, 0.	,40)		•		
0032	100	NA=NT+1 CONTINUE					
0055	<u> </u>	IMREG FOR POOLED DATA				1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 -	
0034		SX=0.					
0035		<u>SY=0</u>			· · · · · · · · · · · · · · · · · · ·	an a	1
0055	•	SY Y=0.					
0089		5XY=0.					
6800		SXXCOR=0.					
0090		SX AC US = 0*			-		
0.091		RNT = NT					
0093.		00 120 I=1,NT				· .	
0094		SX = SX + X(1)					
0095		SX = SX + X(I) + 2				•	
0097		SYY=SYY+Y(I)**2					· ``
0053	120	SXY=SXY+X(I)*Y(I)					
0099	•	XBAR=SX/RNF YBAR=SY/RNT					`
0100		SXYCOR=SXY-(SX*SY)/RNT		···			i
0102		DO 130 I=1,NT			,		
0103		<u>SXXCOR=SXXCOR+(X(I)-XBAR)**2</u> <u>SXXCOR=SXXCOR+(Y(I)-YBAR)**2</u>					
0104	130	BTAW=SXYCOR/SXXCOR					ļ
2 0106		A=YBAR-BTAW*XBAR					`
0107		8=8TAW				• •	N
5) 0109 0109		K=SXTCHR/USAR HISXXCUR*STTCUR/ SFY=DSDRT((SYYCDR-BTAW*SXYCDR)/	(RNT-2.))				
3110		DF=RNT=1.	an territor on all constructions of the second s				l a
0111		REDZ=B*SXYCOR				м. М	·).
0112		RESZ=SYYCOR-REDZ					

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	0.001.						
0113		DFRZ=RNT-2.0					
0114		PRINT 43, (A, B, SEY, R,		10X 11-1 550 5	107 10-1 520		
0115	43.	FORMAT(///12X, SIMRE	G FOR POOLED DATA	//9X, "A=", F20.5;	10X, B= , F20		<i>i</i>
 		1.5//.10X, 'SEY=', F20.	4,10X, "R=", F8.4,10	X, UF= , F6. 0)			
0116		WRITE(6,500)					
0117	500	FORMAT(///,30X,'COVA	RIANCE ANALYSIS")				· ·
 0113		<u> </u>	I(1)+AI(2))				······································
0119		RPDZ=BPC*(BI(1)+BI(2))				
0120		REPZ=CI(1)+CI(2)-RPD	2				
 0121		GDE=DFRS(1)+DFRS(2)					· · · · · · · · · · · · · · · · · · ·
0122		DFPZ=GOE+1.0					
0123		GDA=(RESS(1)+RESS(2))/GOE				
0124		GOB=REPZ-RESS(1)-RES	S(2)				
 0125		GOC=GOB/GCA					
0126		WRITE(6.610)					
0127	610	EORMATI // . 20X . TEST	FOR HOMOGENEITY OF	RESIDUAL VARIAN	ICES!)		
 0129	· · · · · · · · · · · · · · · · · · ·	G01=8255(1)/DER5(1)					
0120		G14=RESS(2)/DERS(2)					
0127		GRN=GEL/GEY					
 		WRITE(6.53010ERS/11) -	DERS(2).GON				
0122		- HALLELO, 290701 ASLI +	5. 1.51279 001				
0152	550		EOR SLOPES ()				
 0133	220	PUSHAT(77)20X)*1231	TUR SCOPES /				
0134	5 ()	- WRITE(0,5507 GUE,600	0.1 - 1.615.31				
0135	2.20	PORMAL SURFERIZING	•0• - •1 19•91	•			
 0135		WRITELO, DIVI	EOD LEVELSEN				
0137	. 570	FURMALLY/,20X, TEST	FUR LEVELS !				
0133		SOF=REPZ/OFPZ					
 0139	·	SUG=RESZ-REPZ		· · ·			
0140		GOH=GOG/GGE	•				
0141		WRITE(5,560) DEP2,GU	н .				
 		WRITE(6,580)					
0143	580	FORMAT(//,20X, OVERA	LL TEST ()			· · · · · ·	
0144		DFOT=DFRZ-GOE					
 0145		GOI=RESZ-RESS(1)-RES	<u>S(2)</u>				
0146		GOJ=GOI/DEDT			·		
0147		GOK=GCJ/GCA					
 0143		WRITE(6,530)DFOT,GOE	+ GOK			·	
 0149	590	FORMAT (30X, *F, *, F5.0	•••/••F5•0•• = ••F1	5.3)			
0150		CALL SCALE(X, NT, 10.,	XMIN, DX, 1)				
0151		CALL SCALE(Y, NT, 10.,	YMIN, DY, 1)		•	•	
 0152		00 12 I=1,2	· · · ·				•
0153	•	XE(I) = (XB(I) - XMIN)/D	X			•	
0154		$x \in (I) = (X \in (I) - X M IN) / D$	x				
 0155		YB(I)=(YB(I)-YMIN)/D	Υ				
0155	ů.	YF(1)=(YE(1)-YMIN)/D	Y				
0157	× 12	CONTINUE					
 0153 *	· · · · · · · · · · · · · · · · · · ·	CALL AXIS(007HY	VALUE, 7, 1090 YM	IN, DY)			
0159	٠,	CALL AXIS (007HX	VAL UE 7 - 10 - 0 XM	IN, DX)			
0157	•	N7=N(1)			•	· .	
 0160	<u>};</u>	$\frac{112 - 10121}{200 + 13}$					
0161	1 3	- DO TO TUTANE	1 07 . 1 . 0 7)				
0152	13	- UALL SIMOULIAIL/9711	1 7 8 0 1 9 1 7 0 8 9 - 1 1				· · ·
 0163	·		•				
0164	• •	UJ 14 LENA,NI				. •	
0165	14	CALL SYMBUL(X(I),Y(I	. 1 + • U / + Z + U • + ** L }				
 0165		CALL PLOT(XB(1),YB(1	.1,+31				
3157		CALL PLOT(XE(1),YE(1	1++21	,	-		
0168		CALL PLCT(XB(2),YB(2	(),+3)			÷	
0169		CALL PLOT (XE(2) YE(2	2),+2)				

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		0170 0171 0172	£ 8 8 9	CALL PLC CONTINUE PRINT 11	IT (15.,0.,-3)							·
	\	0174 0175	ċ9	ST DP END				· .		· ·		
· ·	•	TOTAL	ME MORY RE	QUIREMENTS	001B6C BYTES							
		COMPIL	E TIME =	6.9	SECONDS					· · · · · · · ·		
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62 SEPT/72 ROTOVISK KRIEG YA+8% R= 0.9985. DF= 61. SEY= 0.0228 B= 0.59809 Δ= 1.31005 40SEPT/72 RHEDGEN HEC 2.0+BRIJ 9% YA R= ().9993 DF= 39. SEY= 0.0133 0.59861 Δ= 1.30452 8= SIMBEG FOR POOLED DATA 0.59811 B= Δ = 1.30827 R= 0.9988 DF= 101. 0.0196 SEY= . COVARIANCE ANALYSIS TEST FOR HOMOGENEITY OF RESIDUAL VARIANCES 2.918 F, 60./ 38. = TEST FOR SLOPES F,1/ 98. = 0.003 . TEST FOR LEVELS 1.252 F.1/ 99. = OVERALL TEST F, 2./ 98. = 0.621

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0001		DIMENSION VIGOL VIGOL VIGOL VIGOL CALOL CALOL CALOL DISL NOVAL MARCON	
0001		DIMENSION ACOUNT (00), TE (00), WE (00), EE (3), EZ (3), P(3), MD(3), NAME(9)	
. 0002		UTMENSION TSH (60), TPL(60), TSI (60), TI (60), V(60), Z(60)	
0003		EXTERNAL AUX	
0004		EXTERNAL AUXPL	
0005		EXTERNAL AUXST	· · ·
0006		DATA NI,WZ,EP/20,0.0,0.0001/	· · · ·
0007	1	FORMAT(13,944)	
0008	2	FORMAT(1H1,1X,9A4//)	
0009	3	FORMAT(32X, 2F7.2)	•
0010	4	FORMAT(//7X, 'SHEAR STRESS SHEAR RATE '/19X, 'ACTUAL FITTED'/)	•
0011	5	FORMAT(//IX, ROOT MEAN SQUARE ERROR OF ESTIMATE IN PARAMETERS //)	
0012	6	FORMAT(1X,3G15.5)	
0013	7 .	FORMAT(//7X+'SHEAR RATE SHEAR STRESS'/19X+'ACTUAL FITTED!/)	
0014	8	FORMAT(1X+12+3X+3F10+2)	
0015	9	FORMAT(1H1)	
0016	11	FORMAT(/1X, 'SHANGRAW MODE) PARAMETERS()	
0017	12		
0018	12	FORMATIZIAN FUNDA CAN POUCL FARAMETERS'I	
0010	15	FORMAL (7) 94, "SHEAR RALE", 134, "SHEAR SINESS VALUES"/6X, "ACTUAL ST	
0010		IGR-IPPI ACTUAL SHANGRAW POWER LAW'/)	
0019	14	FORMAT(1x,12,2F10.2,3F12.2)	
0020-	15	FURMAT (/1X, 'STETGER-TRIPPI PARAMETERS')	
0021	· 22	FORMAT(5F12.2)	
. 0022		DU 200 NDK=1,10	
0023	100	READ(5,1) N,NAME	
0024		PRINT 2+(NAME)	
0025		DO 10 $I=1,N$	
026		READ(5,3) Y(I),X(I)	
0027	10	CONTINUE	
0028		PRINT 11	
	С	SHANGRAW MODEL SECTION	
0029		M=3	
0030		P(1)=.05	
0031			
0032			
0032			
0034			
0034		SUB = 5(2)	1
0035		SH0=P(2)	
0036		SH(=P(3)	
0037		PRINT 5	
-0038		PRINT 6, (E2(1), I=1, M)	
0039		PRINT 7	
0040		DO 20 I=1,N	
· 0041 .		PRINT 8, (I, X(I), Y(I), YF(I))	
0042	20	YSH(1)=YF(1)	
	С	POWER LAW MODEL SECTION	
0043		M#2	
0044	32	PRINT 2. (NAME)	
0045		PRINT 12	
0046			
0047	•		
. 0049	70		
0040	10		
0049			
0050		r(z)==>	
0051		LALL DPLNF(V,Z,YF,W,E1,E2,P,WZ,N,M,NI,ND,EP,AUXPL)	
00 52		IF(NU-EQ.0) GO TO 31	

Ο

PEDRURAN [V & CLOMPILEN MAIN US-31-71 17.45.78 PAGE U002 PC53 PELM=PC2) C055 PELM=PC2) C055 PELM=75 C055 PELM=75 PELM	PRIMERAN IV & COMPTLER MAIN 00-21-11 17:05:30 PAGE 0002 C054 PLM=7(2) 0055 PR [NT 5 0055 PR [NT 6 [1:12(11):1-1:1N] 0059 VF [11=7(11)*X(1)**P(2) 0059 VF [11=7(11)*X(1)**P(2) 0060 PR [NT 8 [1:14] V(1)**P(2) 0060 PR [NT 8 [1:14] V(1)**P(1)] 0061 20 VP [11=7(11) 0063 C 00 50 1=1:N 0064 TH PF *X[1] 0065 X (1)=Y11 0066 PR [NT 15 0066 PR [NT 15 0066 PR [NT 15 0066 PR [NT 15 0066 PR [NT 15 0067 PR [NT 15 0068 PR [NT 15 0069 PR [1]=X[1]=X(1)**P(1) 0069 PR [NT 15 0069 PR [1]=X[1]=X(1)**P(1) 0069 PR [1]=X[1]=X(1) 0060 PR [NT 15 0071 PR [NT 6:1:X(1)*V[1])*Y[1]) 0075 PR [NT 6:[2(1],1=1,N] 0075 PR [NT 6:[2(1],1=1,N] 0075 PR [NT 6:[2(1],1=1,N] 0076 PR [NT 15 0077 PR [NT 6:[2(1],1=1,N] 0076 PR [NT 15 0077 PR [NT 14:[1]:X(1)*Y[1]) 0080 PR [NT 15 0081 PR [NT 15]:N 0080 PR [NT 14:[1]:X(1)*Y[1]):X(1)*Y[1]) 0080 PR [NT 14:[1]:X(1)*Y[1]):X(1)*Y[1]) 0080 PR [NT 14:[1]:X(1)*Y[1]):X(1)*Y[1]) 0080 PR [NT 15]:N 0080 PR [NT 14:[1]:X(1)*Y[1]:X(1)*Y[1]) 0080 PR [NT 14:[1]:X(1)*Y[1]:X(1)*Y[1]) 0080 PR [NT 14:[1]:X(1)*Y[1]):X(1)*Y[1]) 0080 PR [NT 15:[1]:X(1)*Y[1]:X[1]*Y[1]) 0080 PR [NT 14:[1]:X[1]*Y[1]:X[1]*Y[1]) 0080 PR [NT 14:[1]:X[1]*Y[1]:X[1]*Y[1]) 0080 PR [NT 14:[1]:X[1]*Y[1]:X[1]*Y[1]) 0080 PR [NT 14:[1]:X[1]*Y[1]:X[1]*Y[1]) 0080 PR [NT 14:[1]*X[1]*Y[1]*Y[1]] 0080 PR [NT 14:[1]*X[1]*Y[1]*Y[1]*Y[1] 0080 PR [NT 14:[1]*X[1]*Y[1]*Y[1]*Y[1]] 0080 PR [NT 14:[1]*X[1]*Y[1]*Y[1]*Y[1]*Y[1]*Y[1]*Y[1]*Y[1]*Y	CO53	IV G COMPI			
C C33 C C34 C C C C C C C C C C C C C C C C C C C	C053 PLM=P(1) C054 FLN=P(2) C055 PRINT 6.(E2(1),F=1,M) C057 PRINT 7.(E2(1),F=1,M) C058 C0 30 [=1,N) C059 FKINT 8.(I),F(1),F(1),F(1) C060 PRINT 8.(I),F(1),F(1),F(1) C061 STEIGEF_TRIPPI, PCDEL_SECTION C062 C0 STEIGEF_TRIPPI, PCDEL_SECTION C063 C0 STEIGEF_TRIPPI, PCDEL_SECTION C064 TEMP=X(1) C065 XIIJ=TEMEAMET C066 FIIJ=STERA C067 PRINT 5. C0669 PRINT 5. C071 CALL DPL(PCX,Y,YF,W,E1,E2,P,WZ,N,M,N1,ND,EP,AUXST) C073 STA=PRINT 5. C074 CRINT 4. C075 PRINT 6.(E2(1),1=1,N) C076 PRINT 6.(E2(1),1=1,N) C077 C0 A.O.D 1=1,N C078 PRINT 6.(E2(1),1,F1,YF(1)) C079 PRINT 6.(E2(1),1,F1,F1,VF(1)) C071 C0 A.O.D 1=1,N C072 PRINT 6.(E2(1),1,F1,F1,VF(1)) C073 PRINT 6.(E2(1),1,F1,F1,F1,VF(1)) C074 PRINT 6.(E2(1),1,F1,F1,F1,VF(1)) <th>0053 0054</th> <th></th> <th>LER MAIN 08-31-71 17:46:38 PAGE 0002</th> <th></th> <th></th>	0053 0054		LER MAIN 08-31-71 17:46:38 PAGE 0002		
0035 100000 100000 100000 0055 PRINT 7 100000 100000 0055 00000 100000 100000 0055 00000 100000 100000 00000 000000 100000 100000 000000 000000 1000000 1000000 0000000 0000000 10000000 10000000 00000000000000000 0000000000000000 1000000000000000000000000000000000000	0035 C PRINT 5 0056 PRINT 7 0057 PRINT 7 0058 CO 30 [1].w(1)=w(1)=.w(1) 0059 Y [1]=v(1)=w(1)=w(1) 0051 CO 30 [1].w(1)=w(1) 0052 CO 30 [1].w(1)=w(1) 0053 CO TINE 0054 CO TINE 0055 CO 30 [1].w(1)=w(1) 0056 CO TINE 0057 PRINT 7 0058 CO 50 [1].w(1)=w(1) 0056 CO 50 [1].w(1)=w(1) 0056 CO 10 [1].w(1) 0057 CO 11].w(1) 0058 CO 11].w(1).w(1).w(1).w(1) 0059 PRINT 2.(XAME) 0051 CO 11].w(1).w(1).w(1).w(1).w(1).w(1).w(1).w(1)	C054		PL = P(1)		
0055 PFINT 5, (E2(1), (=1, M) 0055 PFINT 5, (E2(1), (=1, M) 0055 PFINT 5, (E2(1), YE(1)) 0060 PFINT 4, (I, YE(1), YE(1)) 0061 30 YF(1) + YE(1) 0062 31 YE(105F TRIPPI MODEL SECTION 0063 C DS 10 + 1 + N 0064 TEMPSXI1) 0065 50 Y(1) + FEP 0066 50 Y(1) + FEP 0077 PFINT 2, (MAME) 0071 CALL 0P(QF(X, Y, YE, W, E1, E2, P, WZ, N, M, NT, ND, EP, AUXST) 0073 STC-P(2) 0074 CP(1) + YE(1) 0075 CP(1) + YE(1) 0075 CP(1) + YE(1) 0077 DD 60 10 + N 0077 PFINT 2, (TAME) 0077 PFINT 2, (TAME) 0077 CD 60 10 + 1 N 0077 CD 7 PFINT 2, (TAME) 0077 CD 7 PFINT 2, (TA	0055 PRINT 5, (E2(1), I=1, M) 0055 D0 30 I=1, N 0056 D1 (I), P(1), P(1), Y(1)) 0057 PRINT 8, (I, X(I), Y(I), Y(I)) 0068 Q1 (I), P(1), P(1), Y(I)) 0069 PRINT 8, (I, X(I), Y(I), Y(I)) 0061 Q1 (I), Y(I), Y(I), Y(I)) 0062 C1 SIEIGER-FRIPPI MODE SECTION 0063 D0 S0 I=1, N 0064 TEMPEXII) 0065 Y (I) III (I) (I) (I) 00664 TEMPEXII) 00655 Y (I) III (I) (I) (I) 00667 P (I) III (I) (I) (I) 00678 P (I) III (I) (I) (I) (I) 00679 P (I) III (I) (I) (I) (I) 0071 CALL DP (Def(X, Y, YF, W, E1, E2, P, WZ, N, M, NT, ND, EP, AUXST) 0075 P RINT 5 0075 P RINT 6, (IE2(I), I=1, N) 0076 P RINT 6, (III), YF (II) 0077 D0 (A D 1=1, N) 0078 P RINT 8, (I, X(I), YT (I), X(I), YS (I), YP (I)) 0079 P RINT 2, (NAME) 0083 D0 (A 0 1=1, N) 0084 P RINT 13, (I), YS	0055				
0057 PRINT 7 0058 00 1 1-1.N 0058 00 1 1-1.N 0058 00 1 1-1.N 0059 PRINT 7 0050 PRINT 7 0051 00 VPL(1)=VF(1) 0052 STETEGE-TRIPPI HODEL SECTION 0053 00 VPL(1)=VF(1) 0054 TEMPSATIN 0055 X(1)=Y(1) 0056 X(1)=Y(1) 0057 PRINT 2. (NAME) 0056 X(1)=Y(1) 0056 PRINT 2. (NAME) 0057 PRINT 2. (NAME) 0058 PRINT 3. (X(1), Y(1), YF(1)) 0071 PG(2) 0072 STC=PR2) 0073 STC=PR2) 0074 PRINT 4. 0077 DG (AO 1=1.N) 0078 PRINT 4. 0079 PRINT 4. 0079 PRINT 2. (NAME) 0079 PRINT 2. (NAME) 0079 PRINT 2. (NAME) 0079 PRINT 3. 0079 PRINT 2. (NAME) 0079 PRINT 2. (NAME) 0079 </td <td>0557 PRINT 7 CLUTTIC: 0055 CD 30 1=1.N 0055 YE(1)=Y(1)=Y(1)*Y(1)*Y(1) 0061 O YE(1)=Y(1) 0062 PRINT 8.(1.X(1)*Y(1)) 0063 C STREPT MODEL SECTION 0064 TO 50 1=1.N 0065 X(1)=Y(1) 0066 D 50 1=1.N 0066 TO 50 1=1.N 0066 TO 50 1=1.N 0066 PRINT 15 0066 PRINT 15 0066 PRINT 15 0066 PRINT 15 0071 CALL PUOP(X, Y, YF.W.EL, E2, F.WZ, N.M.N.I.ND, EP, AUXST) 0072 SIC.eP(2) 4 YENT 0073 SIC.eP(2) 4 YENT 0074 PRINT 5, (E2 (1), YE(1) 0075 YSI(1)=YYE(1) 0076 PRINT 8, (I, X(I), YSI(1), XSI(I), YSI(I), YSI(I) 0075 YSI(1)=YYE(1) 0076 PRINT 8, (I, X(I), YSI(I), YSI(I), YSI(I), YSI(I) 0077 PO 40 1=1.N 0078 PRINT 8, (I, X(I), YSI(I), YSI(I), YSI(I), YSI(I) 0079 YSI(I)=YSI(I), YSI(I</td> <td>0055</td> <td></td> <td>$PK_{INI} = 0$</td> <td></td> <td></td>	0557 PRINT 7 CLUTTIC: 0055 CD 30 1=1.N 0055 YE(1)=Y(1)=Y(1)*Y(1)*Y(1) 0061 O YE(1)=Y(1) 0062 PRINT 8.(1.X(1)*Y(1)) 0063 C STREPT MODEL SECTION 0064 TO 50 1=1.N 0065 X(1)=Y(1) 0066 D 50 1=1.N 0066 TO 50 1=1.N 0066 TO 50 1=1.N 0066 PRINT 15 0066 PRINT 15 0066 PRINT 15 0066 PRINT 15 0071 CALL PUOP(X, Y, YF.W.EL, E2, F.WZ, N.M.N.I.ND, EP, AUXST) 0072 SIC.eP(2) 4 YENT 0073 SIC.eP(2) 4 YENT 0074 PRINT 5, (E2 (1), YE(1) 0075 YSI(1)=YYE(1) 0076 PRINT 8, (I, X(I), YSI(1), XSI(I), YSI(I), YSI(I) 0075 YSI(1)=YYE(1) 0076 PRINT 8, (I, X(I), YSI(I), YSI(I), YSI(I), YSI(I) 0077 PO 40 1=1.N 0078 PRINT 8, (I, X(I), YSI(I), YSI(I), YSI(I), YSI(I) 0079 YSI(I)=YSI(I), YSI(I	0055		$PK_{INI} = 0$		
0053 00130 11.N 0059 YF(11=K(1)K(1)+YF(1)) 0064 30 YP(11=YF(1)) 0065 0050 YF(1) 0066 50 Y(1) 0066 YF(1) YF(1) 0067 YF(1) YF(1) 0066 YF(1) YF(1) 0067 YF(1) YF(1) 0068 YF(1) YF(1) 0071 CALL OPLOF(X,Y,YF,W,E1,E2,P,WZ,W,W,NI,ND,EP,AUXST) YF(1) 0073 ST(2,F12) 2 0074 YF(1) YF(1) 0075 YF(1) YF(1) 0076 PRINT 4 YF(1) 0077 YF(1) YF(1) 0078 YF(1) YF(1) 0079 YS(1)-YF(1) YF(1) 0074 YF(1) YF(1) 0075 PRINT 13 YF(1) 0076 PR	0035 0030 <td< td=""><td>0058</td><td></td><td>PRINT 7</td><td>//////////////////////////////////////</td><td></td></td<>	0058		PRINT 7	//////////////////////////////////////	
0055 YF(1)=0(1)=x(1)=xP(1) 0060 PRINT 8+(1,x(1),YF(1))+YF(1) 0061 30 YP(1)=YF(1) 0062 STETGEF-TRIPPI MODEL SECTION 0063 0059 1=1,N 0064 0059 1=1,N 0065 X(1)=YT(1) 0066 PRINT 2, (NAME) 0066 PRINT 2, (NAME) 0066 PRINT 2, (NAME) 0066 PRINT 2, (NAME) 0070 PRINT 2, (NAME) 0071 CALL 0F(X,Y,YF,W,E1,E2,P,WZ,N,N,NI,ND+EP,AUXST) 0073 STETGEF12) 0074 PRINT 3, (-EC2(1),1=1=,N) 0075 PRINT 4, (E2(1),1=1,N) 0076 PRINT 4, (E2(1),Y(1),YF(1)) 0077 DQ 60 [=1,N] 0078 PRINT 3, (-X(1),Y(1),YF(1)) 0079 PRINT 13, (-Y(1),YS(1),X(1),YSH(1),YPL(1)) 0083 DO 40 [=1,N] 0084 WRINT 14, (1,Y(1),YSI(1),X(1),YSH(1),YPL(1)) 0085 DO 40 [=1,N] 0086 PRINT 13, (-Y(1),YSI(1),X(1),YSH(1),YPL(1)) 0087 IPRINT 14, (-Y(1),YSI(1),X(1),YSH(1),YPL(1)) 0083 DO 40 [=1,N]	0059 VF(1)=P(1)*V(1)*VF(1) 0060 PRINT 8,(1,Y,Y(1),Y(1),YF(1)) 0061 30 VP((1)*VF(1) 0063 D0 SO [=1,N 0064 TOP SO [=1,N 0065 PRINT 15,(1,Y,Y(1),Y(1),Y(1),Y(1) 0066 TOP SO [=1,N 0066 PRINT 2,(AAME) 0066 PRINT 2,(AAME) 0066 PRINT 2,(AAME) 0066 PRINT 2,(AAME) 0067 PRINT 2,(AAME) 0068 PRINT 15 0069 PRINT 2,(AAME) 0071 CALL DPLOFCX,Y,YF,W,E1,E2,P,WZ,N,M,NI,ND,EP,AUXST) 0072 STG=PRI2) 0073 STG=PRI2) 0074 PRINT 4 0075 PRINT 4 0076 PRINT 4 0077 D0 60 1=1,N 0078 PRINT 4 0079 PSIT1 + 2(T),Y(T),YF(T)) 0074 PRINT 4 0075 POFILE 4 0076 PRINT 13 0077 D0 60 1=1,N 0078 PRINT 14 0079 PRINT 14 <td< td=""><td>0058</td><td>•</td><td>PO 30 I=1-N</td><td></td><td></td></td<>	0058	•	PO 30 I=1-N		
0060 PRINT 8,(1,x(1),Y(1),YE(1)) 0061 30 YPL(1)=YE(1) 0062 31 CONTINUE 0063 00 50 F1,N 0064 T(1)=X11 HODEL SECTION 0064 T(1)=X11 HODEL SECTION 0064 T(1)=X11 HODEL SECTION 0065 O Y(1)=TEMP 0066 PRINT 15 Control Section 0067 PRINT 15 Control Section 0070 P(2)=1. Control Section 0071 Calue Opt(X,Y,YF,W,E),E2,P,WZ,W,W,N1,ND,EP,AUXST) 0073 SiteP(2) Z 0074 PRINT 4 Control Section 0075 PRINT 4, (12,Y(1),YF(1)) Z 0076 PRINT 4, (12,Y(1),YF(1)) Z 0077 D0 60 1=1.N Z 0078 PRINT 2, (NAME) Z 0079 YS(1)=YS(1),YS(1)	0060 PRINT 8, (I, X(I), Y(I), YE(I)) 0061 30 YP(I)=YE(I) 0063 OF 50 II) HODEL SECTION 0064 OF 50 II) HODEL SECTION 0065 OC (I)=Y(I) HODEL SECTION 0066 S0 (I)=Y(I) HODEL SECTION 0067 PRINT 1: HODEL SECTION 0068 PRINT 1: HODEL SECTION 0067 PRINT 1: HODEL SECTION 0070 P(2)=1 HODEL SECTION 0071 Call OIL (FIX, Y, YF, N, E1, E2, P, NZ, N, M, NI, ND, EP, AUXST) HODEL SECTION 0073 STG=PRINT 1: HODEL SECTION HODEL SECTION 0074 PRINT 1: HODEL SECTION HODEL SECTION 0075 PRINT 4: HIT 2: HIT 2: 0076 PRINT 4: HIT 2: HIT 2: 0077 DO 60 1: HIT 2: HIT 2: <t< td=""><td>0059</td><td></td><td>YF(1)=P(1)*X(1)**P(2)</td><td></td><td></td></t<>	0059		YF(1)=P(1)*X(1)**P(2)		
Coli 30 VPL(1)=VF(1) C STEIGEF-TRIPPI_MODEL_SECTION Coli 30 COLNTINUE C STEIGEF-TRIPPI_MODEL_SECTION Coli 30 Coli 30 Coli 31 COLNTINUE Coli 30 Coli 30 Coli 30 Coli 30 Coli 30 VPL(1)=VL(1) Coli 31 Coli 30 Coli 31 Coli 31 Col 31 Coli 31	0061 30 VPL(1)=YF(1) 0062 31 CONTIAUE 0063 00150 1.1.4 0064 TEMPARILI 0066 FRINT 0066 FRINT 0066 FRINT 0066 FRINT 0067 FRINT 0068 FRINT 0067 FRINT 0071 CALL OPLOF(X,Y,YF,W,E1,E2,P,WZ,N,W,NI,ND,EP,AUXST) 0071 CALL OPLOF(X,Y,YF,W,E1,E2,P,WZ,N,W,NI,ND,EP,AUXST) 0071 CALL OPLOF(X,Y,YF,W,E1,E2,P,WZ,N,W,NI,ND,EP,AUXST) 0072 STC=P12) 0074 FRINT 0075 STC=P12) 0076 FRINT 0077 OD 60 0076 FRINT 2, (NAME) 0077 OD 60 0078 FRINT 3, (TI,Y(T),YT(T),YT(T)) 0079 YST(T)=YT(T) 0074 FRINT 3, (NAME) 0083 OU 40.1=1,N 0083 OU 40.1=1,N 0084 GRAMIT (JX,YA =*, CIG.6,GYB =*, CIG.6,GYC 0085 OU 40.1=1,N 0085 <	0060		PRINT 8,(I,X(I),Y(I),YF(I))		
0062 3.1 CONTINUE 0 C STICRE-FINPT, MODEL SECTION 0063 D0 50 F1.N 0064 TEMP=X(1) 0065 X(1)=TENP 0066 PRINT 1 0067 PEINT 2.(NAME) 0068 PRINT 2.(NAME) 0067 PEINT 2.(NAME) 0073 STG=P(1) 0074 PRINT 5. 0075 PRINT 6.(E2(1),1=1.M) 0076 PRINT 8.(E2(1),1=1.M) 0077 D0 60 1=1.N 0076 PRINT 4.(1),Y(1),YF(1)) 0077 D0 60 10 1=1.N 0078 PRINT 4.(1),Y(1),YF(1)) 0079 YSI(1)=*F(1) 0074 PRINT 4.(1),YSI(1),X(1),YF(1)) 0075 PRINT 13 0080 60 0081 PRINT 13 0082 PRINT 13 0083 10 0084 PRINT 14.(1,V(1),YSI(1),X(1),YEI(1)) 0085 10 0086 10 0087 POPAIT 2.(NAME) 0088 10 1099 <td< td=""><td>0062 31 CONTINUE C STEIGEF-TRIPPI MODEL SECTION 0063 D0 50 1-1.% 0064 TEMP=X11 0065 X111=Y11 0066 PRINT (NAME) 0066 PRINT (NAME) 0066 PRINT (NAME) 0070 PRINT (NAME) 0071 CALL OPLOF(X, Y, YF, W, EL, E2, P, WZ, N, M, NT, ND, EP, AUXST) 0073 STC-P(2) 0074 PRINT 6, (E2(1), 1=1, M) 0075 PRINT 6, (E2(1), 1=1, M) 0076 PRINT 4 0077 D0 60 1=1, N 0078 PRINT 13 0081 PRINT 14, (II), Y(II), YF(II) 0073 PRINT 13 0082 D0 40 1=1, N 0083 D0 40 1=1, N 0084 WRITE(8, 2) Y(I), XI(I), YSI(I), YSI(I</td><td>0061</td><td>30</td><td>YPL(I)=YF(I)</td><td></td><td></td></td<>	0062 31 CONTINUE C STEIGEF-TRIPPI MODEL SECTION 0063 D0 50 1-1.% 0064 TEMP=X11 0065 X111=Y11 0066 PRINT (NAME) 0066 PRINT (NAME) 0066 PRINT (NAME) 0070 PRINT (NAME) 0071 CALL OPLOF(X, Y, YF, W, EL, E2, P, WZ, N, M, NT, ND, EP, AUXST) 0073 STC-P(2) 0074 PRINT 6, (E2(1), 1=1, M) 0075 PRINT 6, (E2(1), 1=1, M) 0076 PRINT 4 0077 D0 60 1=1, N 0078 PRINT 13 0081 PRINT 14, (II), Y(II), YF(II) 0073 PRINT 13 0082 D0 40 1=1, N 0083 D0 40 1=1, N 0084 WRITE(8, 2) Y(I), XI(I), YSI(I), YSI(I	0061	30	YPL(I)=YF(I)		
C STELEGE-TRIPPI MODEL SECTION 063 00 50 T-1,N 0664 TEMP=X11 0665 00 YIINTIS 0666 90 YIINTIS 0667 PINTIS 0668 PINTIS 0670 PILDENTIS 071 CALL DPLOF(X,Y,YF,W,E1,E2,P,WZ,N,M,NI,ND,EP,AUXST) 0771 CALL DPLOF(X,Y,YF,W,E1,E2,P,WZ,N,M,NI,ND,EP,AUXST) 0772 SIC=PILD 0773 SIC=PILD 0773 SIC=PILD 0775 PRINT 6,(E2(1),1=1,M) 0775 PRINT 6,(E2(1),1=1,M) 0775 PRINT 6,(E2(1),1=1,M) 0775 PRINT 6,(E2(1),1=1,M) 0775 PRINT 6,(E2(1),1=1,M) 077 D0 60 1=1,N 077 D0 60 1=1,N 078 PRINT 8,(I,X(I),Y(I),YF(I)) 079 YSIINTY (I) 079 PRINT 13, (I,X(I),YSI(I),YSI(I),YPL(I)) 088 D0 40 1=1,N 088 18 FORMAT(/1X,*N =+,C16,6,*C =+,C16,6,*C =+,C16,6,*C 088 18 FORMAT(/1X,*N =+,C16,6,*C =+,C16,6,*C =+,C16,6,*C 099 PRINT 13, (PLM,*SIC) 088 18 FORMAT(/1X,*N =+,C16,6,*C =+,C16,6,*C =+,C16,6,*C 099 PRINT 13, (PLM,*SIC) 0086 PRINT 14, (SIA,SIC) 099 PRINT 14, (SIA,SIC) 099 PRINT 19, (PLM,*SIC) 099 PRINT 19, (SIA,SIC) 099 PRINT	C STELGER-TRIPPI MODEL SECTION 0063 D0 50 1=1.1% 0066 S0 X(1)=Y(1) 0066 S0 X(1)=Y(1) 0067 PFINT 2.(NAME) 0067 PFINT 2.(NAME) 0068 PPINT 15 0070 C11 = 16 0071 C4LL DPLOF(X,Y,YF,W,E1,E2,P,WZ,N,W,NI,ND,EP,AUXST) 0073 SIC=P(2) 0075 PFINT 6.(E2(1),1=1.W) 0075 PFINT 6.(E2(1),1=1.W) 0076 PRINT 4. 0077 D0 60 1=1.W 0078 PFINT 8.(T,X(1),Y(1),YF(1)) 0079 YST(1)=YF(1) 0079 C0 C0TIAUE 0081 PPINT 2.(NAME) 0083 D0 40 1=1.W 0083 D0 40 1=1.W 0084 PPINT 13 0083 D0 40 1=1.W 0084 PPINT 14. ((I,Y(1),YST(1),X(1),YSH(1),YPL(1)) 0075 40 PFINT 1. 0085 PPINT 13 0086 PPINT 14. ((I,Y(1),YST(1),X(1),YSH(1),YPL(1)) 0086 PPINT 14. ((I,Y(1),YST(1),X(1),YSH(1),YPL(1)) 0086 PPINT 14. ((I,Y(1),YST(1),X(1),YSH(1),YPL(1)) 0086 PPINT 14. ((I,Y(1),YST(1),X(1),YSH(1),YPL(1)) 0087 PPINT 14. ((I,Y(1),YST(1),X(1),YSH(1),YSH(1),YPL(1)) 0086 PPINT 14. ((I,Y(1),YST(1),X(1),YSH(1	0062	31	CONTINUE		·
0063 00 50 11-1;N 0064 TEMP=X(1) 0065 X(1)=TEMP=X(1) 0066 PFINT 2;(NAME) 0067 PFINT 2;(NAME) 0068 PFINT 1; 0070 PFINT 2;(NAME) 0071 CALL DPLOFIX,Y,YF,W,E1,E2,P,WZ,N,M,NI,ND,EP,AUXST) 0072 SIX=P(1) 0073 SIX=P(1) 0074 PFINT 5;(E2(1),1=1,M) 0075 PFINT 5;(E2(1),YF(1)) 0076 PFINT 4;(I),Y(I),YF(I)) 0077 D0 6:0 1=1,N 0078 PFINT 3;(II:Y(I),YF(I)) 0079 YSI(II:YF(I),Y(I),YF(I)) 0074 PFINT 1;(N(I),YSI(I),X(I),YSH(I),YPL(I)) 0075 PFINT 2;(NAME) 0083 D0 4:0 1=1,N 0084 PRINT 13 0085 D0 FORMIT (JX,I'N = +;CI6.6,*IN = +;CI6.6,*/) 0086 TEOPMAT (JX,*M = +;CI6.6,*N = +;CI6.6,*/) 0087 TEOPMAT (JX,*M = +;CI6.6,*IN = +;CI6.6,*/) 0088 IB FORMAT (JX,*M = +;CI6.6,*N = +;CI6.6,*/) 0089 IB FORMAT (JX,*M = +;CI6.6,*N = +;CI6.6,*/) 0089 IB	0063 D0 50 [=1,N 0064 TEMP2X[1] 0065 S (1)=TEMP 0066 PR[NT 15 [MAME] 0066 PR[NT 15 [MAME] 0066 PR[1]=3.5=6 0076 PR[2]=1. 0071 CALL OPLOF(X,Y,YF,W,E],E],E2,P,WZ,N,M,NI,ND,EP,AUXST) 0073 SIG=P(2) 0074 PR[NT 5 0075 PR[NT 6, [E2(1],1=1,M] 0076 PR[NT 4 0077 D0 60 [=1,N 0078 VRINT 8, [I,X(I),Y(I),YF(I)] 0079 VRINT 8, [I,X(I),Y(I),YF(I)] 0070 OF CALL OPLOF(X,Y,YF,W,E],E] 0071 PR[NT 8, [I,X(I),Y(I),YF(I)] 0070 OF CALL OPLOF(X,Y,YF,W,E],E] 0071 PR[NT 8, [I,X(I),Y(I),YF(I)] 0073 VRINT 8, [I,X(I),Y(I),YF(I)] 0074 OF CALL OPLOF(X,Y,YF,W,E] 0075 OF CALL OPLOF(X,Y,YF,W,E] 0076 OF CALL OPLOF(X,Y,YF,W,E] 0077 OF CALL OPLOF(X,Y,YF,W,E] 0078 OF CALL OPLOF(X,Y,YF,W,E] 0079 OF CALL OPLOF(X,Y,YF,W,E] 0079 OF CALL OPLOF(X,Y,YF,W,E] 0083 OF CALL OPLOF(X,Y,YF,W,E] 0084 OF CALL OPLOF(X,Y,YF,W,E] 0085 OF CALL OPLOF(X,Y,YF,W,E] 0086 OF CALL OPLOF(X,Y,YF,W,E] 0086 OF CALL OPLOF(X,Y,YF,W,E] 0087 OF CALL OPLOF(X,Y,Y,K,Y,Y,Y,Y,Y,Y,Y,Y,Y,Y,Y,Y,Y,Y,Y,Y,		C C	STEIGER-TRIPPI MODEL SECTION		
0064 TEMPEX[1] 0065 50 Y[1]=TEMP 0067 PRINT 2.(MAME) 0068 PRINT 3.5 0069 P[1]=3.5=6 0070 P[2]=1. 0071 Call DUQF(X, Y, YF, W, E1, E2, P, WZ, N, M, NI, ND, EP, AUXST) 0072 STA=P(1) 0073 STA=P(1) 0074 PRINT 6. (E2(1), 1=1, M) 0075 PRINT 6. (E2(1), Y(1), YF(1)) 0076 PRINT 8. (I.X(I), Y(1), YF(1)) 0077 D0 60 1=1.N 0076 ORINT 8. (I.X(I), YI), YF(1)) 0077 D0 60 1=1.N 0078 YSI(1)=YF(1) 0079 YSI(1)=YF(1) 0074 PRINT 2. (NAME) 0083 D0 40 .1=1.N 0084 PRINT 14. (I.Y(I),YSI(1),X(I),YSH(1),YPL(1)) 0083 D0 40 .1=1.N 0084 PRINT 14. (I.Y(I),YSI(1),X(I),YSH(1),YPL(1)) 0085 O 0.1=1.N 0086 ENDFILE 8. 0087 T FORMAT(/IX,*M = -(C16.6.)*N = -(C16.6./) 0088 IS FORMAT(/IX,*M = -(C16.6.)*N = -(C16.6./) 0089 PRINT 13. <td>0064 TEMP3K11 0065 50 YI1)=YK11 0066 90 YI1)=TEMP 0067 PRINT 2, (MAME) 0068 PRINT 35 0070 CALL DPLOF(X, Y, YF, W, E1, E2, P, WZ, N, W, NI, ND, EP, AUXST) 0071 CALL DPLOF(X, Y, YF, W, E1, E2, P, WZ, N, W, NI, ND, EP, AUXST) 0071 CALL DPLOF(X, Y, YF, W, E1, E2, P, WZ, N, W, NI, ND, EP, AUXST) 0072 SITE=PRINT 0075 PRINT 6, IE2(1), I=1, M) 0075 PRINT 6, IE2(1), I=1, M) 0076 OD I=1, N 0077 DD 60 I=1, N 0077 DD 60 I=1, N 0077 PRINT 8, IE2(1), Y(1), YF(1)) 0079 YST(1)=YF(1) 0079 YST(1)=YF(1) 0079 VST(1)=YF(1) 0080 60 COCMTINUE 0081 PRINT 1, K(1), YI(1), X(1), YSH(1), YPL(1) 0083 DD 40 I=1, N 0083 DD 40 I=1, N 0084 VRITE(0, 22) Y(11, YST(1), X(1), YSH(1), YPL(1) 0084 VRITE(0, 22) Y(11, YST(1), X(1), YSH(1), YPL(1) 0085 DD 40 I=1, N 0083 DD 40 I=1, N 0084 IF EMPANT 2, (NAME) 0085 IF EMPANT 4, I, I, YSI(1), X(1), YSH(1), YPL(1) 0086 IF EMPANT 4, I, I, YSI(1), X(1), YSH(1), YPL(1) 0086 IF EMPANT 4, I, YSI(1), X(1), YSH(1), YPL(1) 0085 IF EMPANT 4, I, Y, H = ', GL6, 6, 'N = ', GL6, 6, 'I 0080 IF EMPANT 4, I, Y, H = ', GL6, 6, 'N = ', GL6, 6, 'I 0081 IF EMPANT 4, I, Y, H = ', GL6, 6, 'N = ', GL6, 6, 'I 0082 IF EMPANT 1, Y, H = ', GL6, 6, 'N = ', GL6, 6, 'I 0083 IF EMPANT 1, I, YH = ', GL6, 6, 'N = ', GL6, 6, 'I 0090 PRINT 11, 'IS (STA, STC) 0093 PRINT 11, S(FL, S, YAA, SHB, SHC, NAME, PLM, PLN, STA, STC) 0095 PRINT 1, S(STA, SHC, SHC, NAME, PLM, PLN, STA, STC) 0097 20 PRINT 9 0097 20 CONTINUE 0101 END 0101 END 0104 END</td> <td>0063</td> <td></td> <td>00 50 I=1,N</td> <td></td> <td></td>	0064 TEMP3K11 0065 50 YI1)=YK11 0066 90 YI1)=TEMP 0067 PRINT 2, (MAME) 0068 PRINT 35 0070 CALL DPLOF(X, Y, YF, W, E1, E2, P, WZ, N, W, NI, ND, EP, AUXST) 0071 CALL DPLOF(X, Y, YF, W, E1, E2, P, WZ, N, W, NI, ND, EP, AUXST) 0071 CALL DPLOF(X, Y, YF, W, E1, E2, P, WZ, N, W, NI, ND, EP, AUXST) 0072 SITE=PRINT 0075 PRINT 6, IE2(1), I=1, M) 0075 PRINT 6, IE2(1), I=1, M) 0076 OD I=1, N 0077 DD 60 I=1, N 0077 DD 60 I=1, N 0077 PRINT 8, IE2(1), Y(1), YF(1)) 0079 YST(1)=YF(1) 0079 YST(1)=YF(1) 0079 VST(1)=YF(1) 0080 60 COCMTINUE 0081 PRINT 1, K(1), YI(1), X(1), YSH(1), YPL(1) 0083 DD 40 I=1, N 0083 DD 40 I=1, N 0084 VRITE(0, 22) Y(11, YST(1), X(1), YSH(1), YPL(1) 0084 VRITE(0, 22) Y(11, YST(1), X(1), YSH(1), YPL(1) 0085 DD 40 I=1, N 0083 DD 40 I=1, N 0084 IF EMPANT 2, (NAME) 0085 IF EMPANT 4, I, I, YSI(1), X(1), YSH(1), YPL(1) 0086 IF EMPANT 4, I, I, YSI(1), X(1), YSH(1), YPL(1) 0086 IF EMPANT 4, I, YSI(1), X(1), YSH(1), YPL(1) 0085 IF EMPANT 4, I, Y, H = ', GL6, 6, 'N = ', GL6, 6, 'I 0080 IF EMPANT 4, I, Y, H = ', GL6, 6, 'N = ', GL6, 6, 'I 0081 IF EMPANT 4, I, Y, H = ', GL6, 6, 'N = ', GL6, 6, 'I 0082 IF EMPANT 1, Y, H = ', GL6, 6, 'N = ', GL6, 6, 'I 0083 IF EMPANT 1, I, YH = ', GL6, 6, 'N = ', GL6, 6, 'I 0090 PRINT 11, 'IS (STA, STC) 0093 PRINT 11, S(FL, S, YAA, SHB, SHC, NAME, PLM, PLN, STA, STC) 0095 PRINT 1, S(STA, SHC, SHC, NAME, PLM, PLN, STA, STC) 0097 20 PRINT 9 0097 20 CONTINUE 0101 END 0101 END 0104 END	0063		00 50 I=1,N		
0065 50 Y(1)=TEMP 0066 PRINT 2.(MAME) 0068 PRINT 15 0068 PRINT 15 0070 P(2)=1. 0071 CALL DPLQF(X, Y, YF.W.E1,E2,P.WZ,N.M.NI.ND.EP.AUXST) 0072 STC=PP(2) 0073 STC=PP(2) 0074 PRINT 6.(E2(1),1=1,H) 0075 PRINT 6.(E2(1),YT(1),YT(1)) 0076 PRINT 6.(E2(1),YT(1),YT(1)) 0077 D0 60 T=1.N 0078 PRINT 6.(E2(1),YT(1),YT(1)) 0079 YST(1)=YF(1) 0079 YST(1)=YF(1) 0079 YST(1)=YF(1) 0071 D0 60 T=1.N 0083 D0 40 1=1.N 0083 D0 40 -1.1 0084 WRITE(6,22) Y(1),YST(1),X(1),YSH(1),YPL(1)) 0085 D0 40 -1.1 0086 FRINT 14.(1,Y(1),YST(1),YSH(1),YPL(1)) 0087 D0 A0 -1.1 0088 D0 FORMAT//1X.*M = -(616.6,N = -(616.6/1) 0089 PRINT 14.(1,YA,*M = -(616.6,N = -(616.6/1) 0090 PRINT 19.(FLN=NEND 00902 PRINT 10.(FLN=NEND	0065 X(1)=T(1) 0066 50 Y(1)=T(2) 0068 PRINT 2. (NAME) 0068 PRINT 2. (NAME) 0068 PRINT 2. (NAME) 0070 P(2)=1. 0071 CALL DP LOF(X,Y,YF,W,E1,E2,P,WZ,N,W,NI,ND,EP,AUXST) 0072 STA-P(1) 0073 STA-P(1) 0074 PRINT 5. (F2(1),1=1, M) 0075 PRINT 6. (F2(1),Y(1),YF(1)) 0076 PRINT 7. (NO 60 T=1,N) 0077 D0 60 T=1,N 0078 PRINT 8. (F1,X(1),Y(1),YF(1)) 0079 YST(1)=YF(1) 0070 G0 60 0074 PRINT 2. (NAME) 0083 D0 40.1=1,N 0084 PRINT 14. (T,Y(1)=YST(1	0064		TEMP=X(I)		
0066 50 YIIJ=1EMP 0067 PFINT 2.(NAME) 0068 PRINT 15 0066 PRINT 15 0071 CALL OPLOF(X,Y,YF,W,EI,E2,P,WZ,N,M,NI,ND,EP,AUXST) 0072 SIC=11 0073 SC=11 0074 PRINT 5. 0075 PRINT 4.(E211,1=1,M) 0076 PRINT 5. 0077 D0 60 I=1,N 0078 PRINT 8.(I.X(I),Y(I),YF(I)) 0079 YSI(I)=YF(I) 0074 CONTINUE 0083 D0 40.1=1,N 0084 PRINT 2.(NAME) 0083 D0 40.1=1,N 0084 PRINT 14.(I,YII),YSI(I),YKI(I),YPL(I) 0085 D0 40.1=1,N 0086 PRINT 14.(I,YII),YSI(I),YPL(I) 0087 D0 40.1=1,N 0088 D0 40.1=1,N 0084 PRINT 2.(NAME) 0085 D0 40.1=1,N 0086 PRINT 14.(I,YII),YSI(I),YKI(I),YPL(I) 0081 PROPRILE 8. 0082 PRINT 14.(I,Y,YII),YSI(I),YLI(I),YPL(I) 00818 IS FORMAT(I/X,YA = *,GI6.6.6,YC = *,GI6.6/J	0065 50 YIIJALEMP 0067 PFINT 2. (NAME) 0068 PRINT 15 0076 PI2J=1. 0071 CALL OPUOF(X,Y,YF,W,E1,E2,P,WZ,N,M,NI,ND,EP,AUXST) 0073 STC=P[2] 2 0074 PFINT 5.(E2(1),1=1,M) 0076 PRINT 5.(E2(1),1=1,M) 0076 PRINT 4.(I,Y(I),YF(I)) 0070 0.00 1=1,N 0077 D0 60 1=1,N 0078 PRINT 2.(I,X(I),Y(I),YF(I)) 0079 VSI(I)=YF(I) 0080 60 CGNTINUE 0081 D0 40 1=1,N 0083 D0 40 1=1,N 0084 WRITE(8,22) Y(I),YSI(I),X(I),YSH(I),YPL(I) 0086 PRINT 13. 0085 10 FORMAT(1), *A =:C16.6, *B =:,616.6,*C =:,C16.6,*) 0088 18 FORMAT(1), *A =:,C16.6, *B =:,C16.6,*) 0088 18 FORMAT(1), *A =:,C16.6, *B =:,C16.6,*) 0088 18 FORMAT(1), *A =:,C16.6,*C =:,C16.6,*) 0088 18 FORMAT(1), *A =:,C16.6,*C =:,C16.6,*) 0089 19 FORMAT(1), *A =:,C16.6,*C =:,C16.6,*) 0090 PRINT 11. 0091 PRINT 12. 0092 PRINT 12. 0093 PRINT 11. 0093 PRINT 11. 0094 PRINT 12. 0095 PRINT 11. 0095 PRINT 11. 0095 PRINT 12. 0095 PRINT 15. 0095 PRINT 15. 00	0065		X(1) = Y(1)		
0001 Print 15 0066 Print 15 0070 P(1)=1:=.E=6 0071 CALL OPLOF(X,Y,YF,W,E1,E2,P,WZ,N,M,NI,ND,EP,AUXST) 0071 CALL OPLOF(X,Y,YF,W,E1,E2,P,WZ,N,M,NI,ND,EP,AUXST) 0073 STC=P(2) 0074 PRINT 6,fE2(1),1=1,M) 0075 PRINT 6,fE2(1),1=1,M) 0076 PRINT 6,fE2(1),Y(1),YF(1)) 0077 CO Go I =1,N 0077 CO Go I =1,N 0078 PRINT 2,(NAME) 0088 GO 40 0084 PAINT 2,(NAME) 0085 GO 40 0086 O 40 0087 PRINT 14,(1,YI),YST(1),X(1),YSH(1),YPL(1) 0088 GO 40 0089 PRINT 14,(1,YI),YSH(1),YSH(1),YPL(1) 0080 GO 40 0081 PRINT 14,(1,YI,YI),YSH(1),YSH(1),YPL(1) 0082 PRINT 14,(1,YI,YI),YSH(1),YSH(1),YPL(1) 0083 GO 40 PRINT 14,(1,YI,YI),YSH(1),YSH(1),YPL(1) 0084 FORMAT(/1,XI,YI,YSH(1),YSH(1),YPL(1)) 0085 PRINT 14,(1,YI,YI,YSH(1),YSH(1),YPL(1)) 00960 PRINT 14,(1,YH(1),YSH(1),YSH(1),YSH(1),YPL(1)) </td <td>0051 FINT 15 0068 P(I) = 1.E-6 0071 C1.0 P1.0 P(X,Y,YF,N,E1,E2,P,WZ,N,M,NI,ND,EP,AUXST) 0071 C1.0 P1.0 P(X,Y,YF,N,E1,E2,P,WZ,N,M,NI,ND,EP,AUXST) 0071 C1.0 P1.0 P(X,Y,YF,N,E1,E2,P,WZ,N,M,NI,ND,EP,AUXST) 0073 S1C=P(12) 0074 PKINT 6. (E2(11),1=1,N) 0075 PKINT 6. (E2(11),YF(1)) 0076 PKINT 7. (INT) 0077 D0.001 F=1.N 0078 PKINT 2. (NAME) 0079 YSI(1)=YF(1) 0070 PRINT 2. (NAME) 0081 D0.40.1 F=1.N 0083 D0.40.1 F=1.N 0084 WRITE(6,22) Y(1),YSI(1),X(1),YSH(1),YPL(1) 0085 D0.40.1 F=1.N 0086 ENDFILE 8 0087 TORMATI/JX:YA = ".C16.6.6.YC =".C16.6.5/1 0088 18 FORMATI/JX:YA = ".C16.6.6.YC =".C16.6.5/1 0093 PRINT 11 PRINT 12. 0093 PRINT 13. PRINT 14. 0093 PRINT 11. PRINT 12. 0093 PRINT 11. PRINT 12. 0093 PRINT 13. PRINT 10. <</td> <td>0066</td> <td>50</td> <td></td> <td></td> <td></td>	0051 FINT 15 0068 P(I) = 1.E-6 0071 C1.0 P1.0 P(X,Y,YF,N,E1,E2,P,WZ,N,M,NI,ND,EP,AUXST) 0071 C1.0 P1.0 P(X,Y,YF,N,E1,E2,P,WZ,N,M,NI,ND,EP,AUXST) 0071 C1.0 P1.0 P(X,Y,YF,N,E1,E2,P,WZ,N,M,NI,ND,EP,AUXST) 0073 S1C=P(12) 0074 PKINT 6. (E2(11),1=1,N) 0075 PKINT 6. (E2(11),YF(1)) 0076 PKINT 7. (INT) 0077 D0.001 F=1.N 0078 PKINT 2. (NAME) 0079 YSI(1)=YF(1) 0070 PRINT 2. (NAME) 0081 D0.40.1 F=1.N 0083 D0.40.1 F=1.N 0084 WRITE(6,22) Y(1),YSI(1),X(1),YSH(1),YPL(1) 0085 D0.40.1 F=1.N 0086 ENDFILE 8 0087 TORMATI/JX:YA = ".C16.6.6.YC =".C16.6.5/1 0088 18 FORMATI/JX:YA = ".C16.6.6.YC =".C16.6.5/1 0093 PRINT 11 PRINT 12. 0093 PRINT 13. PRINT 14. 0093 PRINT 11. PRINT 12. 0093 PRINT 11. PRINT 12. 0093 PRINT 13. PRINT 10. <	0066	50			
0000 P(1)=3.E=6 0070 P(1)=3.E=6 0071 CALL DPLQF(X, Y, YF, W, E1, E2, P, WZ, N, M, NI, ND, EP, AUXST) 0073 SIC=P(2) 0074 PRINT 5, (E2(1), 1=1, M) 0075 PRINT 6, (E2(1), 1=1, M) 0076 PRINT 6, (E2(1), 1=1, M) 0077 D0 60 1=1, N 0078 PRINT 8, (I, X(I), Y(I), YF(I)) 0079 YST(I)=YF(I) 0080 60 0081 PRINT 2, (NAME) 0082 PRINT 13, (I, Y(I), YST(I), X(I), YSH(I), YPL(I)) 0083 D0 40 1=1.N 0084 WRITE(8,22) Y(I), YST(I), X(I), YSH(I), YPL(I)) 0085 D0 40 1=1.N 0086 ENDFILE 8 0087 T FORMATI/IX, YA = *, C16.6, *Y = *, C16.6, *Y = *, C16.6, *Y 0088 18 FORMATI/IX, *M = *, C16.6, *Y = *, C16.6, *J 0093 PRINT 11, CSTA, STC1 0093 PRINT 18, (PLM, PLN) 0094 PRINT 18, (PLM, PLN) 0095 PRINT 18, (PLM, PLN) 0096 PUNCH 21, (NAME, SHC, NAME, PLM, PLN, STA, STC1 0097 PRINT 19, (STA, SEC1) 0096 <td>C000 P(1)=::- C070 CALL D[LQF(X,Y,YF,W,E],E2,P,WZ,W,M,NI,ND,EP,AUXST) C072 S14=P(1) C073 S14=P(1) C074 PEINT 5 C075 PAINT 6, (E2(1),1=1,M) C076 PAINT 6, (E2(1),1=1,M) C077 D0 60 [=1,N C078 PAINT 6, (E2(1),Y(1),Y(1),Y(1)) C079 PAINT 8, (1,X(1),Y(1),Y(1),Y(1)) C070 C0 60 [=1,N C071 D0 60 [=1,N C073 PAINT 8, (1,X(1),Y(1),YF(1)) C074 PAINT 8, (1,X(1),Y(1),YF(1)) C075 PAINT 12, (NAME) C080 60 ComtNue C081 PAINT 12, (NAME) C082 PAINT 14 C083 40 PAINT 14 YST(1)+X(1),YST(1)+X(1)+YPL(1) C084 PENNT 14 C085 40 PAINT 14 YST(1)+X(1),YST(1)+X(1)+YPL(1) C085 40 PENNT 14 C086 FORMATI(1,Y+1)+X(1)+(S(1)+YPL(1)) C087 PENNT 15 C088 PENNT 14 C089 PENNT 12</td> <td>0067</td> <td></td> <td></td> <td></td> <td></td>	C000 P(1)=::- C070 CALL D[LQF(X,Y,YF,W,E],E2,P,WZ,W,M,NI,ND,EP,AUXST) C072 S14=P(1) C073 S14=P(1) C074 PEINT 5 C075 PAINT 6, (E2(1),1=1,M) C076 PAINT 6, (E2(1),1=1,M) C077 D0 60 [=1,N C078 PAINT 6, (E2(1),Y(1),Y(1),Y(1)) C079 PAINT 8, (1,X(1),Y(1),Y(1),Y(1)) C070 C0 60 [=1,N C071 D0 60 [=1,N C073 PAINT 8, (1,X(1),Y(1),YF(1)) C074 PAINT 8, (1,X(1),Y(1),YF(1)) C075 PAINT 12, (NAME) C080 60 ComtNue C081 PAINT 12, (NAME) C082 PAINT 14 C083 40 PAINT 14 YST(1)+X(1),YST(1)+X(1)+YPL(1) C084 PENNT 14 C085 40 PAINT 14 YST(1)+X(1),YST(1)+X(1)+YPL(1) C085 40 PENNT 14 C086 FORMATI(1,Y+1)+X(1)+(S(1)+YPL(1)) C087 PENNT 15 C088 PENNT 14 C089 PENNT 12	0067				
0070 P12=1. 0071 CALL DPLQF(X,Y,YF,W,E1,E2,P,WZ,N,M,NI,ND.EP,AUXST) 0073 SIC=P12) 0074 PRINT 5 0075 PRINT 6,(E2(1),1=1,M) 0076 PRINT 4 0077 OD 60 1=1,N 0078 PRINT 4,(1,X(1),Y(1),YF(1)) 0079 YST(1)=YF(1) 0070 CONTO 0080 OO CONTINUE 0081 PRINT 3,(1,X(1),YST(1),X(1),YPL(1)) 0082 PRINT 13 0083 DO 40.1=1.N 0084 WRITE(E2) Y(1).YST(1),X(1),YPL(1)) 0085 DO 40.1=1.N 0086 PRINT 14,(1,Y(1),YST(1),X(1),YPL(1)) 0087 PRINT 14,(1,Y(1),YST(1),X(1),YPL(1)) 0088 I8 919 PGRMATI/1X,*A = ',G16.6,'N = ',G16.6/1 0090 PRINT 11 0091 PRINT 11 0092 PRINT 13,(PLM,PLN) 0093 PRINT 14 0094 PRINT 15,(FLM,PLN) 0095 PRINT 16 0096 PUNCH 21,(NAME,SHD,SHC,NAME,PLM,PLN,STA,STC) 0097 PRINT 19,(STA,STC)	C000 C4LL OPLQF(X, Ý, YF, W, E1, E2, P, WZ, N. M. NI, ND, EP, AUXST) C071 C4LL OPLQF(X, Ý, YF, W, E1, E2, P, WZ, N. M. NI, ND, EP, AUXST) C073 STC=P(2) C074 PRINT 5 C075 PRINT 6, (E2(1), 1=1, M) C076 PRINT 4, (1, X(1), Y(1), YF(1)) C077 D0 60 1=1, N C078 PRINT 4, (1, X(1), Y(1), YF(1)) C079 YST(1)=YF(1) C081 PRINT 7, (NAME) C082 PRINT 13 C083 D0 40 1=1, N C084 WRITE(E4, 22) Y(1), YST(1), X(1), YSH(1), YPL(1) C085 40 C086 PRINT 14, (1, Y(1), YST(1), X(1), YSH(1), YPL(1)) C087 17 C088 19 C089 19 PRINT 14 C093 PRINT 16, (DL, MP, PLN) C094 PRINT 17, (SHA, SHB, SHC) C095 PRINT 18, (PLM, PLN) C096 PRINT 16, (SA, SHB, SHC) C097 21 FORMAT(9A, 35HL-5/9AA, 45HL-5) C096 PRINT 18, (PLM, PLN) C097 21 FORMAT(SA, 35HL-5/9AA, 45HL-5) <t< td=""><td>0000</td><td></td><td></td><td>· ·</td><td></td></t<>	0000			· ·	
COTI CALL OPLOF(X, Ý, YF, W, E1, E2, P, WZ, N, M, NT, ND, EP, AUXST) COTI STAP(1) COTI STAP(1) COTI STAP(1) COTI DO 60 1=1, M COTI DO 60 1=1, N COTI DO 60 1=1, N COTI PRINT 6, (12(1), Y(1), YF(1)) COTI PRINT 2, (1, X(1), Y(1), YF(1)) COTI PRINT 2, (NAME) COBI PRINT 1, (1, Y(1), YST(1), X(1), YSH(1), YPL(1)) COBI PRINT 14, (1, Y(1), YST(1), X(1), YSH(1), YPL(1)) COBI PRINT 17, (SHA, SHB, SHC) COBI PRINT 18, (PLM, PLN) COBI PRINT 19, (STA, STC) COBI PRINT 10, (STA, STC) COBI PR	0071 CALL DPLOF(X, Y, YF, W, E1, E2, P, WZ, N, W, NI, ND, EP, AUXST) 0072 STA=P(1) 0073 STC=P(2) 0074 PRINT 6,(E2(1),1=1, M) 0075 PRINT 6,(E2(1),Y(1),Y(1),Y(1)) 0076 PRINT 8,(I,X(1),Y(1),Y(1)) 0077 D0 60 1=1,N 0078 PRINT 8,(I,X(1),Y(1),Y(1)) 0079 YST(1)=YF(1) 0080 60 0081 PRINT 13 0083 D0 40 -1=1,N 0084 WRITE(8,22) Y(1),YST(1),X(1),YSH(1),YPL(1) 0085 D0 40 -1=1,N 0086 PRINT 13 0087 D0 40 -1=1,N 0088 BROFILE 8 0084 WRITE(8,22) Y(1),YST(1),X(1),YSH(1),YPL(1) 0085 PRINT 14,(1,Y,YN = *,G16.6,*C = *,G16.6/) 0086 18 FORMAT(/1X,*N = *,G16.6,*C = *,G16.6/) 0081 18 FORMAT(/1X,*N = *,G16.6,*C = *,G16.6/) 0092 PRINT 17,(SNA,SIB,SHC) Image: SNA,SHB,SHC) 0093 PRINT 18,(PU,M,PUM) Image: SNA,SHB,SHC) 0095 PRINT 19,(STA,STC) Image: SNA,SHB,SHC,NAME,PLM,PUN,STA,STC) 0095	0070				
C072 STA=P(1) C073 STC=P(2) C074 PRINT 5 C075 PRINT 6,(E2(1),1=1,M) C076 PRINT 4 C077 DD 60 1=1,N C078 PRINT 8,(1,X(1),Y(1),YF(1)) C079 VST(1)=YF(1) C079 VST(1)=YF(1) C088 60 CCNTINUE C081 PRINT 2,(NAME) C083 DD 40 1=1,N C083 DD 40 1=1,N C084 RHITE(6,22) Y(1),YST(1),X(1),YSH(1),YPL(1) C085 40 PRINT 14,(1,Y(1),YSH(1),YSH(1),YPL(1)) C086 ENDFILE 8 C087 17 FORMAT(1X,*A =*,C16.6,6,*B =*,C16.6,6') C088 18 FORMAT(1X,*A =*,C16.6,6,*C =*,C16.6,7) C088 19 FORMAT(1X,*A =*,C16.6,*C =*,C16.6,7) C089 19 FORMAT(1X,*A =*,C16.6,*C =*,C16.6,7) C090 PRINT 11 C090 PRINT 12 C092 PRINT 15,(PLM,PLN) C094 PRINT 15,(PLM,PLN) C095 PRINT 19,(STA,STC) C096 PRINT 9,(STA,STC) C097 CONTINUE C096 PRINT 9,(STA,STC) C097 CONTINUE C096 PRINT 9 C096 PRI	C072 STA=P(1) C073 STC=P(2) C074 PRINT 5 C075 PRINT 6, (E2(1),1=1,M) C076 PRINT 4 C077 D0 60 1=1,N C077 D0 60 1=1,N C079 YST(1)=YF(1) C079 CCNT1NUE C081 PRINT 2,(NAME) C082 PRINT 13 C083 D0 40 1=1,N C084 WRITE(8,22) Y(1),YST(1),X(1),YB(1),YPL(1) C085 40 PRINT 14,(1,Y(1),YST(1),X(1),YB(1),YPL(1) C086 ENDFILE 8 C087 17 FORMAT(/1X,'A =',C16.6,'B =',C16.6,'C =',C16.5/) C088 18 FCRMAT(/1X,'A =',C16.6,'C =',C16.6,'C =',C16.5/) C089 19 FORMAT(/1X,'A =',C16.6,'C =',C16.6,'C =',C16.5/) C089 19 FORMAT(/1X,'A =',C16.6,'C	0071		CALL OPLOF(X+Y+YF+W+E1+E2+P+WZ+N+M+NI+ND+EP+AUXST)		
0073 SIC=P(2) 0074 PRINT 5 0075 PRINT 6,(E2(I),I=1,M) 0076 PRINT 8,(I,X(I),Y(I),YF(I)) 0077 D0 60 I=1,N 0078 PRINT 8,(I,X(I),Y(I),YF(I)) 0079 YST(I)=YF(I) 0080 60 0081 PRINT 12,(NAME) 0083 D0 40.1=1.N 0084 WRITE(8,22) Y(I),YST(I),X(I),YSH(I),YPL(I) 0083 D0 40.1=1.N 0084 WRITE(8,22) Y(I),YST(I),X(I),YSH(I),YPL(I) 0085 D0 40.1=1.N 0084 WRITE(8,22) Y(I),YST(I),X(I),YSH(I),YPL(I) 0085 PRINT 13, (I),YST(I),YSH(I),YPL(I) 0086 ENDFILE 8 0087 I7 FORMAT(/IX,'M =',GL6.6,'N =',GL6.6,'C =',GL6.5/) 0088 I8 FORMAT(/IX,'M =',GL6.6,'N =',GL6.6,'C =',GL6.5/) 0089 I9 FORMAT(/IX,'M =',GL6.6,'N =',GL6.6,'I 0091 PRINT 11 0092 PRINT 12 0093 PRINT 14,(ISA,SEL) 0094 PRINT 15,(STA,STC) 0095 PRINT 9 0096 PRINT 9 0097 PRINT 9	0073 STC=P(2) 0074 PRINT 5 0075 PRINT 6,(E2(1),1=1,M) 0076 PRINT 6,(E2(1),Y(1),YF(1)) 0077 D0 60 1=1,N 0078 PRINT 8,(1,X(1),Y(1),YF(1)) 0079 YST(1)=XF(1) 0070 PSINT 8,(1,X(1),YF(1),YF(1)) 0071 D0 60 1=1,N 0080 60 CONTINUE 0081 D 40.1=1,N 0082 PRINT 13 0083 D0 40.1=1,N 0084 WRITE(8,22) Y(1),YST(1),X(1),YPL(1) 0085 10 40.1=1,N 0086 EMDFILE 8 0087 17 FORMAT(/1X,'M =+',G16.6,'N =+',G16.6,'C = ',G16.5/) 0088 18 FORMAT(/1X,'M =+',G16.6,'N =+',G16.6,') 0083 19 FORMAT(/1X,'M =+',G16.6,'C =+',G16.6/) 0093 PRINT 11 0094 PRINT 11 0095 PRINT 12 0096 PNINT 13 0097 PRINT 14, FM =+',G16.6, NAME,PLM,PLN,STA,STC) 0097 PRINT 15 0097 PRINT 16, FM,SHA,SHB,SHC) 0097 PRINT 16, FM,SHA,SHB,SHC,MAME,PLM,STA,STC,	072		STA=P(1)	×	
0074 PRINT 5 0075 PRINT 6, (E2(1), I=1, M) 0076 PRINT 4 0077 D0 60 I=1,N 0078 PRINT 8, (1,X(I),Y(I),YF(I)) 0079 YS1(I)=YF(I) 0080 60 CCNTINUE 0081 PRINT 2, (NAME) 0082 PRINT 13 0083 D0 40 I=1,N 0084 WRITE(18,22) Y(I),YST(I),X(I),YSH(I),YPL(I) 0085 D0 40 I=1,N 0086 ENDFILE 8 0087 17 0088 18 0089 19 0081 PRINT 17, (SHA,SHB,SHC) 0082 PRINT 12, (SHA,SHB,SHC) 0093 PRINT 13, (SIA,STC) 0094 PRINT 14, (I,PLN) 0095 PRINT 16, (PLN,PLN) 0096 PRINT 17, (SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 PRINT 18, (PLN,PLN) 0096 PRINT 19, (STA,STC) 0097 PRINT 16, (PLN,PLN) 0096 PRINT 9, (STA,STC) 0097 PRINT 9, (STA,STC) 0096 PRINT 9, (STA,STC) 0097	0074 PRINT 5 0075 PRINT 6, (E2(1),1=1,M) 0076 PRINT 4 0077 D0 60 1=1,N 0078 PRINT 8,(1,X(1),Y(1),YF(1)) 0079 YST(1)=YF(1) 0080 60 0081 PRINT 2,(NAME) 0083 D0 40.1=1,N 0084 WRITET(8,22) Y(1),YST(1),X(1),YSH(1),YPL(1) 0085 40 0086 ENDFILE 8 0087 17 0088 18 0089 19 0090 PRINT 11 0091 PRINT 12,(NA,SHB,SHC) 0092 PRINT 12, 0093 PRINT 15,(DK,PLM,PLN) 0094 PRINT 15,(DK,PLM,PLN,STA,STC) 0095 PRINT 19,(STA,STC) 0096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 PRINT 15,(DP 0096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 PRINT 19,(STA,STC) 0096 PUNCH 21,	0073	•	STC = P(2)		
0075 PRINT 6, (E2(1), I=1, M) 0077 D0 60 I=1,N 0078 PRINT 8, (I,X(I),Y(I),YF(I)) 0079 YST(I)=YF(I) 0080 60 0081 PRINT 2, (MAME) 0082 PRINT 13 0083 D0 40 I=1,N 0084 WRITE(8,22) Y(I),YST(I),X(I),YSH(I),YPL(I) 0085 D0 40 I=1,N 0086 PRINT 14, (I,Y(I),YST(I),X(I),YSH(I),YPL(I)) 0086 ENDFILE 8 0086 ENDFILE 8 0087 17 0088 18 FORMATI/IX, *A =*, G16.6, *C =*, G16.6/1 0088 18 0090 PRINT 17 0091 PRINT 17, (SHA,SHB,SHC) 0092 PRINT 12 0093 PRINT 19, (STA,STC) 0095 PRINT 19, (STA,STC) 0095 PRINT 19, (STA,STC) 0095 PRINT 4 0096 PRINT 19, (STA,STC) 0095 PRINT 9 0095 PRINT 9 0096 PRINT 9 0097 20 CONT INUE 0096 PRINT 19	0075 PRINT 6, (E2(1),1=1,M) 0076 PRINT 4 0077 D0 60 1=1,N 0078 PRINT 8,(1,X(1),Y(1),YF(1)) 0079 YST(1)=YF(1) 0080 60 CCNTINUE 0081 D 40.1=1,N 0082 PRINT 12,(NAME) 0083 D 0 40.1=1,N 0084 WRITE(8,22) Y(1),YST(1),X(1),YSH(1),YPL(1) 0085 D 0 40.1=1,N 0086 ENDFILE 8 0087 17 FORMAT(/1X,*A =*,616.6,*B =*,616.6,*C =*,616.6/) 0086 ENDFILE 8 0087 17 FORMAT(/1X,*A =*,616.6,*N =*,616.6/) 0088 18 FORMAT(/1X,*A =*,616.6,*C =*,616.6/) 0090 PRINT 11 0091 PRINT 12,(PLM,PLN) 0092 PRINT 18,(PLM,PLN) 0093 PRINT 18,(PLM,PLN) 0094 PRINT 15 0095 PRINT 15 0096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 PLINT 19,(STA,STC) 0098 PRINT 10,(DM,A;SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 PRINT 11 0098 PRINT 10,(DM,A;SHA,SHB	. 0074		PRINT 5		
0076 PRINT 4 0077 D0 60 I=1,N 0078 PRINT 8,(I,X(I),Y(I),YF(I)) 0079 YST(I)=YF(I) 0080 60 0081 PRINT 2,(NAME) 0083 D0 40 - I=1,N 0083 D0 40 - I=1,N 0084 WRITE(8,22) Y(I),YST(I),X(I),YPL(I) 0085 40 0086 ENDFILE 8 0087 17 0088 18 0088 18 0089 19 0084 YEINT 11 0088 18 0088 18 0090 PRINT 11 0091 PRINT 11 0092 PRINT 11 0093 PRINT 11 0094 PRINT 12 0095 PRINT 13, (PLM,PLN) 0096 PUNCH 21, (NAME, SHA, SHB, SHC, NAME, PLM, PLN, STA, STC) 0097 21 FORMAT(9A4, 3E11.5/944, 4E11.5) 0095 PRINT 19, (STA, STC) 0096 PUNCH 21, (NAME, SHA, SHB, SHC, NAME, PLM, PLN, STA, STC) 0097 21 0088	0076 PRINT 4 0077 D0 6 0 [-1, N 0078 PRINT 8, (1, X(1), Y(1), YF(1)) 0079 YSI(1)=YF(1) 0080 60 CO81 PRINT 2, (NAME) C082 PRINT 13 0083 D0 40 [=1, N C084 WRITE(8,22) Y(1),YSI(1),X(1),YSH(1),YPL(1) C085 40 PRINT 14, (1, Y(1),YSI(1),X(1),YSH(1),YPL(1)) 0086 ENDFILE 8 0087 17 FORMAT(/1X, *A =*, c16.6, *C =*, c16.6	0075		PRINT 6,(E2(I),1=1,M)		
0077 00 60 1=1.N 0078 PRINT 8.(1,X(1),Y(1),YF(1)) 0079 YST(1)=YF(1) 0080 60 CCNTINUE 0081 PRINT 2.(NAME) 0082 PRINT 13 0083 D0 40.1=1.N 0084 WRITE(8,22) Y(1),YST(1),X(1),YSH(1),YPL(1) 0085 D0 40.1=1.N 0086 ENDFILE 8 0087 17 FORMAT(/1X,*A =*,C16.6,*B =*,616.6,*C =*,616.5/) 0088 18 FORMAT(/1X,*A =*,C16.6,*C =*,616.6/) 0089 19 PRINT 11 0091 PRINT 12 0092 PRINT 13, (PLM,PLN) 0093 PRINT 12 0094 PRINT 15, (PLM,PLN) 0095 PRINT 19, (STA,STC) 0096 PUNCH 21, (NAME, SHA, SHB, SHC, NAME,PLM,PLN,STA,STC) 0097 21 0098 PRINT 19 0095 PRINT 19 0096 PUNCH 21, (NAME, SHA, SHB, SHC, NAME,PLM,PLN,STA,STC) 0097 21 0098 PRINT 19 0097 21 0088 <	0077 00 60 1=1,N 0079 PRINT 8,(I,X(I),Y(I),YF(I)) 0079 YST(I)=YF(I) 0080 60 CCNTINUE 0081 PRINT 2,(NAME) 0082 PRINT 13 0083 D0 40.1=1,N 0084 WRITE(8,22) Y(I),YST(I),X(I),YSH(I),YPL(I) 0085 40 0086 PRINT 14,(I,Y(I),YST(I),X(I),YSH(I),YPL(I)) 0086 ENDFILE 8 0087 17 0088 18 0089 19 0081 16 0090 PRINT 11 0091 PRINT 12,(SHA,SHB,SHC) 0092 PRINT 12,(STA,STC) 0093 PRINT 19,(STA,STC) 0094 PRINT 19,(STA,STC) 0095 PRINT 19,(STA,STC) 0096 PRINT 19,(STA,STC) 0097 21 0098 PRINT 19,(STA,STC) 0096 PRINT 19,(STA,STC) 0097 21 0096 PRINT 19,(STA,STC) 0097 21 0097 21 0097 PRINT	0076		PRINT 4		
C073 PRINT 8,(1,Y(1),Y(1),Y(1)),Y(1)) C079 YST(1)=YF(1) C080 60 CCNTINUE C081 PRINT 2,(NAME) C082 PRINT 13 C083 D0 40 1=1,N C084 WRITE(8,22) Y(1),YST(1),X(1),YSH(1),YPL(1) C085 40 C086 PRINT 14,(1,Y(1),YST(1),X(1),YSH(1),YPL(1)) C087 17 FORMAT(/1X,*A =*,G16.6,*B =*,G16.6,*C =*,G16.5/) C088 18 FORMAT(/1X,*M =*,G16.6,*C =*,G16.6/) C089 19 OPRINT 11 C090 PRINT 12,(SHA,SHB,SHC) C091 PRINT 12, C092 PRINT 12, C093 PRINT 18, (PLM,PLN) C094 PRINT 18, C095 PRINT 19,(STA,STC) C096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) C097 21 C098 PRINT 9 C097 21 C096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) C097 21 C098 PRINT 9 C099 200 <	0073 PRINT 8,(1,X(1),YF(1),YF(1)) 0079 YST(1)=YF(1) 0080 60 CCNTINUE 0081 PRINT 2,(NAME) 0082 PRINT 13 0083 D0 40 1=1,N 0084 WRITE(8,22) Y(1),YST(1),X(1),YSH(1),YPL(1) 0085 40 PRINT 14,(1,Y(1),YST(1),YSH(1),YPL(1)) 0086 ENDFILE 8 ENDFILE 8 0087 17 FORMAT(/1X,'M =',G16.6,'N =',G16.6/) 0088 18 FORMAT(/1X,'M =',G16.6,'N =',G16.6/) 0089 19 FORMAT(/1X,'M =',G16.6,'C =',G16.6/) 0090 PRINT 11 0091 PRINT 12 0092 PRINT 12 0093 PRINT 18, (PLM,PLN) 0094 PRINT 19, (STA,STC) 0095 PRINT 19, (STA,STC) 0096 PUNCH 21, NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 0098 PRINT 19, 0097 21 0098 PRINT 19 0097 21 0096 PRINT 19 0097 21 008 PRINT 19 <td>0077</td> <td></td> <td>DD 60 I=1,N</td> <td></td> <td></td>	0077		DD 60 I=1,N		
C079 VS1(1)=VF(1) C080 60 CCNTINUE C081 PRINT 2,(NAME) C082 PRINT 13 C083 D0 40.1=1,N C084 WRITE(8,22) Y(1),YST(1),X(1),YSH(1),YPL(1) C084 WRITE(8,22) Y(1),YST(1),X(1),YSH(1),YPL(1) C085 O PRINT 14,(1,YI1),YSH(1),YSH(1),YSH(1),YPL(1) C086 ENDFILE 8 C087 17 FORMAT(/1X, 'M =',G16.6,'S = ',G16.6,'C =',G16.6/) 0088 18 FORMAT(/1X, 'M =',G16.6, 'C =',G16.6/) 0089 19 FORMAT(/1X, 'A =',G16.6, 'C =',G16.6/) 0090 PRINT 11 C091 PRINT 17,(SHA,SHB,SHC) 0092 PRINT 18, (PLM,PLN) 0093 PRINT 15 0094 PRINT 15 0095 PRINT 15 0096 PUNCH 21, (NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 0088 PRINT 4 0097 21 0084 PRINT 5 0097 21 0084 PRINT 4 0097 PRINT 4	C079 VST(1)=V(1) C080 60 CCNTINUE C081 PRINT 2, (NAME) C082 PRINT 13 0083 D0 40.1=1,N C084 WRITE(8,22) Y(1),YST(1),X(1),YPL(1) C085 40 PRINT 14,(I,Y(1),YST(1),X(1),YPL(1)) C086 ENDFLE 8 C087 17 FORMAT(/1X, *A =*, G16.6, *B =*, G16.6/) 0088 18 FORMAT(/1X, *A =*, G16.6, *C =*, G16.6/) 0088 18 FORMAT(/1X, *A =*, G16.6, *C =*, G16.6/) 0090 PRINT 11 0091 PRINT 12, (STA, SHB, SHC) 0092 PRINT 18, (PLM, PLN) 0093 PRINT 19, (STA, STC) 0094 PRINT 19, (STA, STC) 0095 PRINT 19, (STA, STC) 0096 PUNCH 21, (NAME, SHB, SHC, NAME, PLM, PLN, STA, STC) 0097 21 FORMAT(9A, SE11.5) 0096 PRINT 9 0097 21 FORMAT(9A, SE11.5) 0098 PRINT 9 0101 END 0101 END	0079		PRINT 8,(I,X(I),Y(I),YF(I))	•	
0080 60 CENTINCE 0081 PRINT 2; (NAME) 0082 PRINT 13 0083 D0 40 1=1,N C084 HRITE(8,22) Y(1),YST(1),X(1),YSH(1),YPL(1) 0085 ENDFILE C087 17 FDRMAT(/1X,*A =',G16.6,*B =',G16.6,*C =',G16.6/) 0088 18 FORMAT(/1X,*M =',G16.6,*C =',G16.6/) 0088 18 FORMAT(/1X,*A =',G16.6,*C =',G16.6/) 0089 19 FORMAT(/1X,*A =',G16.6,*C =',G16.6/) 0090 PRINT 11 0091 PRINT 12 0092 PRINT 15 0093 PRINT 15, (PLM,PLN) 0094 PRINT 15, (STA,STC) 0095 PRINT 10, (STA,STC) 0096 PUNCH 21, (NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0096 PUNCH 21, (NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 0088 PRINT 9 0101 END	0080 60 CENTINUE 0081 PRINT 13 0082 PRINT 13 0083 D0 40 1=1,N 0084 HRITE(8,22) Y(I),YST(I),X(I),YSH(I),YPL(I) 0085 40 0086 ENDFLEE 8 0087 17 0088 18 0089 19 0080 17 0081 18 0082 PRNAT(/1X,*A =*,616.6,*C =*,616.6/) 0083 18 0084 18 0085 19 0086 18 0087 17 0088 18 0090 PRINT 11 0091 PRINT 14,*A =*,616.6,*C =*,616.6/) 0092 PRINT 17.(SHA,SHB,SHC) 0093 PRINT 18, (PLM,PLN) 0094 PRINT 19, (STA,STC) 0095 PRINT 19, (STA,STC) 0096 PUNCH 21, (NAME, SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 FORMAT(9A,43E11.5) 0098 200 CONT INUE 0100 111 STOP <td< td=""><td>0079</td><td></td><td>YS1(1)=YF(1)</td><td></td><td></td></td<>	0079		YS1(1)=YF(1)		
C081 PRINT 13 0083 D0 40.1=1.N C084 WRITE(8,22) Y(1),YST(1),Y(1),YPL(1) C085 40 C086 ENDFILE 8 C087 17 FORMAT(/1X,'A =',G16.6,'B =',G16.6,'C =',G16.5/) 0088 18 FORMAT(/1X,'A =',G16.6,'C =',G16.6/) 0089 19 FORMAT(/1X,'A =',G16.6,'C =',G16.6/) 0090 PRINT 11 0091 PRINT 12 0092 PRINT 18, (PLM,PLN) C094 PRINT 18, (PLM,PLN) C095 PRINT 19, (STA,STC) 0096 PUNCH 21, (NAME, SHA, SHB, SHC, NAME,PLM,PLN, STA, STC) 0097 C097 21 FORMAT(9A4,3E11.5/9A4,4E11.5) C097 200 C011 END C102 11 STOP END	C031 PRINT 13 0083 D0 40.1=1,N C084 WRITE(8,22) Y(I),YST(I),X(I),YSH(I),YPL(I) C085 40 C086 ENDFILE 8 C087 17 FORMAT(/1X,*A =*,G16.6,*D =*,G16.6,'C =*,G16.6/) 0088 18 FORMAT(/1X,*A =*,G16.6,*C =*,G16.6/) 0089 19 FORMAT(/1X,*A =*,G16.6,*C =*,G16.6/) 0089 19 FORMAT(/1X,*A =*,G16.6,*C =*,G16.6/) 0090 PRINT 11 0091 PRINT 12,(S1A,SHB,SHC) 0092 PRINT 18,(PLM,PLN) 0093 PRINT 15 0094 PRINT 15, 0095 PRINT 16,(STA,STC) 0096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 0087 21 0087 PRINT 9 0098 PRINT 9 0099 200 CONTINUE 0101 END	0080	60			
0083 D0 40 1=1,N 0084 WRITE(8,22) Y(1),YST(1),X(1),YSH(1),YPL(1) 0085 40 PRINT 14,(I,Y(1),YST(1),X(1),YSH(1),YPL(1)) 0086 ENDFLEE 8 0087 17 FORMAT(/1X,*A =*,G16.6,*B =*,G16.6,*C =*,G16.5/) 0088 18 FORMAT(/1X,*A =*,G16.6,*C =*,G16.6/) 0089 19 FORMAT(/1X,*A =*,G16.6,*C =*,G16.6/) 0090 PRINT 11 0091 PRINT 12 0092 PRINT 18,(PLM,PLN) 0093 PRINT 19,(STA,STC) 0094 PRINT 19,(STA,STC) 0095 PNINT 19,(STA,STC) 0096 PRINT 15 0097 21 FORMAT(9A4,3E11.5/9A4,4E11.5) 0098 PRINT 9 0100 END	0002 D0 40 1=1.N 0003 D0 40 1=1.N 0084 WRITE(8,22) Y(1),YST(1),X(1),YSH(1),YPL(1) 0086 ENDFILE 8 0087 17 FORMATI/1X,'M =',G16.6,'C =',G16.5/) 0088 18 FORMATI/1X,'M =',G16.6,'C =',G16.6/1 0089 19 FORMATI/1X,'M =',G16.6,'C =',G16.6/1 0090 PRINT 17.(SHA,SHB,SHC) 0092 PRINT 12,(STA,SHB,SHC) 0093 PRINT 18,(PLM,PLN) 0094 PRINT 19,(STA,STC) 0095 PRINT 19,(STA,SHC,NAME,PLM,PLN,STA,STC) 0096 PUNCH 21, (NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 FORMAT(9A4,3E11.5/9A4,4E11.5) 0100 111 STOP 0101 END 11 STOP 0101 END	0081		PRINT 2 (INAME)		
0003 WRITE(B,22) Y(I),YST(I),X(I),YSH(I),YPL(I) 0035 40 PRINT 14,(I,Y(I),YST(I),X(I),YSH(I),YPL(I)) 0036 ENDFILE 8 0037 17 FORMAT(/IX,'A =',GI6.6,'B =*,GI6.6,'C =',GI6.5/) 0088 18 FORMAT(/IX,'A =',GI6.6,'N =',GI6.6/) 0039 19 FORMAT(/IX,'A =',GI6.6,'C =',GI6.6/) 0090 PRINT 11 0091 PRINT 17,(SHA,SHB,SHC) 0092 PRINT 18,(PLM,PLN) 0093 PRINT 18,(PLM,PLN) 0094 PRINT 15 0095 PRINT 19,(STA,STC) 0096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 0098 PRINT 19,(STA,STC) 0097 21 0098 PRINT 19,(STA,STC) 0097 21 0098 PRINT 19,(STA,STC) 0099 200 0091 PRINT 18, (PLM,PLN,STA,STC) 0095 PRINT 19,(STA,STC) 0096 PRINT 19,(STA,STC) 0097 21 008 PRINT 19 0099 200 0001 E	C0034 WRITE(8,22) Y(I),YST(I),X(I),YSH(I),YPL(I) C035 40 PRINT 14,(I,YII),YST(I),X(I),YSH(I),YPL(I)) C036 ENDFILE 8 C037 17 FORMAT(/IX,'A =',G16.6,'B =',G16.6,'C =',G16.5/) 0088 18 FORMAT(/IX,'A =',G16.6,'B =',G16.6/) 0090 PRINT (11,Y,'A =',G16.6,'C =',G16.6/) 0090 PRINT 11 0091 PRINT 17,(SHA,SHB,SHC) 0092 PRINT 12 0093 PRINT 19,(STA,STC) 0094 PRINT 19,(STA,STC) 0095 PRINT 19,(STA,STC) 0096 PUNCH 21, (NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 FORMAT(9A4,3E11.5/9A4,4E11.5) 0098 PRINT 9 0099 200 CONTINUE 0101 END 11 STOP 0101 END	0083	*			
COB5 40 PRINT 14, (I, Y(I), YST(I), X(I), YSH(I), YPL(I)) OO86 ENDFILE 8 COB7 17 FORMAT(/1X, *A =*, G16.6, *B =*, G16.6, *C =*, G16.5/) OO88 18 FORMAT(/1X, *A =*, G16.6, *C =*, G16.6/) OC89 19 FORMAT(/1X, *A =*, G16.6, *C =*, G16.6/) OC90 PRINT 11 CO91 PRINT 17, (SHA, SHB, SHC) OC92 PRINT 12 OO93 PRINT 15, (PLM, PLN) OO94 PRINT 15, (PLM, PLN) OO95 PRINT 19, (STA, STC) OO96 PUNCH 21, (NAME, SHA, SHB, SHC, NAME, PLM, PLN, STA, STC) OC97 21 FORMAT(9A4, 3E11.5 / 9A4, 4E11.5) OC98 PR INT 9 OC99 200 CONT INUE O101 END	C035 40 PRINT 14,(I,V(I),VST(I),X(I),YPL(I)) 0086 ENDFILE 8 C087 17 FORMATI/1X,*M = *,G16.6,*B = *,G16.6,*C = *,G16.6/1 0088 18 FORMATI/1X,*M = *,G16.6,*C = *,G16.6/1 0089 19 FORMAT(/1X,*A = *,G16.6,*C = *,G16.6/1 0090 PRINT 11 0091 PRINT 11,r,(SHA,SHB,SHC) 0092 PRINT 12, 0093 PRINT 18,(PLM,PLN) C094 PRINT 19,(STA,STC) 0095 PRINT 19,(STA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 FORMAT(9A4,3E11.5/9A4,4E11.5) 0098 PRINT 19 0101 END 11 STOP 0101 END	0084		WRITE (8.22) Y(1), YST(1), X(1), YSH(1), YPL(1)		
0086 ENDFILE 8 C087 17 FORMAT(/1X,*A =*,G16.6,*B =*,G16.6,*C =*,G16.5/) 0088 18 FORMAT(/1X,*M =*,G16.6,*C =*,G16.6/) 0089 19 FORMAT(/1X,*A =*,G16.6,*C =*,G16.6/) 0090 PRINT 11 *,G16.6,*C =*,G16.6/) 0091 PRINT 17,(SHA,SHB,SHC) 0092 PRINT 18,(PLM,PLN) 0093 PRINT 18,(PLM,PLN) 0094 PRINT 15 0095 PRINT 19,(STA,STC) 0096 PUNCH 21, (NAME,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 0098 PR INT 9 0099 200 CONTINUE 0101 END	0086 ENDFILE 8 C087 17 FORMAT(/1X,*A =*,G16.6,*B =*,G16.6,*C =*,G16.6/) 0088 18 FORMAT(/1X,*A =*,G16.6,*C =*,G16.6/) 0089 19 FORMAT(/1X,*A =*,G16.6,*C =*,G16.6/) 0090 PRINT 11 0091 PRINT 17.(SHA.SHB,SHC) 0092 PRINT 18.(PLM,PLN) 0093 PRINT 19.(STA.STC) 0094 PRINT 19.(STA.STC) 0095 PUNCH 21.(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0096 PUNCH 21.(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 0098 PR INT 19 0099 200 0091 PR INT 9 0092 PR INT 19.(STA,STC) 0095 PUNCH 21.(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0096 PUNCH 21.S/9A4.4E11.5) 0097 20 CONT INUE 0100 END 0101 END TOTAL MEMORY REQUIREMENTS 001546 BYTES .	085	40	PRINT 14.(1.Y(1),YST(1),X(1),YSH(1),YPL(1))	· · · ·	
C087 17 FORMAT(/1X,*A =*,G16.6,*B =*,G16.6,*C =*,G16.6/) 0088 18 FORMAT(/1X,*M =*,G16.6,*N =*,G16.6/) 0089 19 FORMAT(/1X,*A =*,G16.6,*C =*,G16.6/) 0090 PRINT 11 0091 PRINT 17,(SHA,SHB,SHC) 0092 PRINT 12,(SHA,SHB,SHC) 0093 PRINT 18,(PLM,PLN) 0094 PRINT 19,(STA,STC) 0095 PRINT 19,(STA,STC) 0096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 0098 PR INT 9 0099 200 CONTINUE 0101 END	COB7 17 FORMAT(/1X,*A =*,G16.6,*B =*,G16.6,*C =*,G16.6/) O088 18 FORMAT(/1X,*M =*,G16.6,*C =*,G16.6/) O089 19 FORMAT(/1X,*A =*,G16.6,*C =*,G16.6/) O090 PRINT 11 C091 PRINT 17,(SHA,SHB,SHC) O092 PRINT 18,(PLM,PLN) C094 PRINT 15, O095 PRINT 19,(STA,STC) O096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) O097 21 FORMAT(9A4,3E11.5/9A4,4E11.5) C096 PR INT 9 C097 200 C0101 END	0086		ENDFILE 8		
0088 18 FORMAT(/1X, 'M = ', G16.6/) 0089 19 FORMAT(/1X, 'A = ', G16.6/) 0090 PRINT 11 0090 PRINT 17, (SHA, SHB, SHC) 0092 PRINT 12, (SHA, SHB, SHC) 0093 PRINT 18, (PLM, PLN) 0094 PRINT 19, (STA, STC) 0095 PRINT 19, (STA, STC) 0096 PUNCH 21, (NAME, SHA, SHB, SHC, NAME, PLM, PLN, STA, STC) 0097 21 FORMAT(9A4, 3E11.5/9A4, 4E11.5) 0098 PRINT 9 0099 200 0101 END	0088 18 FORMAT(/1X,'M =',G16.6,'N =',G16.6/) 0089 19 FORMAT(/1X,'A =',G16.6,'C =',G16.6/) 0090 PRINT 11 0091 PRINT 17,(SHA,SHB,SHC) 0092 PRINT 12 0093 PRINT 13,(PLM,PLN) 0094 PRINT 15 0095 PRINT 19,(STA,STC) 0096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 FORMAT(9A4,3E11.5/9A4,4E11.5) 0099 200 0101 END TOTAL MEMORY REQUIREMENTS 001546 BYTES	C087	17	FORMAT(/1X, 'A =', G16.6, 'B =', G16.6, 'C =', G16.5/)		
0089 19 FORMAT(/1X, 'A = ', G16.6, 'C = ', G16.6/) 0090 PRINT 11 0091 PRINT 17, (SHA, SHB, SHC) 0092 PRINT 12 0093 PRINT 18, (PLM, PLN) 0094 PRINT 15 0095 PRINT 19, (STA, STC) 0096 PUNCH 21, (NAME, SHA, SHB, SHC, NAME, PLM, PLN, STA, STC) 0097 21 0098 PRINT 9 0099 200 0101 END	0C89 19 FORMAT(/1X, 'A = ', G16.6, 'C = ', G16.6/) 0C90 PRINT 11 0C91 PRINT 17, (SHA, SHB, SHC) 0C92 PRINT 12, 0C93 PRINT 18, (PLM, PLN) C094 PRINT 15, 0C95 PRINT 19, (STA, STC) 0C96 PUNCH 21, (NAME, SHA, SHB, SHC, NAME, PLM, PLN, STA, STC) 0C97 21 FORMAT(9A4, 3E11.5/9A4, 4E11.5) 0C98 PR INT 9 0C100 111 STOP 0C101 END TOTAL MEMORY REQUIREMENTS 001546 BYTES	0088	18	FORMAT(/1X, 'M = ',G16.6, 'N = ',G16.6/)		
0090 PRINT 11 0091 PRINT 17.(SHA,SHB,SHC) 0092 PRINT 12 0093 PRINT 18, (PLM,PLN) 0094 PRINT 15 0095 PRINT 19, (STA,STC) 0096 PUNCH 21, (NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 0098 PRINT 9 0099 200 0101 END	0090 PRINT 11 0091 PRINT 17,(SHA,SHB,SHC) 0092 PRINT 12 0093 PRINT 18,(PLM,PLN) 0094 PRINT 15 0095 PRINT 19,(STA,STC) 0096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,STA,STC) 0097 21 0098 PRINT 9 0099 200 00101 END TOTAL MEMORY REQUIREMENTS 001546 BYTES .	0089	19	FORMAT(/1X,'A =',G16.6,'C =',G16.6/)	•	
C091 PRINT 17, (SHA, SHB, SHC) 0092 PRINT 12 0093 PRINT 18, (PLM, PLN) 0094 PRINT 15 0095 PRINT 19, (STA, STC) 0096 PUNCH 21, (NAME, SHA, SHB, SHC, NAME, PLM, PLN, STA, STC) 0097 21 PRINT 9 0099 200 CONT INUE 0101 END	C091 PRINT 17,(SHA,SHB,SHC) 0092 PRINT 12 0093 PRINT 18,(PLM,PLN) C094 PRINT 15 0095 PRINT 19,(STA,STC) 0096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 FORMAT(9A4,3E11.5/9A4,4E11.5) 0099 200 00101 END TOTAL MEMORY REQUIREMENTS 001546 BYTES	00'90		PRINT 11		
U092 PRINT 12 0093 PRINT 18, (PLM, PLN) 0094 PRINT 15 0095 PRINT 19, (STA, STC) 0096 PUNCH 21, (NAME, SHA, SHB, SHC, NAME, PLM, PLN, STA, STC) 0097 21 FORMAT(9A4, 3E11.5/9A4, 4E11.5) 0099 200 00101 END	0092 PRINT 12 0093 PRINT 18 0094 PRINT 15 0095 PRINT 19,(STA,STC) 0096 PUNCH 21,(NAME,SHA,SHB,SHC,NAME,PLM,PLN,STA,STC) 0097 21 FORMAT(9A4,3E11.5/9A4,4E11.5) 0099 200 00101 END TOTAL MEMORY REQUIREMENTS 001546 BYTES	0091		PRINT 1/, (SHA,SHB,SHC)		<u> </u>
UU93 PRINT 18, IPLM, PLN7 C094 PRINT 15 0095 PRINT 19, (STA, STC) 0096 PUNCH 21, (NAME, SHA, SHB, SHC, NAME, PLM, PLN, STA, STC) 0097 21 FORMAT(9A4, 3E11.5/9A4, 4E11.5) 0099 200 CONT INUE 0101 END	UU93 PRINT 18, (PLM, PLN) C094 PRINT 19, (STA, STC) 0095 PRINT 19, (STA, SHD, SHC, NAME, PLM, PLN, STA, STC) 0096 PUNCH 21, (NAME, SHA, SHB, SHC, NAME, PLM, PLN, STA, STC) 0097 21 FORMAT(9A4, 3E11.5/9A4, 4E11.5) 0099 200 0101 END TOTAL MEMORY REQUIREMENTS 001546 BYTES	0092			· 6	•
CU34 PRINT 15 Stand 0095 PRINT 19, (STA,STC) 0096 0096 PUNCH 21, (NAME, SHB, SHC, NAME, PLM, PLN, STA, STC) 0097 0098 PR INT 9 0099 0099 200 CONT INUE 0100 111 STDP 0101 END	CU34 PRINT 13 St 0095 PRINT 19 Sta,STC) 0096 PUNCH 21, (NAME, SHA, SHB, SHC, NAME, PLM, PLN, STA, STC) 0097 0097 21 FORMAT(9A4, 3E11.5/9A4, 4E11.5) 0098 PR INT 9 0099 200 CONT INUE 0100 111 STOP 0101 END ;	0093				
OOPS PUNCH 21, (NAME, SHA, SHB, SHC, NAME, PLM, PLN, STA, STC) 0096 PUNCH 21, (NAME, SHA, SHB, SHC, NAME, PLM, PLN, STA, STC) 0097 21 FORMAT (9A4, 3E11.5/9A4, 4E11.5) 0098 PR INT 9 0099 200 0100 111 STOP 0101 END	O057 FERRET 21, INAME, SHC, NAME, PLM, PLN, STA, STC) 0096 PUNCH 21, INAME, SHC, NAME, PLM, PLN, STA, STC) 0097 21 0098 PR INT 9 0099 200 0101 STOP 0101 END TOTAL MEMORY REQUIREMENTS 001546 BYTES .	0094		$\frac{1}{10}$	15	
00.97 21 FORMAT(9A4,3E11.5/9A4,4E11.5) 00.98 PRINT 9 00.99 200 0100 111 STOP 0101 END	COMP FORMAT(944,3E11.5/9A4,4E11.5) CO98 PRINT 9 CO99 200 CO100 111 STOP O101 END TOTAL MEMORY REQUIREMENTS 001546 BYTES	0095		DINCH 27 CONFECTOR SHA SHA SHA SHA SHA SHA SHA SHA STA STA STA STA STA		
OC98 PRINT 9 C099 200 CONTINUE O1c0 111 STOP O101 END ;	0096 PR INT 9 0099 200 CONT INUE 0100 111 STOP 0101 END TOTAL MEMORY REQUIREMENTS 001546 BYTES	0097	21	FORMAT(9A4-3E11-5/9A4-4E11-5)		
C099 200 CONTINUE 01c0 111 STOP 0101 END ;	CO99 200 CONTINUE Olco 111 STOP Olol END TOTAL MEMORY REQUIREMENTS 001546 BYTES .	0098	<u> </u>	PRINT 9	· · · ·	
OLCO 111 STOP OLOI END	0100 111 STOP 0101 END TOTAL MEMORY REQUIREMENTS 001546 BYTES .	0099	200	CONTINUE		
0101 END	OIOI END : TOTAL MEMORY REQUIREMENTS 001546 BYTES .	0100	111	STOP		
	TOTAL MEMORY REQUIREMENTS 001546 BYTES .	0101		END		
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FORTRAN IV G COMPI	LER AUX	08-31-71	17:47:20	PAGE 0001				
0001 0002 0003 0004	FUNCTION AUX(P,D,X,L) DIMENSION P(3),D(3) ECX=EXP(-P(3)*X) D(1)=X						· .	
0005 0006 0007 0008 0009	D(2)=1ECX D(3)=P(2)*X*ECX AUX=P(1)*X+P(2)*D(2) RETURN END					. .		
TCTAL MEMORY REQ	UIREMENTS 0001CO BYTES							
COMPILE TIME =	C.4 SECONDS	• ب						
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	FORTRAN IV G COMP	ILER A	UXST	08-31-71	17:47:21	PAGE 0001	················	· · · · · · · · · · · · · · · · · · ·	.)
	0001 0002 0003 0004	FUNCTION AU DIMENSION P D(1)=X**3 D(2)=X	XST(P,D,X,L) (2)+D(2)						
	0005 0006 000 7	AUXST=P(1)* RETURN END	(X**3)+P(2)*X	·					
	TOTAL MEMORY RE	QUIREMENTS 00	018C BYTES				•		
	COMPILE TIME =	0.3 SE	C OND S						
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ſ	FORTRAN IN	V G CUMPILER AU	XPL	08-31-71	17:47:20	PAGE 0001	•					
	0001 0002 0003 0004	FUNCTION AUX DIMENSION P(D(1)=1./P(1) D(2)=V	PĹ(P,D,V,L) 2),D(2)									
	0005 0006 0007	AUXPL=ALOG(P RETURN END	(1))+P(2)*V	· · · · · · · · · · · · · · · · · · ·	_ · · ·							
	TOTAL ME	EMORY REQUIREMENTS 000	19E BYTES			•						
-	COMPILE	TIME = 0.3 SEC	ONDS									
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SERIES A 2.	0% + BRIJ 30	4.0%								
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SHANGRAW MODEL	PARAMETERS									
INTERMEDIATE E	STIMATES OF PA	RAMETERS, SUM OF S	QUARES							
0.500C0E-01	760.00	0.10000E-01	0.18424E	07				.		
0.70706	253.95	0.10169E-01	13227.						•	
0.71170	253.20	0.10686E-01	13004.							
0.71281	250.76	0.10729E-01	13004.							
C.71318	250.55	0.10743E-01	13003.							
0.71331	250.48	0.107485-01	13003		· · · · ·					•
0.71336	250.45	0.10750E-01	13003.					-		
FINAL ESTIMATE:	OF PARAMETER	S		NO OF ITE	RATIONS= 9)				
0.71337	250.45	0.10750E-01								
SUM OF SQUARES	13003.						•			
ROOT MEAN SQUAR	RE ERROR OF ES	TIMATE IN PARAMETE	ERS	•						
ROOT MEAN SQUA 0.36264E-0	RE ERROR OF ES	TIMATE IN PARAMETE 0.11583E-02	ERS			•				
ROOT MEAN SQUA 0.36264E-0 SHEAR RA	RE ERROR OF ES 1 18.794 TE SHEAR ST ACTUAL	TIMATE IN PARAMETE 0.11583E-02 RESS FITTED	ERS			、 . *				
ROOT MEAN SQUA 0.36264E-0 SHEAR RA	RE ERROR OF ES 1 18.794 TE SHEAR ST ACTUAL 5 42.93	TIMATE IN PARAMETE 0.11583E-02 RESS FITTED 27.81	ERS			·				
ROOT MEAN SQUA 0.36264E-0 SHEAR RA 1 8.44 2 16.9	RE ERROR OF ES 1 18.794 TE SHEAR ST ACTUAL 5 42.93 1 70.28	TIMATE IN PARAMETE 0.11583E-02 RESS FITTED 27.81 53.69	ERS			· ·				
ROOT MEAN SQUA 0.36264E-0 SHEAR RA 1 8.44 2 16.9 3 25.3	RE ERROR OF ES 1 18.794 TE SHEAR ST ACTUAL 5 42.93 1 70.28 7 94.28 (12.94)	TIMATE IN PARAMETE 0.11583E-02 RESS FITTED 27.81 53.69 77.88	ERS			、 .•				· · ·
ROOT MEAN SQUA 0.36264E-0 SHEAR RA 1 8.44 2 16.9 3 25.3 4 50.7 5 76.1	RE ERROR OF ES 1 18.794 TE SHEAR ST ACTUAL 5 42.93 1 70.28 7 94.28 4 149.36 1 191.97	TIMATE IN PARAMETE 0.11583E-02 RESS FITTED 27.81 53.69 77.88 141.49 194.23	ERS			•				
ROOT MEAN SQUA 0.36264E-0 SHEAR RA 1 8.44 2 16.9 3 25.3 4 50.7 5 76.1 6 152.2	RE ERROR OF ES 1 18.794 18.794 FE SHEAR ST ACTUAL 42.93 170.28 7 94.28 149.36 4 149.36 191.97 2 298.89 191.97	TIMATE IN PARAMETE 0.11583E-02 RESS FITTED 27.81 53.69 77.88 141.49 194.23 310.27	ERS			•				· · · · · · · · · · · · · · · · · · ·
ROOT MEAN SQUA 0.36264E-0 SHEAR RA 1 8.44 2 16.9 3 25.3 4 50.7 5 76.1 6 152.2 7 228.3	RE ERROR OF ES 1 18.794 18.794 FE SHEAR ST ACTUAL 3 3 5 42.93 1 6 42.93 1 7 94.28 3 4 149.36 1 1 191.97 2 2 298.89 3 3 424.45	TIMATE IN PARAMETE 0.11583E-02 RESS FITTED 27.81 53.69 77.88 141.49 194.23 310.27 391.81	ERS			•				· · · · · · · · · · · · · · · · · · ·
ROOT MEAN SQUAR 0.36264E-0 SHEAR RA 1 8.4 2 16.9 3 25.3 4 50.7 5 76.1 6 152.22 7 228.3 8 456.6 9 685.6	RE ERROR OF ES 1 18.794 18.794 FE SHEAR ST ACTUAL 5 42.93 5 42.93 170.28 7 94.28 149.36 1 191.97 2 2 298.89 3 424.45 3 424.45 617.50 0 747.50 70	TIMATE IN PARAMETE 0.11583E-02 RESS FITTED 27.81 53.69 77.88 141.49 194.23 310.27 391.81 574.37 738.94	ERS			•				· · · ·
ROOT MEAN SQUA 0.36264E-0 SHEAR RA 1 8.4 2 16.9 3 25.3 4 50.7 5 76.1 6 152.2 7 228.3 8 456.6 9 685.0 10 456.6	RE ERROR OF ES 1 18.794 18.794 FE SHEAR ST ACTUAL 5 42.93 5 42.93 170.28 7 94.28 4 4 149.36 191.97 2 298.89 3 424.45 7 617.50 747.50 7 611.00 747.50	TIMATE IN PARAMETE 0.11583E-02 RESS FITTED 27.81 53.69 77.88 141.49 194.23 310.27 391.81 574.37 738.94 574.37	ERS			•				· · · ·
ROOT MEAN SQUA 0.36264E-0 SHEAR RA 1 8.4 2 16.9 3 25.3 4 50.7 5 76.1 6 152.2 7 228.3 8 456.6 9 685.0 10 456.6 11 228.3	RE ERROR OF ES 1 18.794 18.794 FE SHEAR ST ACTUAL 5 42.93 5 42.93 70.28 7 94.28 149.36 1 191.97 2 2 98.89 3 424.45 7 617.50 747.50 7 611.00 3 418.60	TIMATE IN PARAMETE 0.11583E-02 RESS FITTED 27.81 53.69 77.88 141.49 194.23 310.27 391.81 574.37 391.81	ERS			•				· · · · · · · · · · · · · · · · · · ·
ROOT MEAN SQUAR 0.36264E-0 SHEAR RA 1 8.44 2 16.9 3 25.3 4 50.7 5 76.1 6 152.2 7 228.3 8 456.6 9 685.0 10 456.6 11 228.3 12 152.2	RE ERROR OF ES 1 18.794 18.794 FE SHEAR ST ACTUAL 42.93 70.28 7 94.28 149.36 1 191.97 298.89 3 424.45 7617.50 7 617.50 747.50 7 618.60 2289.98 2 289.98 98	TIMATE IN PARAMETE 0.11583E-02 RESS FITTED 27.81 53.69 77.88 141.49 194.23 310.27 391.81 574.37 391.81 310.27 391.81 310.27	ERS			•		۲. ۲. ۲. ۲. ۲. ۲.		· · · · · · · · · · · · · · · · · · ·
ROOT MEAN SQUAR 0.36264E-0 SHEAR RA 1 8.4 2 16.9 3 25.3 4 50.7 5 76.1 6 152.2 7 228.3 8 456.6 9 685.0 10 456.6 11 228.3 12 152.2 13 76.1	RE ERROR OF ES 1 18.794 18.794 FE SHEAR ST ACTUAL 42.93 70.28 7 94.28 149.36 1 191.97 2.298.89 3 424.45 7617.50 7 617.50 747.50 7 611.00 3418.60 2 289.98 186.30 1 186.30 186.30	TIMATE IN PARAMETE 0.11583E-02 RESS FITTED 27.81 53.69 77.88 141.49 194.23 310.27 391.81 574.37 391.81 310.27 194.23 141.49	ERS			•		<u>الم</u>		· · · · · · · · · · · · · · · · · · ·
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