THE BIOPHARMACEUTICAL PROPERTIES OF

SOLID DOSAGE FORMS

The Operating Characteristics of a Continuous

Flow Dissolution Apparatus

by

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B. S. P., University of British Columbia, 1966

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

Master of Science in Pharmacy (M. S. P.)

in the

Faculty of Pharmacy

We accept this thesis as conforming to the

required standard

THE UNIVERSITY OF BRITISH COLUMBIA

April, 1968

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ABSTRACT

A completely automatic continuous flow dissolution procedure was developed and tested. Pertinent dissolution conditions were investigated and chosen to study the dissolution characteristics of seven brands of phenylbutazone tablets. A pumping system enabled the simulated digestive fluid to flow from the dissolution vessel into the flow cell of a recording spectrophotometer for a continuous recording of the drug concentration in the dissolution medium, which was gradually changed from an acidic medium to a basic one.

From the "in vitro" data obtained by this test procedure, a $T_{50\%}$ value of 120 minutes was chosen as a limit of acceptance for the test products. The "in vivo" characteristics of six of the brands were compared with those observed for a pharmaceutically acceptable product. Of the seven test products, only four were acceptable on the basis of both the "in vitro" and the "in vivo" data. Correlation of the "in vitro" and the "in vivo" data resulted in "least squares" lines with negative slopes.

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I. INTRODUCTION

Tablet disintegration implies that the solid dosage form has broken up into smaller particles. However, it does not necessarily mean that the active ingredient has been released from the primary particles. This was first pointed out in the early 1950's by several researchers (23, 28) and more recently by Levy and Hayes (13) and Yen (34). By the mid 1950's, Chapman and his co-workers (5, 6), in separate studies on products containing riboflavin and p-amino salicylic acid, showed that physiological availability could be predicted from the disintegration times determined by the official disintegration test (30). However, their results did suggest that the more important criterion to consider in relation to availability is the release of drug from the primary drug particle.

Even though the correlation between disintegration time and dissolution has recently been shown to be invalid (1, 9, 18), the disintegration time is still an indication of drug release because, if the solid dosage form remains intact, the surface area for dissolution is limited. As shown by the Noyes-Whitney Equation (13), the amount of drug dissolved is dependent on the surface area of the dissolving solid.

$$\frac{da}{dt} = KS (Cs - C)$$

where a = amount of drug dissolved in time t

S = surface area of the dissolving solid

K = solution rate constant of the solid

C = concentration of the dissolving solid in the medium

Cs = concentration of the dissolving solid in the
        diffusion layer surrounding the solute particles.

Dissolution is the process whereby solid particles
go into solution. It can be considered as specific types of
heterogeneous reactions in which a mass transfer is effected
through the net result of escape and deposition of solute
molecules at the solute-solvent interface. From this layer
of dissolved particles, diffusion occurs carrying the
dissolved solute from the interface into the main body of
the dissolution medium. Because the reaction at the interface
is much slower than the convection transport process, it
ultimately determines the rate of dissolution (32).

Even though it is generally recognised to-day
that disintegration times do not necessarily bear a relation-
ship to the "in vivo" action of the tablet, the disintegration
time test is still the only official "in vitro" check on
drug release from tablets. It has been stated that this
test is inadequate and should be replaced by a dissolution
test. Since the early 1960's, several workers have designed
dissolution tests ranging from Levy's beaker method (13)
to completely automated systems (24).

The great variations in the equipment used for "in vitro" dissolution studies can be attributed to the wide differences in the physical forms of the test preparations as well as to the attempts to duplicate "in vivo" conditions. However, basically they all consist of a vessel for the dissolution medium and the test preparation, a means of agitation, a sampling system and a means of controlling the temperature of the dissolution medium.

Most of the "in vitro" dissolution studies have been done in a static system, i.e., the dissolution medium remains unchanged throughout the entire dissolution run. This system may encounter a saturation problem especially with the less soluble drug preparations. Several researchers (7, 22, 33) have used a continuous flow system to carry out dissolution studies. This type of system eliminates the possibility of saturation of the medium by the drug. It may also simulate "in vivo" conditions more than the static system because under "in vivo" conditions the digestive juices are continuously being secreted and absorbed by the mucosal cells of the gastro-intestinal tract.

In an attempt to investigate the potentials of this type of system, an apparatus for continuous flow was developed with a gradual change in the pH of the medium, from that of gastric juice to intestinal juice. This system was investigated and using a standard product, pertinent

dissolution conditions were established for this study. Under these conditions, seven brands of commericially available phenylbutazone tablets were tested. The "in vitro" dissolution data obtained was then correlated with "in vivo" data obtained for several subjects.

II. LITERATURE SURVEY

The official U.S.P. disintegration apparatus (30) has the basic parts needed in a dissolution test. Workers have either used the disintegration apparatus itself or modified it to carry out disintegration as well as dissolution studies.

The apparatus consists of a basket rack assembly that can be raised and lowered at a constant frequency rate of between twenty-eight to thirty-two cycles per minute through a distance of not more than six cm. and not less than five cm. The volume of the dissolution medium in the thermostatically controlled vessel ($35^{o}C$ - $39^{o}C$) is such that at the highest point of the upward stroke the wire mesh remains at least 2.5 cm. below the surface of the medium and descends to not less than 2.5 cm. from the bottom of the vessel on the downward stroke. The basket rack assembly consists of six vertically held open-ended tubes whose lower ends are covered by a sieve of varying mesh size. Each tube is provided with a slotted and perforated cylindrical disk of plastic. The disk just fits the tube and moves up and down with the movement of the basket as it is raised and lowered.

Using this apparatus, Schroeter and his co-workers (25) determined the disintegration times and dissolution rates of seventy-six lots of compressed tablets, including

an anti-inflammatory steroid, a sulfonamide, an anti-diabetic agent and an aspirin-phenacetin combination. Without stopping the agitation of the U.S.P. tablet disintegration apparatus, aliquots of the dissolution medium were withdrawn at different intervals for analysis. Time for 50% of the drug to go into solution ($t_{50\%}$) or the amount of drug in solution at a specific time was used as the criterion for the rate of dissolution. Disintegration times were obtained with and without the use of the plastic disks.

These workers found for the steroid a highly significant linear correlation between the rate of dissolution and the average disintegration time without the use of the plastic disks. This correlation was absent when disks were used. For the sulfonamide tablets, a similar correlation was observed when sodium chloride was present as an ingredient. Both the anti-diabetic agent and the aspirin-phenacetin combination showed no significant correlation between dissolution rate and disintegration time.

The results indicated that there was an extreme specificity in the absence or presence of a relationship between rate of dissolution and disintegration times. When a quantitative relationship existed, the "least squares" lines relating the variables were found to vary widely depending upon the particular drug as well as on the other adjuvants in the tablet. The use of plastic disks in the

disintegration test was observed to mask real differences between the various lots tested.

Middleton and his co-workers (19), using the U.S.P. disintegration apparatus, found a significant relationship between disintegration time, dissolution rate and physiological availability of riboflavin in sugar-coated tablets. The tablets were immersed for thirty minutes in simulated gastric fluid and the remainder of the time in simulated intestinal fluid. Without stopping the agitation of the apparatus, aliquots of the simulated digestive fluids were withdrawn at various intervals for analysis. From the results, these workers concluded that the disintegration time provided a valid indication of the rate at which riboflavin went into solution from the sugar-coated tablets, thus either disintegration time or dissolution rate can provide a useful estimate of the physiological availability of riboflavin from sugar-coated tablets. However, this relationship may not exist for other drugs.

In their study of the dissolution rates of eighteen brands of commericially available tolbutamide tablets in gastric fluid, Brudney and his co-workers (1) found that there was no correlation between dissolution rates and the disintegration times. Disintegration time was determined by the official method of the Food and Drug Directorate (3). Dissolution was determined by the method described by Levy and Hayes (13) with modifications. Six litres of 0.1 N.HCl

containing 0.2% NaCl was used as the dissolution medium. The
stirring rate was maintained at 250 r.p.m. and the temperature
controlled at $37^{\circ}C \pm 0.5^{\circ}C$. Twenty-five ml. samples of the
medium were withdrawn through a nylon filter pad at five
minute intervals over a sixty minute period. Following
each withdrawal, twenty-five ml. of fresh medium was added
to maintain a constant volume.

Lu and his co-workers (18), in their comparative
study of twenty-six brands of commericially available
tolbutamide tablets, found that there was no correlation
between disintegration time and dissolution rate in gastric
fluid as had been reported earlier (1), but that there was
a statistically significant correlation between disinteg-
ration time and dissolution rate in intestinal fluid. The
disintegration times were determined by using the Food and
Drug Directorate method. The dissolution rates were deter-
mined in both gastric and intestinal fluids of pH 1.5 and
7.5 respectively. Two and a half litres of the solution
was heated to $37^{\circ}C$ in a three-litre glass jar. The tablet
was placed at the bottom of the jar and the solution stirred
by a blade stirrer set at one inch from the bottom of the
jar at 300 r.p.m. In two of the lots, the disintegration
time exceeded the Food and Drug Directorate limit of sixty
minutes, whereas the other twenty-four lots disintegrated
well within this limit. Dissolution rates were calculated

on the basis of the amount in mg. dissolved in one hour and the time required to reach 20% and 40% dissolution in gastric fluid and 50% and 90% dissolution in intestinal fluid. The results showed a considerable variation in the dissolution rates among the different brands tested. These findings tend to reinforce the observations of Schroeter and his co-workers (25) that the existence of a relationship between dissolution and disintegration time depends on the particular drug as well as on the conditions under which the dissolution and disintegration tests are carried out.

Among the various factors to be considered in the design of a dissolution test, the means and intensity of agitation are varied most and have been reported to have a significant effect on the dissolution rate.

Hamlin and his co-workers (8) used three different methods to study constant surface pellets of two polymorphic forms of methylprednisolone compressed at high pressure. One form had greater water solubility and hence should have a greater initial dissolution rate in water.

The first method was that of Nelson (21), a method in which free convection, diffusion coefficient and concentration were stated to be the rate determining factors. The only modification was that instead of determining weight loss of the pellets, the fluid surrounding the steroid pellets was assayed spectrophotometrically. In the second method, the pellets were held in a polyethylene holder at

the center of oval four fluid ounce bottles containing
120 ml. of deionized water. The bottles were attached to the
machine described by Wurble (31). After rotation for differ-
ent intervals of time, the fluid surrounding the pellet
was assayed spectrophotometrically. The dimensions of the
pellet before and after exposure to the dissolution medium
were also determined. The machine was rotated at 6 r.p.m.
and at 12 r.p.m. The third method was similar to the second
except that the machine described by Souder and Ellenbogen
(29) was used instead of the Wurble machine. The bottles
were rotated at 40 r.p.m. during exposure in a'constant
temperature bath held at $37^{o}C$.

It was found that when the intensity of agitation
or the velocity of the dissolution medium across the dissolv-
ing solid was of a low order of magnitude, a significant
difference in dissolution rates was observed for both forms
of the steroid. When the speed of rotation of the wheel in
the Wurble machine was increased from 6 r.p.m. to 12 r.p.m.,
the rates of dissolution of the two polymorphs became equal.
Rotation at 40 r.p.m. in the machine described by Souder and
Ellenbogen showed no observable significant difference in
the dissolution rates of the two polymorphs. In the "in vivo"
studies carried out by implanting the pellets in rats, the
two polymorphs showed significantly different rates of
weight loss. The "in vivo" data tend to indicate that the
"in vitro" test in which there was a relatively low intensity

of agitation correlated best with the "<u>in vivo</u>" results.

Levy (11), in his study of the effects of agitation on dissolution, used two methods that varied greatly in agitation intensity - the beaker method (13) and the oscillating tube method. In the second method, a plexiglass cylinder with a 100-mesh stainless steel wire screen on the bottom was attached to the basic unit of the U.S.P. disintegration apparatus and immersed in a beaker containing 800 ml. of 0.1 N.HCl at 37°C. With the apparatus in motion, a tablet was dropped into the cylinder and the medium sampled at intervals by a fritted-glass immersion filter tube for analysis. Two proprietary brands of aspirin were tested. One contained alkaline additives while the other did not. With the beaker method, which utilized a very low agitation rate and permitted the solid particles to remain as an aggregate on the bottom of the beaker, the tablets containing aspirin and the alkaline additives dissolved much more rapidly than the plain aspirin tablets. This was in agreement with the "<u>in vivo</u>" absorption tests carried out. The dissolution half-time of one was approximately three times that of the other. On the other hand, there was practically no difference in the dissolution rates of the two tablet formulations when tested by the oscillating tube method, which involved relatively high agitation intensities and caused the solid particles to be dispersed.

Levy attributed this difference to the fact that in an aggregate of disintegrated tablet solids, the alkaline components of the buffered aspirin tablet caused an increase in the pH of the micro-environment from pH 1 to about pH 5.6. This increase in pH resulted in a more rapid dissolution of the aspirin particles. This effect was absent when aspirin and the alkaline components were physically separated by intensive agitation.

The method developed by Levy and Hayes (13) in their study of the dissolution rate of plain and buffered aspirin tablets has been used by Levy and other workers in dissolution studies with only minor modifications. The dissolution assembly consisted of a 400-ml. Pyrex Griffin beaker immersed in a constant temperature bath adjusted to $37^{o}C \pm 0.1^{o}C$. A three-blade, 5-cm. diameter polyethylene stirrer was attached to an electronically controlled stirring motor. Two hundred and fifty ml. of 0.1 N.HCl was placed in the beaker and allowed to equilibrate to $37^{o}C$ and the acetysalicylic acid tablet was dropped along the side of the beaker. The polyethylene stirrer was immersed in the dissolution medium to a depth of 27 mm. and accurately centered by means of a guide. The stirring rate was 59 r.p.m. - just sufficient to keep the solution homogeneous but low enough to allow the solids of the disintegrated tablet to remain as an aggregate at the centre of the bottom of the beaker within an area of one or two sq. cm. Seven ml. samples

were taken at five, ten, twenty and thirty minutes by means of a fritted-glass immersion filter tube of medium porosity. Six brands of plain acetysalicylic acid tablets, one brand of the buffered drug, and one brand of calcium acetysalicylate carbamide complex product were tested. Six tablets were subjected to the dissolution test; another six to disintegration test in 0.1 N.HCl by the U.S.P. method.

The results showed that there was a great difference in the solution rates of the various brands of plain tablets. The tablet with the calcium salt dissolved at a faster rate than all the other products tested. This was expected due to the greater solution of the salt in aqueous medium. They found that the dissolution curve did not progress arithmetically and that it would take much longer for the second half of the drug to go into solution. The rapidly dissolving products exhibited longer disintegration times than the more slowly dissolving products. It was concluded that the disintegration time which is often alluded to as an index of drug availability is no criterion of availability or rate of solution. When disintegration times are abnormally long, the rate of solution and absorption of a drug will be seriously affected since disintegration time is just the time required by the tablet to fall apart into reasonably small particles and not the time required for the drug to go into solution.

Using the method just described (13), Levy and his co-workers (17) correlated the effect of stirring rates with the intestinal absorption of three different dosage forms of aspirin. These dosage forms differed markedly in drug absorption rate as well as in the principal mechanism involved in the release of drug to the dissolution medium. One was a rapidly disintegrating tablet containing aspirin as micro-encapsulated particles, another was a rapidly disintegrating "plain" aspirin tablet and the third was a rapidly disintegrating tablet containing aspirin and alkaline additives. Different stirring rates in a clock-wise direction using the precision stirring apparatus of Levy and Tanski (15) were used with 0.1 N.HCl as the dissolution medium.

The resulting comparison of dissolution at 60 r.p.m. with plasma levels obtained by "in vivo" studies showed that the "in vitro" dissolution from the micro-encapsulated particles was too rapid relative to the other dosage forms. Dissolution from the plain tablets was found to be very much more sensitive than from the micro-encapsulated particles which release drug by a diffusion process. At 50 r.p.m., it was found that the ratio of "in vivo" absorption rates from the plain tablets and the micro-encapsulated particles was equal to the ratio of the dissolution rates. At 30 r.p.m., the more rapidly absorbed plain tablets were found to dissolve

more slowly than the much more slowly absorbed micro-encap-
sulated particles. In this study, it was observed that a
change of only 20% in stirring rates made a difference
between successful correlation or failure with "in vivo"
data. Changes in the composition of the dissolution medium
was subsequently reported to have similar effects.

Besides stirring rate, Levy and his co-workers (16)
found that certain formulation factors have an effect on the
dissolution rate of the active ingredient. Using the method
described (13), these workers observed that the dissolution
rate of salicylic acid in compressed tablets increased with
decreasing granule size but this increase was not strictly
proportional to the increase in the apparent surface area
of the granules. The increase in dissolution rate from the
tablets containing 20 - 40 mesh and 40 - 60 mesh granules
was not as great as the increase in the apparent surface
area since the disintegrated tablet particles remain
aggregated on the beaker bottom due to the low intensity of
agitation. The much greater dissolution of the tablets with
60 - 80 mesh granules was due to the fact that these granules
were small enough to be dispersed somewhat in the medium
despite the low intensity of agitation, thus permitting the
moving solvent to come in contact with a greater portion
of the potentially available surface. An increase of starch
content in the tablets from 5 - 20% resulted in an increase

in the dissolution rate of salicylic acid, probably because
of more rapid and thorough disintegration of the granules.
Dissolution rates were also found to increase with an
increase in the precompression pressure of the tablets. This
may be due to the fracturing of the drug particles at the
higher slugging pressure, thus yielding smaller primary
particles. Fragmentation of the more highly compressed
granules during subsequent tableting may also occur. Finally,
the softer granules obtained at the lower precompression
pressures are more likely to undergo bonding during tablet-
ing and thus yield larger granules.

In their study of the effects of lubricants on
dissolution rates of tablets, Levy and Gumtow (12) used the
beaker method (13) and the rotating disk method (14). These
workers found that magnesium stearate, a hydrophobic lubri-
cant, decreased appreciably the dissolution rate of salicylic
acid tablets compressed from granules of the pure drug while
sodium lauryl sulfate, a hydrophilic lubricant, had the
opposite effect. This enhancing effect of sodium lauryl
sulfate was even greater with tablets made from granules
that contained salicylic acid and starch. Experiments with
nondisintegrating disks of salicylic acid indicated that
the more commonly used hydrophobic lubricants (magnesium
stearate, aluminum stearate, stearic acid, talc) decreased
the effective drug-solvent interfacial area and thereby
decreased the rate of dissolution of the drug, while

water-soluble lubricants (sodium oleate, sodium lauryl sulfate) did not have this effect. The dissolution rate enhancing effect of sodium lauryl sulfate was not due to any modification of the micro-environmental pH or solubiliz-ation by micelles, but rather to the better penetration of the solvent into the tablets and their component granules and the resulting greater availability of drug surface.

Levy and Sahli (14), in their comparative study of the gastro-intestinal absorption of acetysalicylic acid and its aluminum salt, correlated the urinary salicylate excretion with the dissolution rate obtained by the rotat-ing disk method. The compressed tablets were mounted on Plexiglas holders with paraffin wax so that only one surface of the tablet was exposed. The holder was connected to an electronically controlled precision stirring motor. A two hundred ml. quantity of the dissolution medium was placed in a 500-ml. three-neck round-bottom flask, which was immersed in a constant temperature bath adjusted to 37°C. After temperature equilibration, the tablet attached to the holder was immersed into the dissolution medium to a depth of one inch, with the stirrer turned on at 555 r.p.m. Aliquots of five or ten ml. were removed from the flask at appropriate intervals of time for analysis. A similar volume of medium was added to maintain a constant volume. The tablet was weighed before and after the dissolution run as a check on the assay. The conditions of the experiment was such that

the concentration of drug in the medium was maintained at
a small fraction of its total solubility.

In 0.1 N.HCl, the dissolution rate of acetysalicy-
lic acid was found to be 65.1 mg./hr.cm. and that of aluminum
acetysalicylate in terms of salicylic acid was 8.88 mg./hr.cm.
Similar differences were found when alkaline medium was used.
Similarly, "in vivo" studies showed that urinary salicylate
excretion from subjects taking aluminum acetysalicylate was
markedly less than that from subjects taking the acid. Since
the absorption of salicylates is rate-limited by their
dissolution rate in gastro-intestinal fluids, these workers
concluded that the less rapid absorption and subsequent
excretion of aluminum acetysalicylate was probably due to
its slow dissolution.

Recently, Searl and Pernarowski (26) evaluated the
disintegration times and dissolution rates of twenty-three
brands of phenylbutazone tablets. The "in vivo" character-
istics of three brands were compared with that observed for
a clinically acceptable product by a comparison of the levels
of the drug in the blood after oral administration. Disinteg-
ration times were determined by using the Erweka tablet
disintegration apparatus. The procedure is in a publication
issued by the Food and Drug Directorate (4). Six tablets
were placed in the apparatus and the mean disintegration
times calculated. Dissolution rates were determined by an

apparatus similar to that of Levy and Hayes (13). Two and a
half litres of simulated intestinal fluid in a three-litre
glass jar was allowed to equilibrate in a constant temper-
ature water bath set at $37^{\circ}C \pm 1^{\circ}C$. One tablet was placed
in a cylindrical wire basket (2.2 cm. in diameter and 2.8 cm.
in length) which was attached below the impeller of a stirr-
ing shaft (three-blade, Teflon-coated propeller, 5 cm. in
diameter). The shaft which was connected to a Fisher Stedi-
Speed stirrer was inserted to a depth of ten cm. below the
surface of the liquid and rotated at exactly 100 r,p.m. in
a clockwise direction. Ten ml. aliquots were taken at
fifteen-minute intervals for the first hour, at thirty-minute
intervals for the second hour and hourly thereafter for
seven hours.

Results showed that nine of the twenty-three
products had disintegration times of more than thirty minutes.
Twelve products (some with disintegration times greater than
thirty minutes and some with disintegration times less than
thirty minutes) were selected for more extensive study. Of
these twelve products, three were found to have a disinteg-
ration time of more than thirty minutes with a range of
more than thirty minutes. From the disintegration time data,
it would appear that the drug in these tablets may not be
available to the patient. Dissolution studies showed that
four of the twelve products had $T_{50\%}$ value of more than

120 minutes but most of the twenty-three products disinteg-
rated and released their phenylbutazone content to the medium
quickly. A standard $T_{50\%}$ value of 120 minutes was chosen by
these workers on the basis of the data available. It was
not possible to correlate the "in vivo" data to that obtained
"in vitro". For the tablets examined, the best correlation
was still to tablet disintegration time. However, maximum
disintegration times would be more meaningful than mean
disintegration times.

Nash and Marcus (20) used a periodic solvent
exchange method to study d-amphetamine sulfate "sustained
release" capsules and tripelennamine hydrochloride "sustained
release" tablets. The test sample was put into a 600-ml.
Buchner type funnel with a medium porosity fritted disk
filter bed and gently agitated in 400 ml. of simulated gastric
juice. Finer porosity filters prevent proper drainage of the
fluid while coarser types leak during sampling periods.
Positive air pressure was maintained between sampling periods
to prevent leakage. After thirty minutes, 200 ml. was drawn
off by vacuum through the filter bed into the suction flask
and collected in a 250 ml. beaker. A four-inch standard
two-way stop cork fused into the bottom of the suction flask
facilitated the removal of fluid samples during the course
of each run without upsetting the positive pressure at the
bottom of the filter bed. An additional 200 ml. portion of
simulated gastric fluid was added to the funnel to replace

the withdrawn volume. Further samples were withdrawn at one and a half, two, three, five, seven and twenty-four hour intervals, each time with replacement of the fluid.

Norby (22) developed a continuous solvent exchange system to study the release pattern of "sustained release" tablets. One unit of the drug was placed in a beaker containing ten ml. of dissolution medium at thermostatically controlled temperature. This solution was kept at a constant level with the reservoir of fresh medium to ensure a constant volume in the dissolution vessel. The medium from the dissolution vessel flowed through tubing which had a cotton filter at the open end into a collecting vessel at a rate (0 - 10 ml./min.) controlled by a magnetic valve. There was an automatic mechanism controlling this valve which controlled the flow rate through the system to give a reproducible test. The opening and closing of the valve was controlled by an electronically driven mechanical device. The stirrer was power driven. A screen around the propeller protected the test preparation from coming in contact with the blades. The stirrer was moving fast enough so that the drug was moving freely and did not stick to the sides or the bottom of the dissolution vessel. Concentration of the medium was determined either by analysing a fraction of the collected medium or by a continuous recording on a spectrophotometer.

In their study of the effect of compression pressure on dissolution, Ganderton and his co-workers (7) used two methods to test compressed tablets of phenindione of different formulations, all containing 100 mg. crystalline lactose with 15 mg. of potato starch dispersed within the granules, over a pressure range of 60 - 2500 Kg.cm.$^{-2}$ on a single punch machine. In the first method, the dissolution vessel was a 2-litre beaker (containing 1.5 litres of dissolution medium) immersed in a water bath. The medium was stirred by a perspex paddle 11 cm. in diameter, held 0.5 cm. above the bottom of the vessel and rotating at 56 r.p.m. The two blades of the paddle were 2.5 cm. deep and pitched at 45° to promote axial mixing. Two diametrically opposed baffles 1.3 cm. wide were fixed in the vessel. The test tablet was placed in a cube of 100-mesh stainless steel gauze of sides 1.5 cm., rigidly suspended in the bath 4 cm. from the paddle axis and 2 cm. below the surface of the liquid. The test was performed in 0.001 N.NaOH at 37°C. Five ml. samples were withdrawn through a filter tube at suitable intervals over a period of one hour, diluted and assayed. The second method was a continuous dissolution process, using a cylindrical perspex cell 5.1 cm. in diameter. A 100-mesh, concave, stainless steel gauze was fixed across the cell and the tablet held lightly at the centre with a vertical pin. Water buffered at pH 7 was admitted through the centre of the cell

base and directed radially on the gauze below the tablet.
When the tablet was wetted, the retaining pin was removed
and the liquid issuing from the top of the cell was collected
and assayed. The test was carried out at pH 7 and 20°C to
allow the direct assay of the emerging solution without
further dilution. The first litre of solution was collected
and assayed. The test lasted approximately eleven minutes,
giving a mean liquid velocity in the cell of 0.075 cm./sec.
Disintegration tests were carried out using the method
described in the British Pharmacopeia 1963.

From the results, it was found that the speed of
disintegration progressively decreased as the compression
pressure increased. The dissolution rates fell steeply at
the low compression pressures and then rise to form a peak
at pressures which varied with formulation from 500 to
800 Kg. cm.$^{-2}$. The rate then decreased to give an extended
high pressure region in which dissolution rate was independ-
ent of both pressure and formulation. Although very weak
and easily penetrated by the dissolution medium, tablets
produced at very low pressures did not break up extensively
during the test. Little fragmentation had occurred so that
particle loss and dissolution rate were low. At higher
pressures, penetration still occurred quickly and stress
release and the loss of small air bubbles caused much more
disruption. The van der Waals forces holding the tablet

together in the dry state were ineffectual in the presence
of a liquid of high dielectric constant and penetration by
the dissolution medium caused the tablet to break up. With
further increase in pressure, rebonding of the material
occurred and a stronger and denser tablet was formed, which
was less easily penetrated. Particle loss and dissolution
rate were, therefore, depressed. Ultimately, high strength
and low penetration prevented break-up of the tablet, and
dissolution occurred only from the surface of the tablet
and was therfore independent of any formulation variables.
At low pressure, the dissolution rate of tablets increased
as the filler size or the granule size decreased. These
results indicated that these factors greatly affect the
size of the particles liberated by penetration and break-up.
In the case of the filler, decrease in size increased the
homogeneity of the original mix, opposing the formation of
large agglomerates of phenindione. Decrease in granule size
modified the disposition of the external starch, a factor
which has been shown to greatly affect penetration and
break-up of the tablet. Smaller granules would allow its
more effective distribution as a hydrophilic or antibonding
layer. Both these effects will disappear at high pressures
of compaction when break-up is depressed and solution
occurs only from the surface of the tablet.

A continuous flow system was designed by Woo (33) to study eleven brands of commericially available tolbutamide tablets. The dissolution vessel was a two-litre aspirator bottle. The rubber stopper at the bottom outlet of the bottle carried a short piece of glass tubing that was connected on the inside of the dissolution vessel to a piece of rubber tubing. A piece of very fine gauze that covered the open end of the rubber tubing acted as the filter for the outflowing medium. The glass tube that projected out of the vessel was connected to a T-glass tube, one arm of which was joined to an air supply, while the other arm led to a 500-ml. suction flask via rubber tubing. The rubber stopper at the top of the dissolution vessel carried a thermometer and an inlet tube from a reservoir of simulated gastric fluid. The dissolution vessel was set on a pyro-magnetstir, that kept the medium in the vessel at a temperature of $37^{\circ}C \pm 0.5^{\circ}C$, and caused the magnetic stirrer in the dissolution vessel to stir the medium at varying speeds. The dissolution vessel was filled with one and a half litres of simulated gastric fluid. After the medium had equilibrated to $37^{\circ}C$, a test tablet of tolbutamide (500 mg.) was dropped into the dissolution vessel. The stirrer was turned on to give a vigorous stirring intensity. After an initial ten minutes, the clamp on the

tube to the suction flask was partially unscrewed to allow
a flow rate of 500 ml./30 minutes, when suction was applied.
At the same time, the inflow rate from the reservoir was
adjusted to deliver 500 ml./30 minutes, by partially unscrew-
ing the clamp on the delivery tube. This ensured that the
volume in the dissolution vessel was kept constant. During
the changing of the suction flasks (after each thirty-minute
interval) both the inflow and outflow tubes were clamped
off by a second clamp. As the fluid flowed through the fine
gauze filter, particles of the test tablet collected on the
filter and caused it to be clogged up, thus slowing the
outflow rate. This was overcome by turning on the air supply
occassionally to blow the particles off the gauze back into
the dissolution medium. The dissolution test was carried
on for a period of three hours, collecting in total a volume
of three litres. Individual analyses were carried out on
each portion of dissolution medium collected. Disintegration
tests were carried out on these tolbutamide tablets using
the official U.S.P. disintegration apparatus (30). The
disintegration studies were carried out without the use
of the plastic disks.

The various brands of tolbutamide tablets seemed
to follow a similar pattern of dissolution. In the initial
ten minutes, most of the tablets broke up into very fine
particles or flakes. The release of the active ingredient

increased gradually till a maximum was reached in the first half hour. The level remained constant for about an hour and then gradually decreased due to a dilution process by the incoming solvent, thus giving a plateau-like curve. Even though the dissolution pattern was similar for the different brands, the total amount of the active ingredient released in three litres of solution ranged from 60 mg. to 270 mg. No correlation with the disintegration times could be found, confirming an earlier report by Brudney and his co-workers (1). However, the dissolution test was carried out on only one tablet of each product, so definite conclusions about the tablet quality could not be made. The dissolution test described was very time consuming and required constant supervision. Moreover, the filtering system was not too efficient and tend to clog up towards the end of the dissolution run and hence would be inadequate for longer dissolution runs.

III. THE "IN VITRO" CHARACTERISTICS OF PHENYLBUTAZONE

The drug being investigated is phenylbutazone and is used for the relief of joint pain caused by rheumatoid arthritis, gout, bursitis and other related disorders. Phenylbutazone (1,2-Diphenyl-4-butyl-3,4 Pyrazolidinedione), a weak organic acid of pKa 4.4, is very slightly soluble in water (less than 0.7 mg./ml. at $25^{o}C$) but freely soluble in alcohol (50 mg./ml.), acetone, ether and ethyl acetate.

Phenylbutazone powder tends to agglomerate and float on the surface of an aqueous medium. Attempts at recrystallization yielded long needles that float on the surface of aqueous solutions. Hence, Butazolidin (Geigy) tablets (which have been reported to give good clinical response (2, 27)) were chosen as a standard for this investigation.

(a) The Solubility of Phenylbutazone in Buffered Solutions

It is necessary, during the dissolution test, to change from an acidic medium of pH 1.2 to a pH 6.2. Since the solubility of phenylbutazone is affected by the pH of the dissolving medium, solubility studies were carried out in buffers of different pH values.

Procedure - Using the Smith, Kline & French disintegration apparatus (29), phenylbutazone powder is put into each of six bottles containing 50 ml. of buffer (two samples of each buffer are used). The bottles are suspended

in a water bath maintained at $37^{\circ}C$ and rotated so as to provide good mixing for a period of twenty-four hours. At the end of this period, the solutions are filtered quickly, diluted if necessary with the buffer and assayed spectro-photometrically.

Results - The solubility curve (Figure 1), drawn from the data obtained, showed that the solubility of phenylbutazone is very low in buffers of low pH values. However, once the pH value reached 6, the solubility increased greatly.

(b) Determination of the Isosbestic Point

The isosbestic point of a solution is the wave-length at which changes in the pH of the solution do not affect the absorbancy (As) reading of the solution. Since the conditions of this dissolution test involve a change from an acidic to a basic medium, the wavelength at which absorbancy readings are to be recorded must be at the isosbestic point.

Procedure - Weigh accurately 100 mg. of phenyl-butazone powder and dissolve in 100 ml. of 95% ethanol. Ten ml. aliquots of this solution are diluted accurately to 1000 ml. with buffers of various pH values (ranging from pH 1.2 to pH 7.5). The spectrum of these solutions are recorded on a recording spectrophotometer (Spectronic 505, Bausch and Lomb). From the spectra of the solutions,

an isosbestic point was observed at between 238 mu and 245 mu.

The absorbancy of these solutions are then read on a Beckman DU spectrophotometer from 238 mu to 245 mu with each solution blanked against the respective buffer. A plot of the absorbancy readings for the solutions showed that the wavelength that is closest to being the isosbestic point for phenylbutazone is 240 mu (Figure 2). This point was chosen as the wavelength at which all subsequent absorbancy readings were recorded.

(c) Determination of the Absorptivity Value

The absorptivity (a_s) is a constant for a particular solute in a particular solvent at a certain wavelength. According to Beer's Law, it is the slope of the line relating the absorbancy of a solution and its concentration.

$$As = a_sbc$$

where As is the absorbancy of the solution

a_s is the absorptivity

b is the cell length in cm.

c is the concentration in gm./L.

Procedure - Weigh accurately 100 mg. phenylbutazone powder and dissolve in 100 ml. of 95% ethanol. Dilute aliquots of five to twenty ml. to 1000 ml. with Simulated Intestinal Fluid U.S.P. The absorbancy of each solution is read on a Beckman DU spectrophotometer at 240 mu, using Simulated Intestinal Fluid U.S.P. as a blank.

<u>Results</u> - The absorbancy readings were plotted
and a straight line was obtained. The absorptivity was
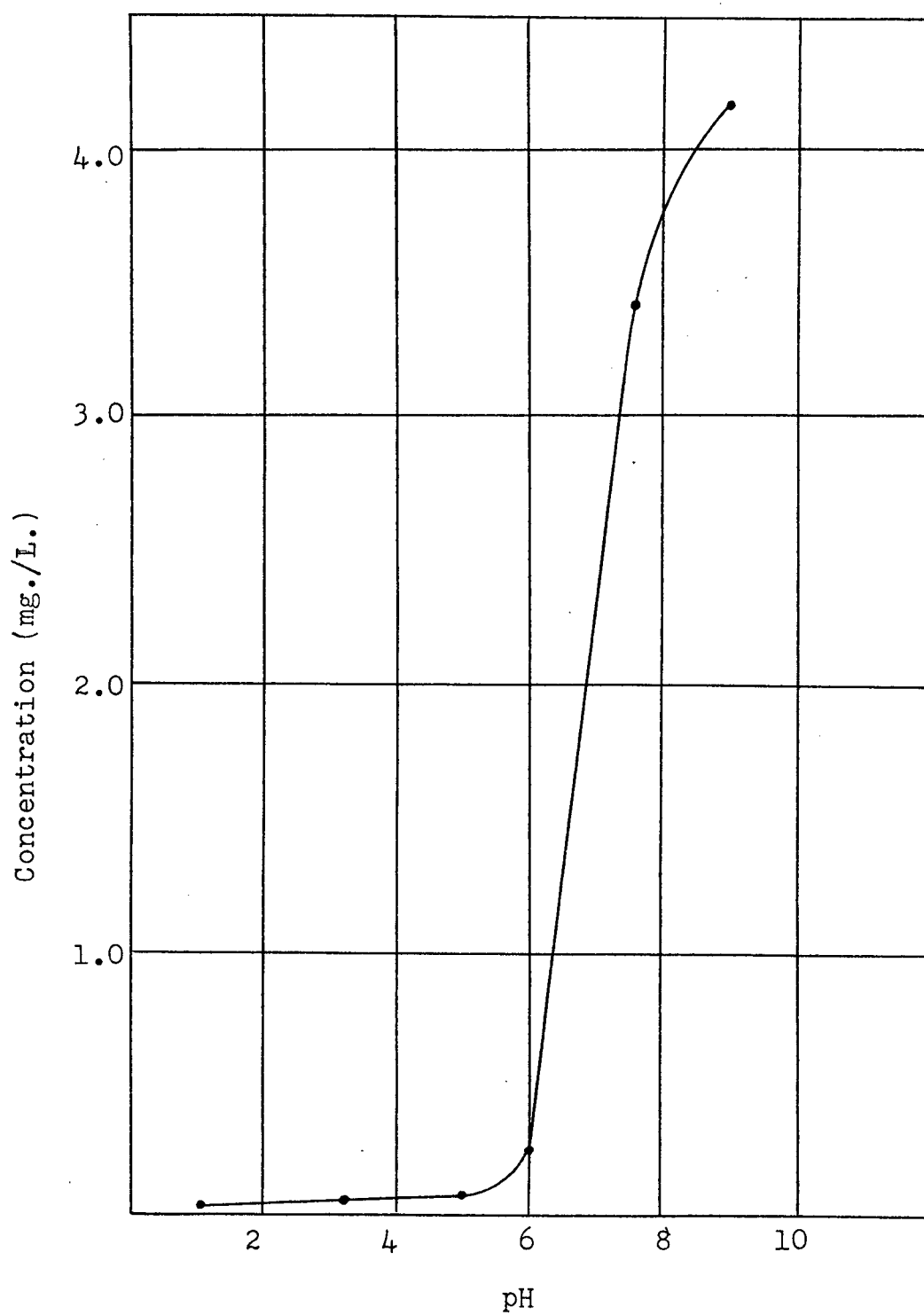calculated from the slope of this line and found to be 41.5
(Figure 3).

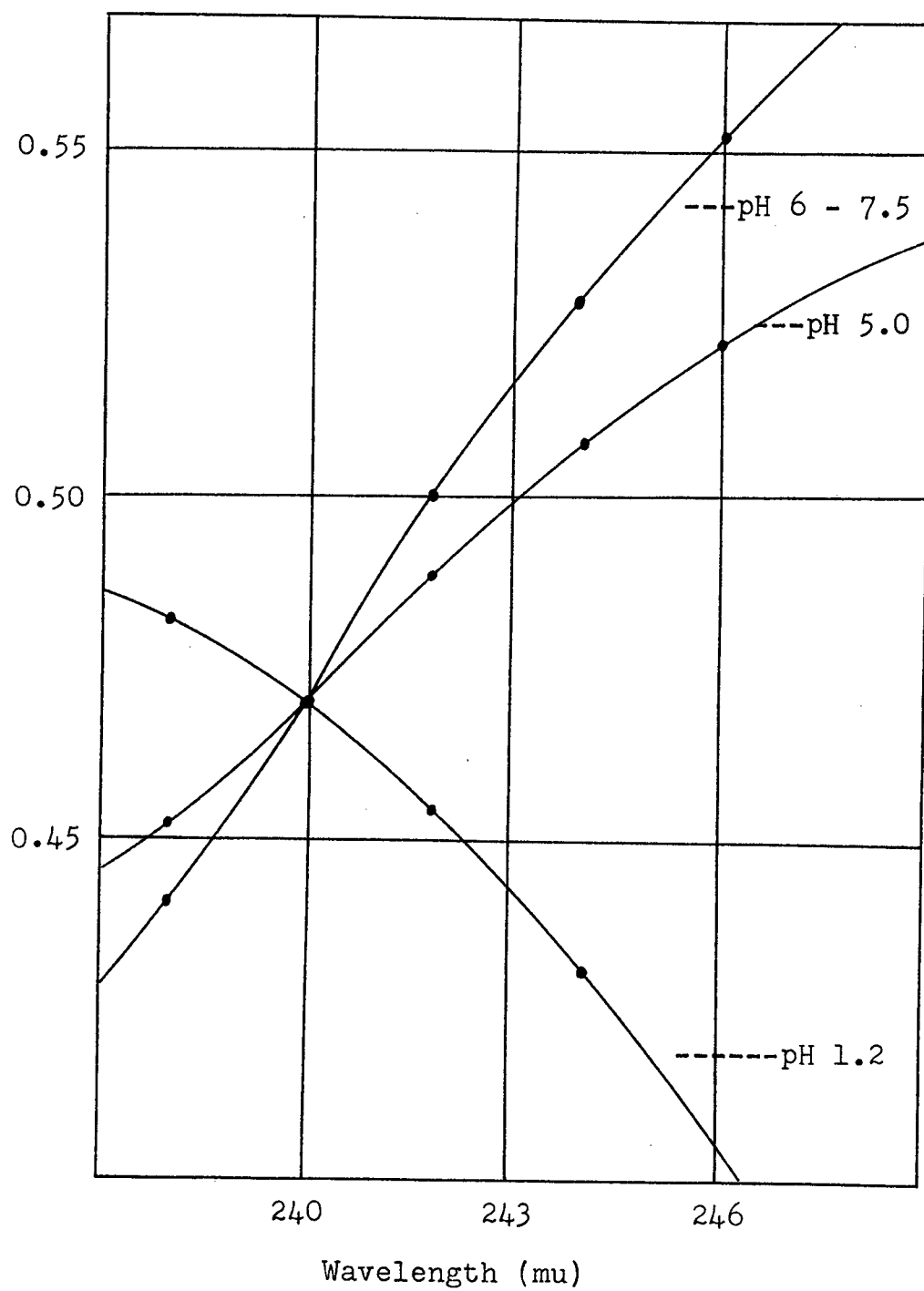Figure 1. The Effect of pH on the Solubility of Phenylbutazone

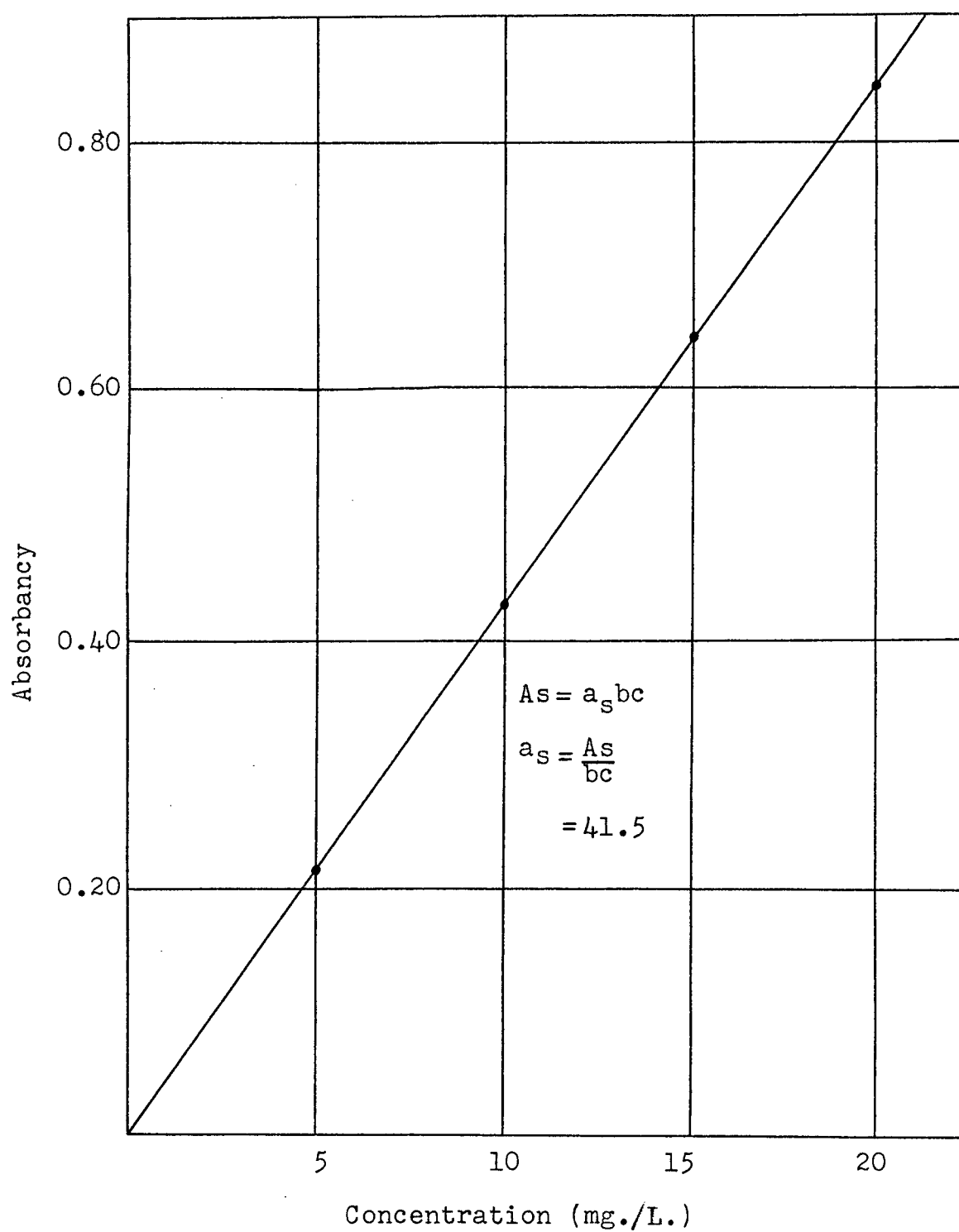Figure 2. The Isosbestic Point of Phenylbutazone

Figure 3. Calibration Curve for Phenylbutazone in Simulated
Intestinal Fluid at 240 mu

IV. THE OPERATING CHARACTERISTICS OF A CONTINUOUS FLOW
DISSOLUTION APPARATUS

(a) Description of the Apparatus

The dissolution vessel (a one-litre three-neck round-bottom flask) is immersed in a constant temperature water bath at $37^{\circ}C \pm 0.5^{\circ}C$. Dipping into the central neck of the flask is the shaft of a Fisher Stedi-Speed adjustable stirrer (Model 12) with a four-blade impeller blade (3 cm. in diameter) and a cylindrical wire basket at its bottom. The basket which is 4 cm. long and 2.5 cm. in diameter is made from 10-mesh stainless steel wire cloth.

A glass tube which acts as the inlet tube for the dissolution medium dips through the right side neck into the dissolution vessel to a depth of 10 cm. Connected to this tube is a two-way stop cork, one arm of which is connected to a reservoir of simulated gastric juice (2 gm. NaCl + 7 ml. HCl in 1000 ml. distilled water, pH 1.2) while the other arm is joined to a reservoir of simulated intestinal juice (6.8 gm. KH_2PO_4 + 1.52 gm. NaOH in 1000 ml. distilled water, pH 7.5). Both reservoirs of dissolution medium are placed on heaters to keep the solution at $37^{\circ}C \pm 0.5^{\circ}C$.

An inverted sintered glass funnel (30 ml. capacity) of coarse porosity dips into the left side arm of the dissol-ution vessel. It is joined to a short length of glass tube

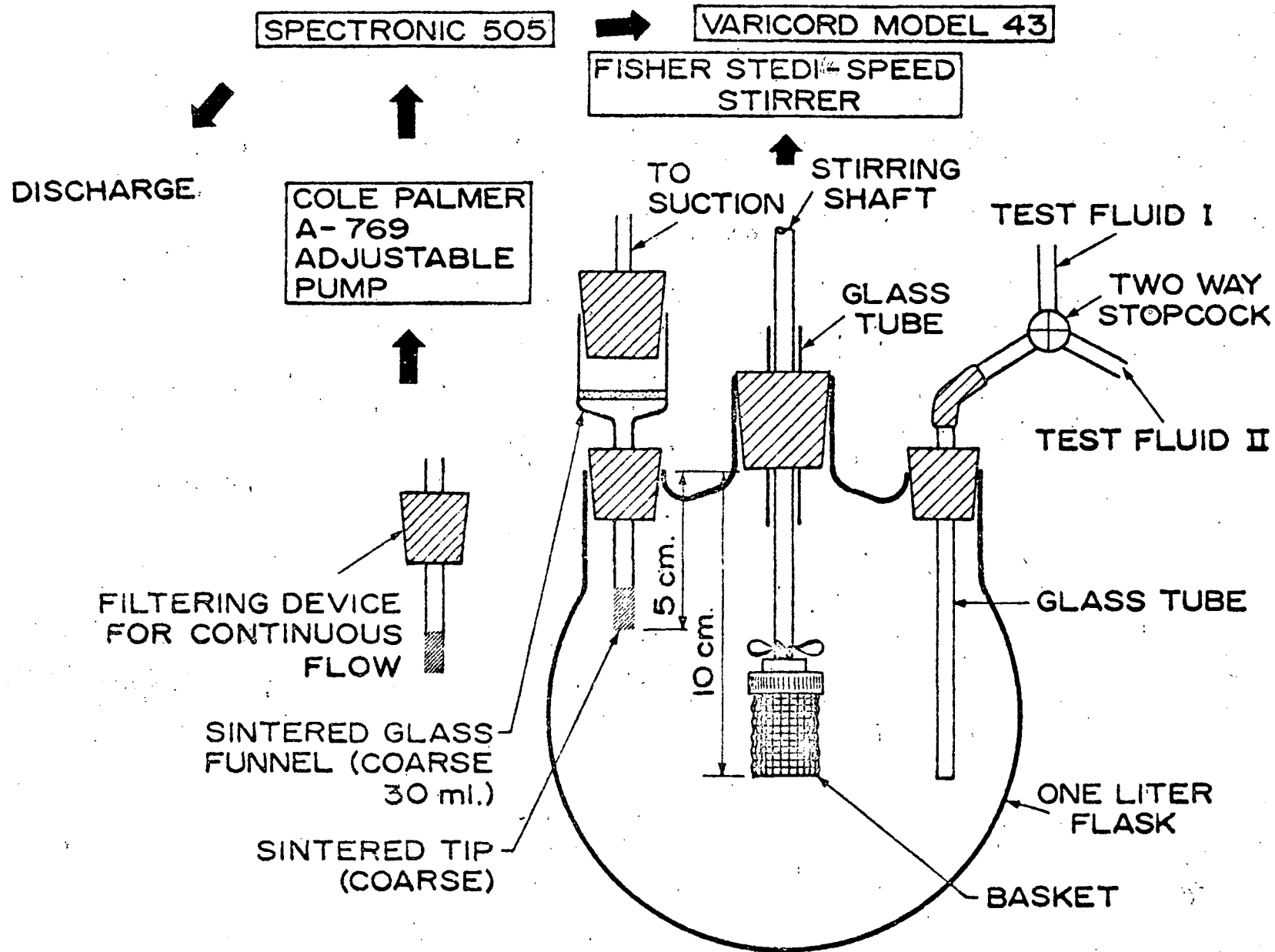carrying a sintered tip (coarse porosity), that dips into the dissolution vessel to a depth of 5.0 cm.

A combination glass electrode (not illustrated in Figure 4) leading from a recording potentiometer (Potentiograph E336A) and a short piece of glass tube, which acts as the outlet tube, dip into the broad end of the sintered glass funnel. The outlet tube is joined by Tygon tubing to an adjustable pump (Cole Palmer A-769) from which tubing leads to a flow cell (1 cm. in length) in a recording spectrophotometer (Spectronic 505, Bausch & Lomb). A recorder (Varicord Model 43) is attached to the spectrophotometer for a direct recording of the concentration of the solution passing through the flow cell. From the flow cell, the solution is delivered into a twelve-litre covered glass vessel, that acts as the collecting vessel.

(b) <u>Calibration of the Recorder</u>

<u>Procedure</u> - The recorder is set on the 25 and mV range. It is zeroed with gastric juice in the sample cell and air as the blank. Solutions of known concentration of phenylbutazone are read in the sample cell of the spectrophotometer at 240 mu and the chart readings on the recorder scale are recorded.

From the known concentrations and the chart readings on the recorder scale, a graph is plotted (Figure 5).

Figure 4. Diagram of Continuous Flow Dissolution
Apparatus

SPECTRONIC 505

VARICORD MODEL 43

FISHER STEDI-SPEED STIRRER

DISCHARGE

COLE PALMER A-769 ADJUSTABLE PUMP

TO SUCTION

STIRRING SHAFT

TEST FLUID I

TWO WAY STOPCOCK

GLASS TUBE

TEST FLUID II

FILTERING DEVICE FOR CONTINUOUS FLOW

5 cm.

10 cm.

GLASS TUBE

SINTERED GLASS FUNNEL (COARSE 30 ml.)
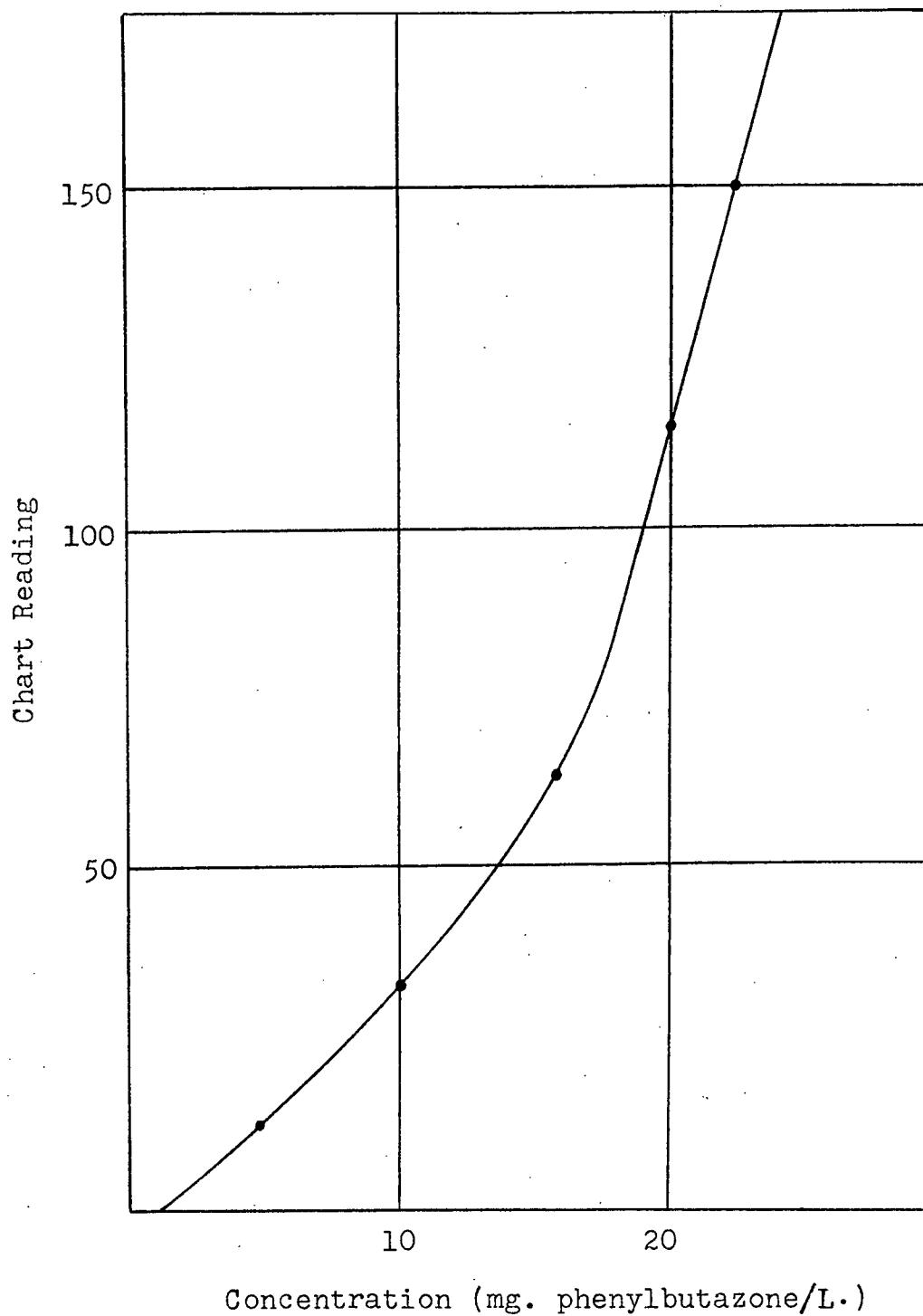
SINTERED TIP (COARSE)

ONE LITER FLASK

BASKET

Figure 5. Calibration Curve for Recorder External to the
Spectronic 505

(c) The Effect of Stirring Rate on Dissolution

The stirring rate has been reported by many researchers (8, 11, 17) to have a considerable effect on the dissolution rate. Levy (11) has stated that too intensive an agitation rate is to be avoided since X-ray photographs have shown that tablet particles tend to remain as an aggregate on the stomach surface. This implies that the mixing process in the stomach is very low. However, in the small intestine, the particles appeared to be very well dispersed indicating that the mixing in this region is quite vigorous.

Since phenylbutazone is nearly insoluble in solutions of pH 1.2 but very soluble in solutions of pH 7.5, it would appear that the absorption of phenylbutazone occurs mainly under the basic conditions of the small intestine. Hence, a stirring rate that causes the drug particles to be well dispersed throughout the medium may be desirable in the dissolution test under study.

Consequently, stirring rates of 65, 100 and 115 r.p.m. in the forward direction were investigated using the designed dissolution apparatus and test procedure. These stirring rates were investigated with the stirrer at different depths in the dissolution medium, using Butazolidin tablets as the test preparation, and at a constant pumping rate of 60 ml./minute. Each rate was tested in duplicate.

Results - The data obtained from the dissolution runs are tabulated in Table I. It can be seen that when the stirring is not enough to move the particles, the release rate of the drug is low even though the solution in the dissolution vessel appears to be homogeneous. The low release rate is due to the fact that the tablet particles remain as an aggregate on the dissolution vessel bottom, thus presenting a limited surface area to the dissolution medium.

When the basket is 6 cm. from the vessel bottom, the stirring is insufficient even at the high stirring rate of 115 r.p.m. At 3.5 cm. from the bottom of the vessel, the stirring is adequate except at the lowest rate of 65 r.p.m., when about half of the tablet particles remain aggregated on the vessel bottom. The other two stirring rates caused the particles to move through the medium, the higher rate of 115 r.p.m. giving a more vigorous movement. At a depth of 1 cm. from the vessel bottom, the stirring effect is quite vigorous even at the rate of 65 r.p.m. To avoid this stirring effect, this depth was not chosen for product testing.

The depth finally chosen was 3.5 cm. with a stirring rate of 100 r.p.m. rather than 115 r.p.m. The former rate produced the desired stirring effect. At this speed, the particles move slowly through the medium.

Table I. The Effect of Stirring Rate on Dissolution

Stirring rate (forward direction)	Depth of basket from vessel bottom	Mg. phenylbutazone in solution in 3 hours
	1 cm.	87.5 mg.
65 r.p.m.	3.5 cm.	62.1 mg.
	6 cm.	55.4 mg.
	1 cm.	83.1 mg.
100 r.p.m.	3.5 cm.	83.5 mg.
	6 cm.	75.0 mg.
	1 cm.	90.0 mg.
115 r.p.m.	3.5 cm.	85.0 mg.
	6 cm.	78.5 mg.

(d) The Effect of Pumping Rate on Dissolution

Three pumping rates were studied for their effect
on dissolution rate. The dissolution test was carried out
with Butazolidin tablets as the test preparation and with
the basket at 3.5 cm. from the vessel bottom stirring at
a rate of 100 r.p.m. The pumping rates studied were 50 ml./min.,
60 ml./min. and 70 ml./min. Rates lower than 50 ml./min.
were not studied due to instrumental limitations in reading
the more concentrated solutions.

Results - The data obtained are tabulated in
Table II. This data shows that there is no significant differ-
ence in the release of the drug in the three-hour period.

The pH changes in the medium are affected by the
pumping rate to a slight extent. Higher pumping rates gave
a much faster pH change from acidic to basic pH. At the
pumping rate of 60 ml./min., the sharp rise in pH from about
pH of 2 to pH of 6.2 occurred within twenty-five minutes
(Figure 6), while at a pumping rate of 70 ml./min., it
occurred within twenty minutes. However, at 70 ml./min.,
the final volume of solvent is too great to be handled
easily. At 50 ml./min., the pH change occurred in thirty
minutes but at this rate, the solution is becoming too
saturated to be read on the spectrophotometer. A pumping
rate of 60 ml./min. was therefore, finally chosen for the
dissolution test.

Table II. The Effect of Pumping Rate on Dissolution

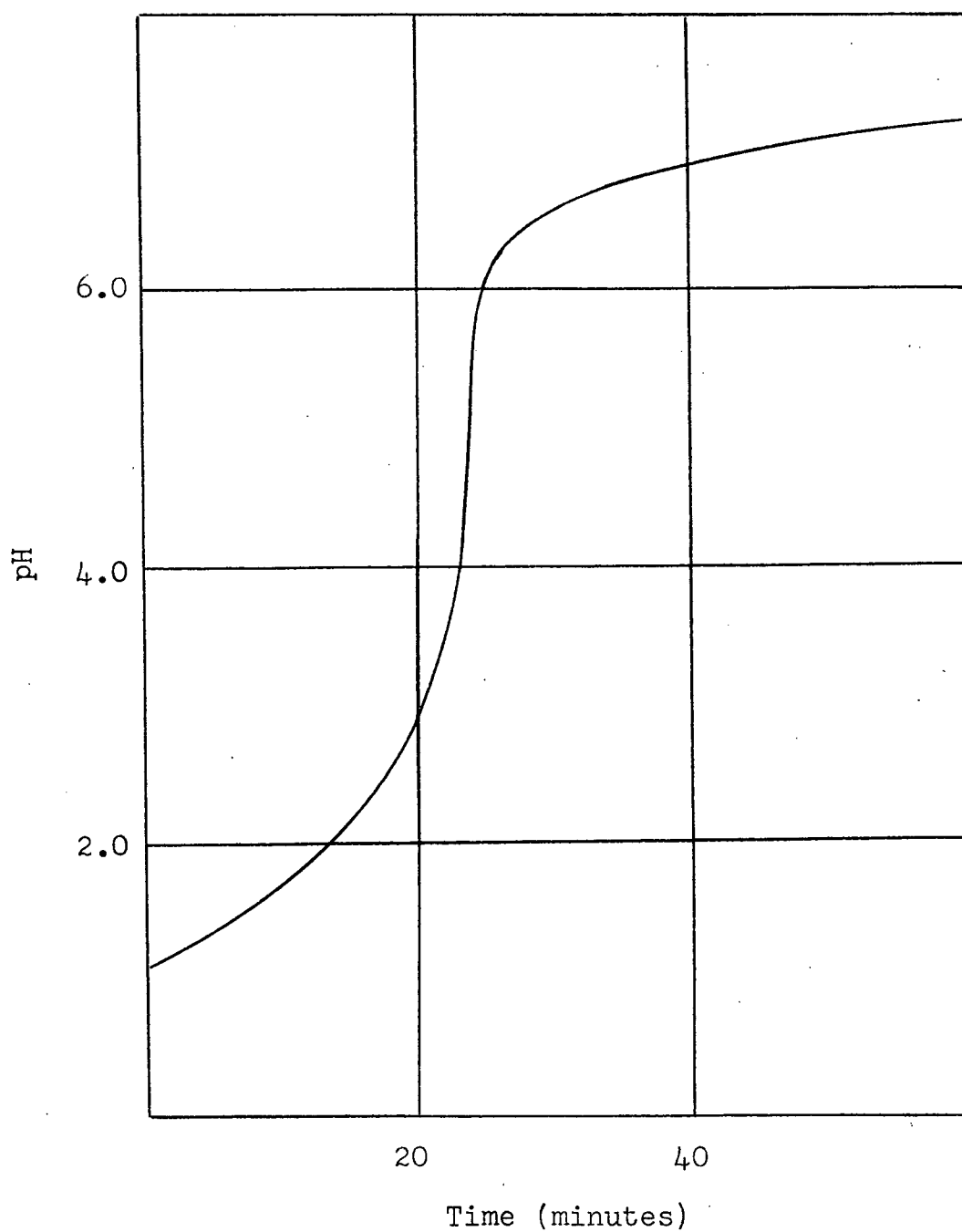| Pumping rate		Mg. of phenylbutazone in solution		
		1 hour	2 hours	3 hours
50 ml./min.	1.	4.0 mg.	56.0 mg.	86.5 mg.
	2.	3.9 mg.	51.0 mg.	86.4 mg.
60 ml./min.	1.	9.0 mg.	68.4 mg.	89.6 mg.
	2.	8.3 mg.	62.6 mg.	86.4 mg.
70 ml./min.	1.	5.9 mg.	62.2 mg.	86.5 mg.
	2.	6.7 mg.	63.0 mg.	88.2 mg.

Figure 6. pH Changes at a Pumping Rate of 60 ml./min.

(e) Test Procedure

With the apparatus set up as described and as shown
in Figure 4, the dissolution vessel (containing one litre of
simulated gastric juice) is allowed to equilibrate in a
constant temperature water bath at $37^{\circ}C \pm 0.5^{\circ}C$. The entire
system is flushed out with simulated gastric juice to remove
air from the system. The recorder is zeroed with simulated
gastric juice in the sample flow cell and air as the blank.

A single phenylbutazone tablet (100 mg.) is put
into the wire basket below the impeller blade and the whole
apparatus is set in motion. The stirring rate is 100 r.p.m.
in a forward (clockwise) direction at a depth of 3.5 cm.
from the bottom of the dissolution vessel. With the inlet
tube from the reservoir of simulated gastric juice opened,
the pump is turned on to deliver 60 ml./min. through the
entire system.

After the initial thirty minutes, simulated intest-
inal juice is allowed into the system. At this point, the
potentiometer is switched on to record pH changes as the
medium is gradually changed from an acidic medium to a
basic one.

Aliquots from the collecting vessel are taken at
hourly intervals for analysis on a Beckman DU spectrophoto-
meter at 240 mu, with simulated intestinal juice as the
blank. As the solution from the dissolution vessel passes

through the flow cell in the spectrophotometer set at 240 mu, the Varicord records the concentration. This gives a continuous recording of the concentration of the solution as dissolution occurs.

The dissolution run is carried on for three to six hours depending on the dissolution rate of the individual products. At the end of each run, the entire system is flushed out with 95% ethanol and water.

Using this test procedure, seven brands of commericially available phenylbutazone tablets (100 mg.) were tested in triplicate. Four of the products are sugar-coated tablets (Products A, E, W, X) while the other three are enteric coated tablets (Products AA, CC, DD_1). Each product was tested in triplicate.

(f) Results

An average continuous concentration plot was obtained for each product from the curves drawn out on the recorder. This plot gave the dissolution profile of the product and also allows the calculation of the total amount of drug released in any period of time (Figures 7a, b, c). The hourly analysis on the Beckman DU spectrophotometer also gave the amount of drug released at each hourly interval, thus providing a check on the amount registered by the recorder (Table III).

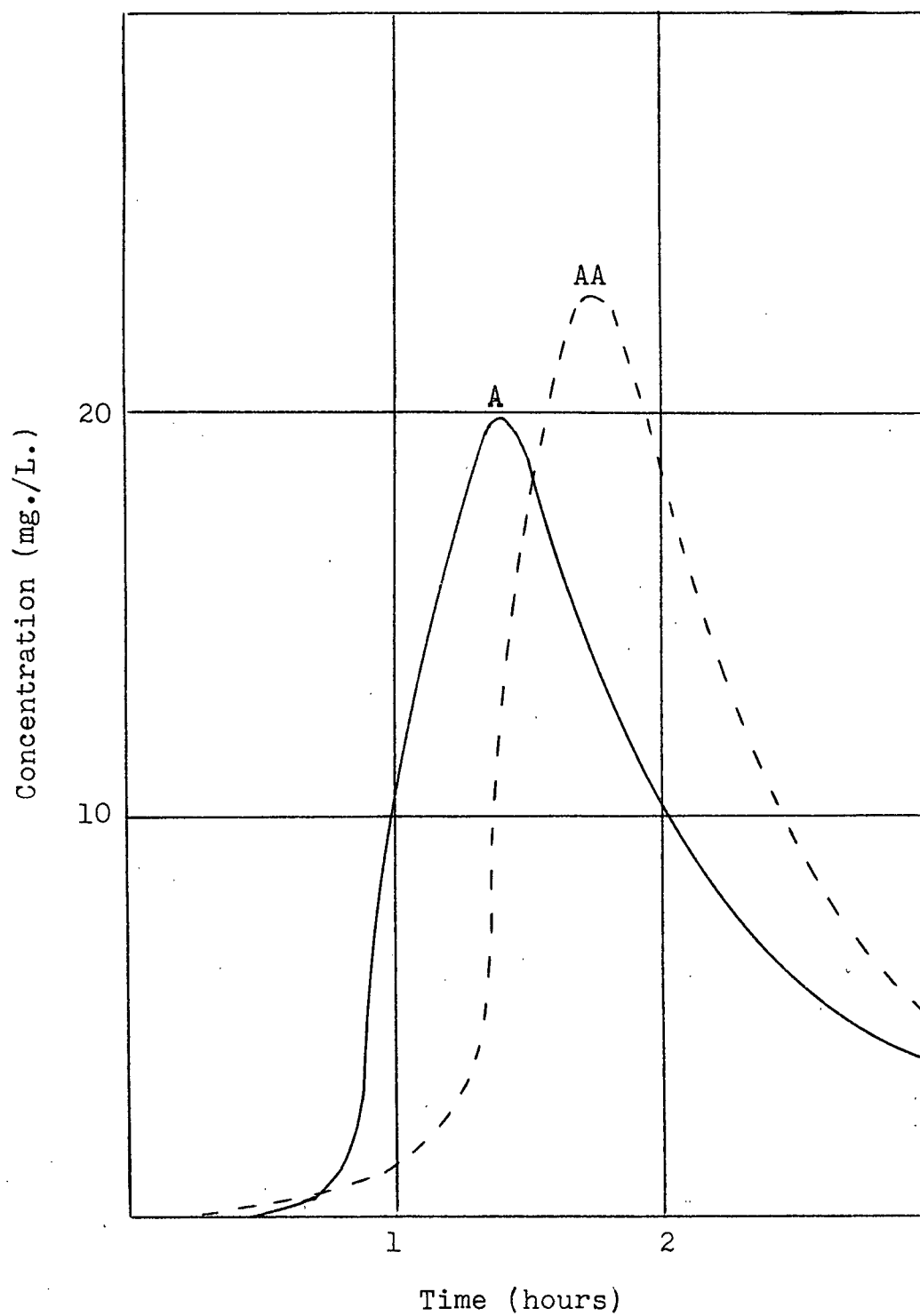From the data on the products obtained by the two

Figure 7a. Dissolution Profiles for Two Brands of
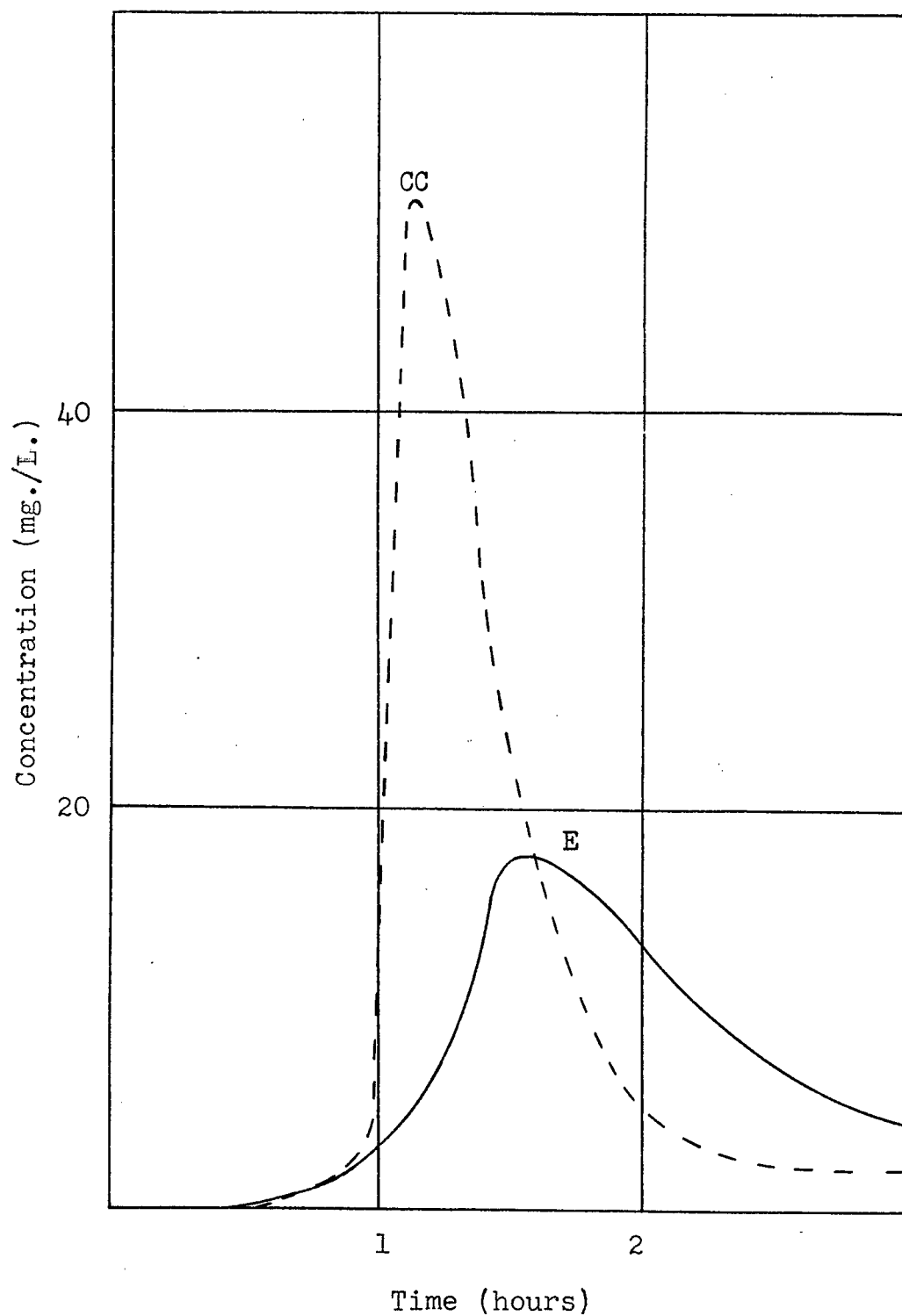Phenylbutazone Tablets

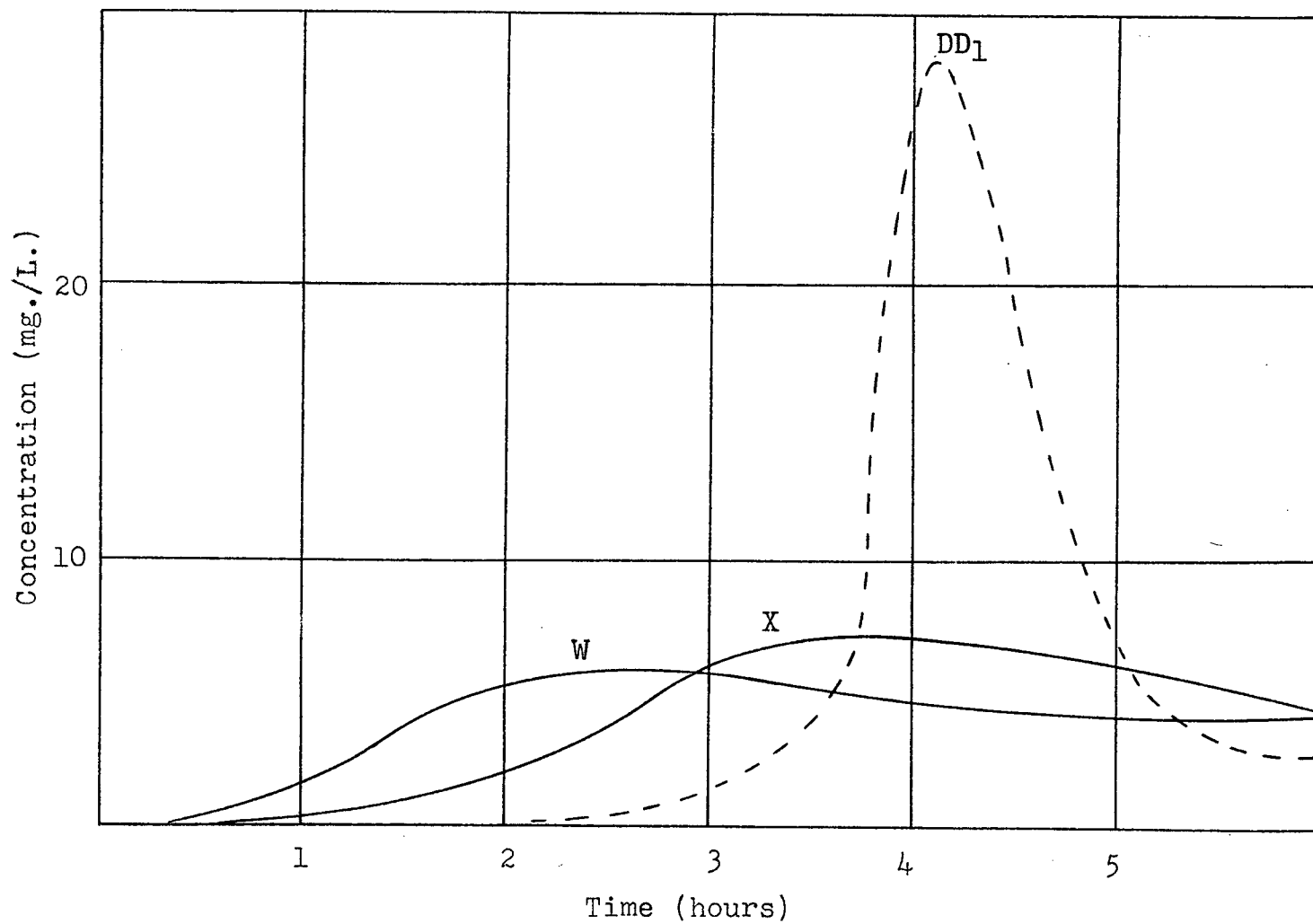Figure 7b. Dissolution Profiles for Two Brands of
Phenylbutazone Tablets

Figure 7c. Dissolution Profiles for Three Brands of Phenylbutazone Tablets

Table III. Dissolution Data for Seven Brands of
Phenylbutazone Tablets

Product		Mg. of phenylbutazone in solution		
		1 hour	2 hours	3 hours
	1.	5.2 mg.	62.5 mg.	86.5 mg.
A	2.	5.2 mg.	61.9 mg.	88.0 mg.
	3.	5.2 mg.	65.9 mg.	93.5 mg.
	1.	1.2 mg.	52.5 mg.	86.5 mg.
E	2.	1.8 mg.	50.4 mg.	81.8 mg.
	3.	1.5 mg.	48.0 mg.	79.2 mg.
	1.	0.8 mg.	43.2 mg.	85.3 mg.
AA	2.	0.8 mg.	43.2 mg.	86.5 mg.
	3.	1.2 mg.	51.5 mg.	89.6 mg.
	1.	1.4 mg.	91.4 mg.	96.2 mg.
CC	2.	1.7 mg.	95.7 mg.	100.0 mg.
	3.	1.7 mg.	90.7 mg.	95.8 mg.

Table III (Continued)

Product		Mg. of phenylbutazone in solution			
		3 hours	4 hours	5 hours	6 hours
	1.	7.4 mg.	23.6 mg.	55.8 mg.	75.7 mg.
X	2.	16.2 mg.	55.8 mg.	78.7 mg.	93.0 mg.
	3.	23.8 mg.	50.8 mg.	75.0 mg.	92.2 mg.
	1.	36.0 mg.	55.2 mg.	70.6 mg.	86.3 mg.
W	2.	36.2 mg.	55.0 mg.	70.3 mg.	86.0 mg.
	3.	36.3 mg.	55.3 mg.	70.5 mg.	86.2 mg.
	1.	5.4 mg.	27.0 mg.	94.0 mg.	101.5 mg.
DD_1	2.	4.5 mg.	22.5 mg.	91.7 mg.	99.0 mg.
	3.	4.5 mg.	22.3 mg.	90.9 mg.	98.0 mg.

Table IV. $T_{50\%}$ and $T_{90\%}$ Values for Seven Brands of
Phenylbutazone Tablets

Product	$T_{50\%}$ value	$T_{90\%}$ value
A	100 minutes	180 minutes
E	120 minutes	215 minutes
W	225 minutes	735 minutes
X	255 minutes	735 minutes
AA	125 minutes	185 minutes
CC	80 minutes	120 minutes
DD_1	225 minutes	300 minutes

methods, time for 50% of the drug ($T_{50\%}$) and 90% of the
drug ($T_{90\%}$) to go into solution was calculated and tabulated
in Table IV.

The four brands of sugar-coated tablets showed
little dissolution in simulated gastric fluid. However,
once the medium reached a pH of 6.2, the concentration of
the active ingredient increased greatly. This change in pH
occurred in twenty-five minutes at the pumping rate of
60 ml./minute.

Products A and E (which disintegrated within
fifteen minutes of the start of the experiment) showed
similar dissolution patterns. The concentration of active
ingredient continued to increase gradually once the medium
reached a pH of 6. A peak was reached in about one and a
half hours. The curve then gradually declined due to a
dilution process by the incoming solvent. Product E released
slightly less active ingredient from the tablet than did
Product A.

The other two sugar-coated products showed differ-
ent dissolution profiles due to the lack of disintegration.
Product W did not disintegrate at all even at the end of
six hours. Dissolution by this product was very low and
stayed at the same level throughout the entire dissolution
run. The active ingredient seemed to dissolve out from the
surface of the tablet, which was smaller but still intact

at the end of the dissolution run. Product W showed very little tablet variation. Product X was found to vary from one tablet to another in the same lot. After the tablet coating came off after three hours, large particles could be seen coming off and, at this point, the concentration of the active ingredient registered on the recorder was seen to increase suddenly but not greatly. The concentration level remained approximately the same for about an hour, then decreased very slightly for the rest of the time.

The dissolution rate of Products W and X was so low that the dissolution run had to be carried on for six hours instead of three hours. Products A and E released about 90% of the active ingredient in three hours while it took Products W and X six hours to release the same amount of active ingredient.

The three enteric coated Products AA, CC and DD_1 remained intact till the dissolution medium reached a pH of 7. Products AA and CC broke up very quickly into small particles. Product DD_1 did not start to disintegrate until about three and a half hours after the start of the dissolution run.

Product CC gave a much faster dissolution rate than Product AA, with a concentration peak much higher than those of the other test products and, even earlier than the sugar-coated products. This was probably due to its

almost immediate disintegration in the alkaline medium into very fine particles. The dissolution profile for Product AA was similar to those for the sugar-coated Products A and E, except for a delay of about twenty-five minutes in its peak due to the enteric coating. The fall in the dissolution curve of Product CC was very sharp while that of Product AA was much more gradual. Product DD_1 released its active ingredient rapidly after disintegration occurred, giving a peak second only to Product CC. Hence, it would appear that the disintegration time of the tablet had an effect on the dissolution of the tablet when the disintegration time was excessively long.

A $T_{50\%}$ value of 120 minutes would seem to be a reasonable limit of acceptance of the products that could be said to be effective "in vivo". This implies that only four of the products tested, A, E, AA and CC are acceptable. This "in vitro" estimation can be supported by the "in vivo" data that showed the three Products E, AA and CC were at least 75% as effective as Product A (a product tested and found to give good clinical response). Product AA would be a border-line case by both the "in vivo" and the "in vitro" results.

V. THE "IN VIVO" CHARACTERISTICS OF PHENYLBUTAZONE TABLETS

Burns and his co-workers (2) claimed that due to the affinity of phenylbutazone for plasma proteins as compared to tissue proteins, a great portion of administered phenylbutazone is found in the plasma. They reported that peak plasma levels were reached in about two hours after oral administration, indicating that the drug was rapidly absorbed from the gastrointestinal tract. Plasma levels did not increase proportionately with increasing doses of the drug but tend to reach a limiting concentration, which varied considerably among subjects. On repeated daily dosage, the drug accumulated in the body with a progressive increase in the plasma concentration until a plateau was reached on the third or fourth day.

In a comparative study of commericially available brands of phenylbutazone tablets, Searl and Pernarowski (26) determined serum levels after administration of the products to human subjects.

The seven products were administered to nine subjects as shown in Table V. Each subject was given two tablets, that is approximately 200 mg. of phenylbutazone. In general, the product was given to the subject shortly after breakfast. Three to five samples of blood were taken over a 48-hour period but only the results to 30 hours are shown.

Determination of Phenylbutazone in Serum

Fifteen ml. of blood are withdrawn by means of a dry sterile syringe and needle from a large vein in the bend of the elbow. The blood is allowed to clot, then centrifuged and the serum is removed. Two ml. of serum are transferred to a 50-ml. glass-stoppered centrifuge tube. Five ml. of 3 N.HCl solution and 20.0 ml. of heptane are added and the tube is shaken for thirty minutes in an automatic shaker and centrifuged at 1200 r.p.m. for five minutes. Fifteen ml. of heptane are withdrawn and transferred to a 200-ml. bottle. Five ml. of 2.5 N.NaOH solution are added and swirled gently. The solution is then shaken for five minutes and poured into a 50-ml. centrifuge tube and centrifuged at 1200 r.p.m. for three minutes. The absorbancy of the sodium hydroxide solution is read at 265 mu. The absorptivity of phenylbutazone at 265 mu in 2.5 N.NaOH is 65.2.

It may be necessary to dilute the sodium hydroxide solution or to decrease the amount of serum taken for analysis if the concentration of phenylbutazone in the serum exceeds 30 mg. per litre.

A blood sample taken before the administration of the drug serves as a control or "blood-blank". This sample when treated as described above, absorbs some ultraviolet radiant energy at 265 mu. Consequently, all subsequent assay values must be adjusted to compensate for this "blood-blank".

Results

Peak plasma levels were obtained in five rather
than in two hours as had been reported by Burns and his
co-workers (2). A typical blood curve is shown in Figure 8.
After the peak region, the serum drug level decreased
quite gradually. The areas under the blood curves were
determined by a planimeter and are tabulated in Table V.

Using Product A as a chosen standard, only three
other products, E, AA and CC appeared to be at least 75%
as effective as Product A, and thus considered acceptable.
Since data for subjects 3 - 9 was incomplete, it was not
possible to use it for a comparison. However, available
data from these subjects tend to indicate that response to
the products follow the same trend as in subjects 1 and 2.
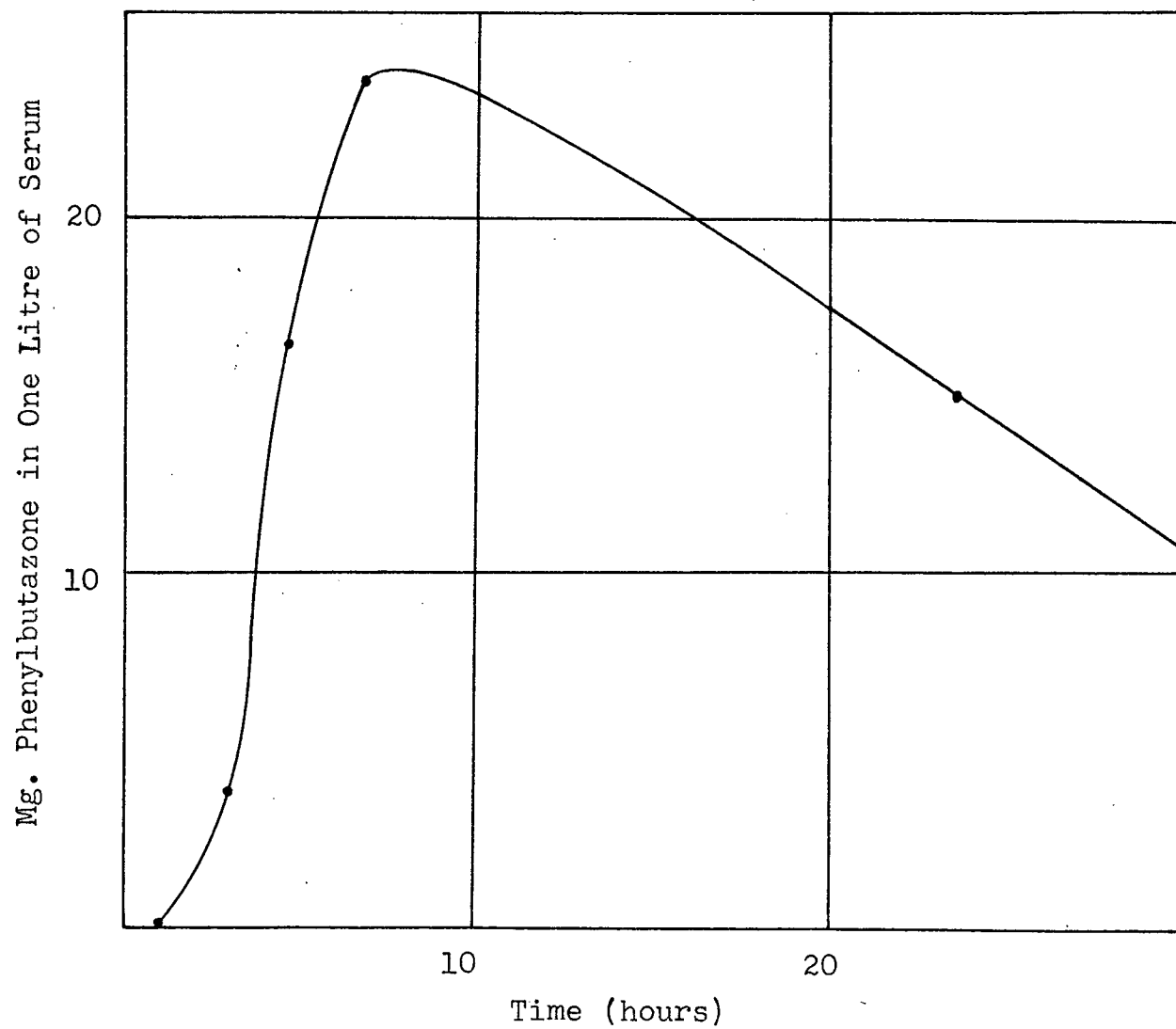
Figure 8. Concentration of Phenylbutazone in Serum after Administration of Product A to Subject 1

Table V. Areas under Blood Curves for Seven Brands of
Phenylbutazone Tablets

Product Subject	A	E	W	X	AA	CC	DD$_1$
1	18.57	14.8	1.82	13.3	12.42	15.33	6.55
2	20.55	15.2	4.61	7.0	15.51	22.84	11.21
3	24.1	26.4	8.9	17.0	—	—	—
4	—	—	—	—	8.62	—	—
5	—	—	—	—	10.48	—	—
6	—	—	—	—	—	23.34	—
7	—	—	—	—	—	11.48	—
8	—	—	—	—	—	—	3.79
9	—	—	—	—	—	—	4.65

VI. "IN VIVO" - "IN VITRO" CORRELATION

"In vitro" results only serve to reduce the number
of samples considered suitable for "in vivo" testing.
However, they are significant when they can be quantitatively
correlated with "in vivo" data. Even though the "in vivo"
data available is not complete for all test products, an
attempt was made to correlate this data with the $T_{50\%}$ and
the $T_{90\%}$ values obtained by the "in vitro" test procedure.

Correlation was attempted only for the two subjects
with complete "in vivo" data, since data for Product A was
not available for the other subjects. However, the response
shown by these subjects seem to follow the same trend as
that of subjects 1 and 2. It can be assumed, therefore, that
the same type of correlation could be obtained for these
subjects, taking into account the possible differences in
the metabolism of the drug in these subjects.

By the use of linear regression, the line of
"least squares" drawn for each set of data for subjects
1 and 2 (Figures 9, 10, 11, 12). The points for subject 2
seem to fit better on the line of "least squares" drawn
than those for subject 1. One of the reasons for the
deviations from the "least squares" line could be that
some of the "in vivo" blood curves were drawn from the
inadequate data. Tablet variability (especially for Product X)
could also have contributed to the deviations.

The lines of "least squares" had negative slopes
indicating an inverse relationship between the "in vivo" and
the "in vitro" data. The slopes of these lines ranged from
-0.042 to -0.075, with the slopes of the $T_{50\%}$ lines greater
than the $T_{90\%}$ lines of both subjects. The slopes of the
lines for subject 2 were greater than those of subject 1.
This was expected since subject 2 showed greater response
to the drug than subject 1. The difference between the
slopes of the $T_{50\%}$ line and the $T_{90\%}$ line of subject 1 was
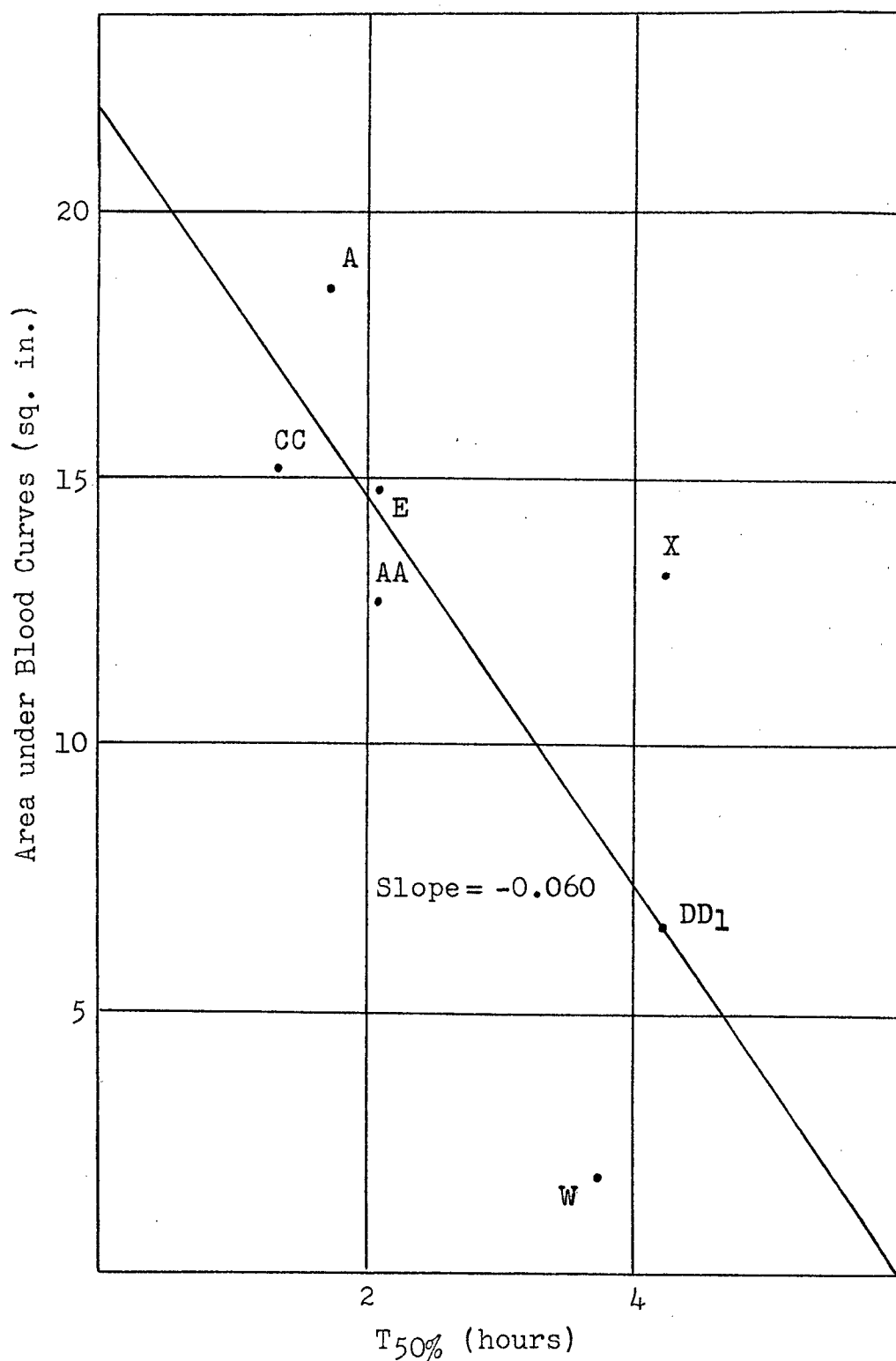twice that of subject 2.

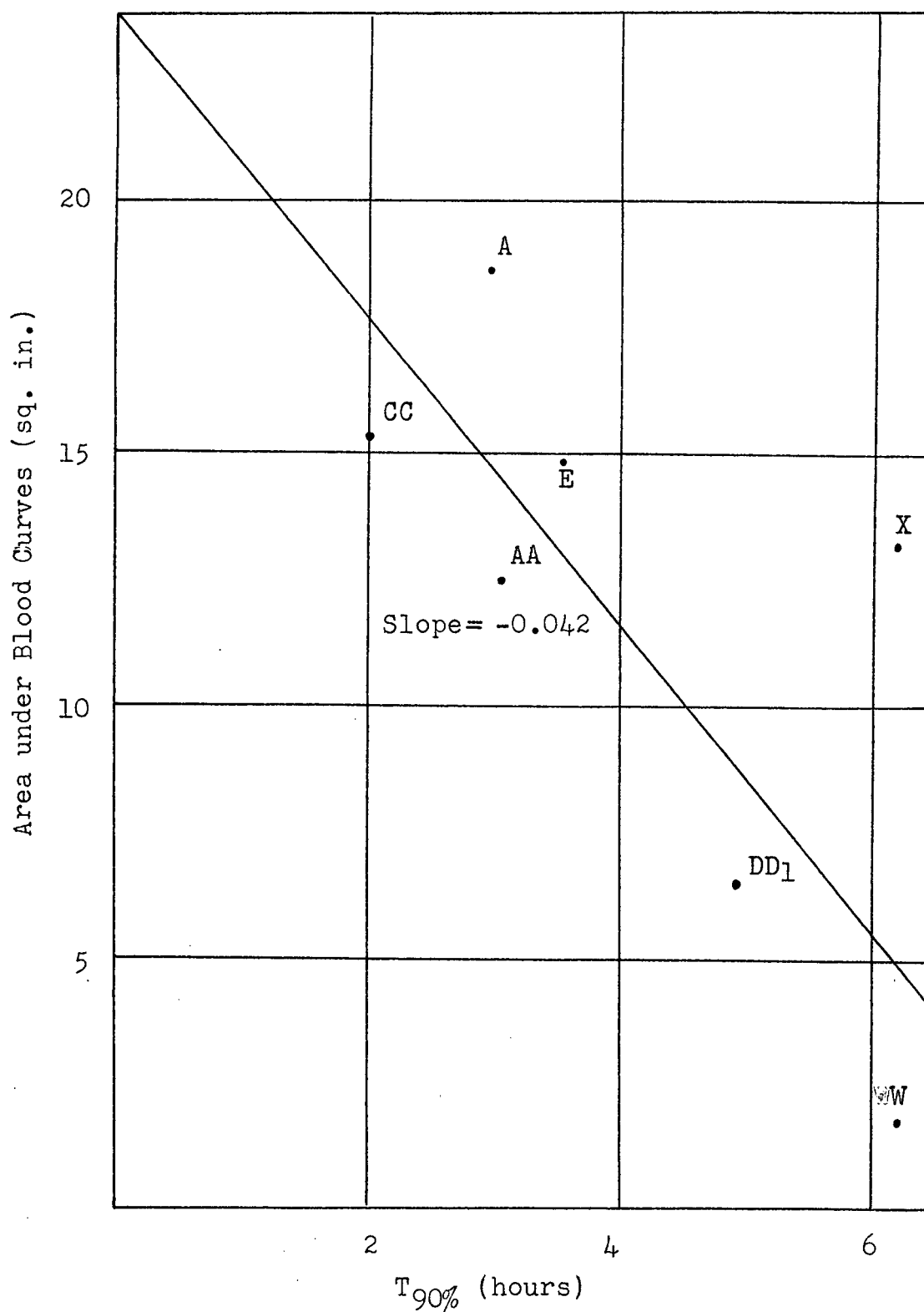Figure 9. Correlation of $T_{50\%}$ Values with "_In Vivo_" Data for Subject 1

Figure 10. Correlation of $T_{90\%}$ Values with "In Vivo" Data
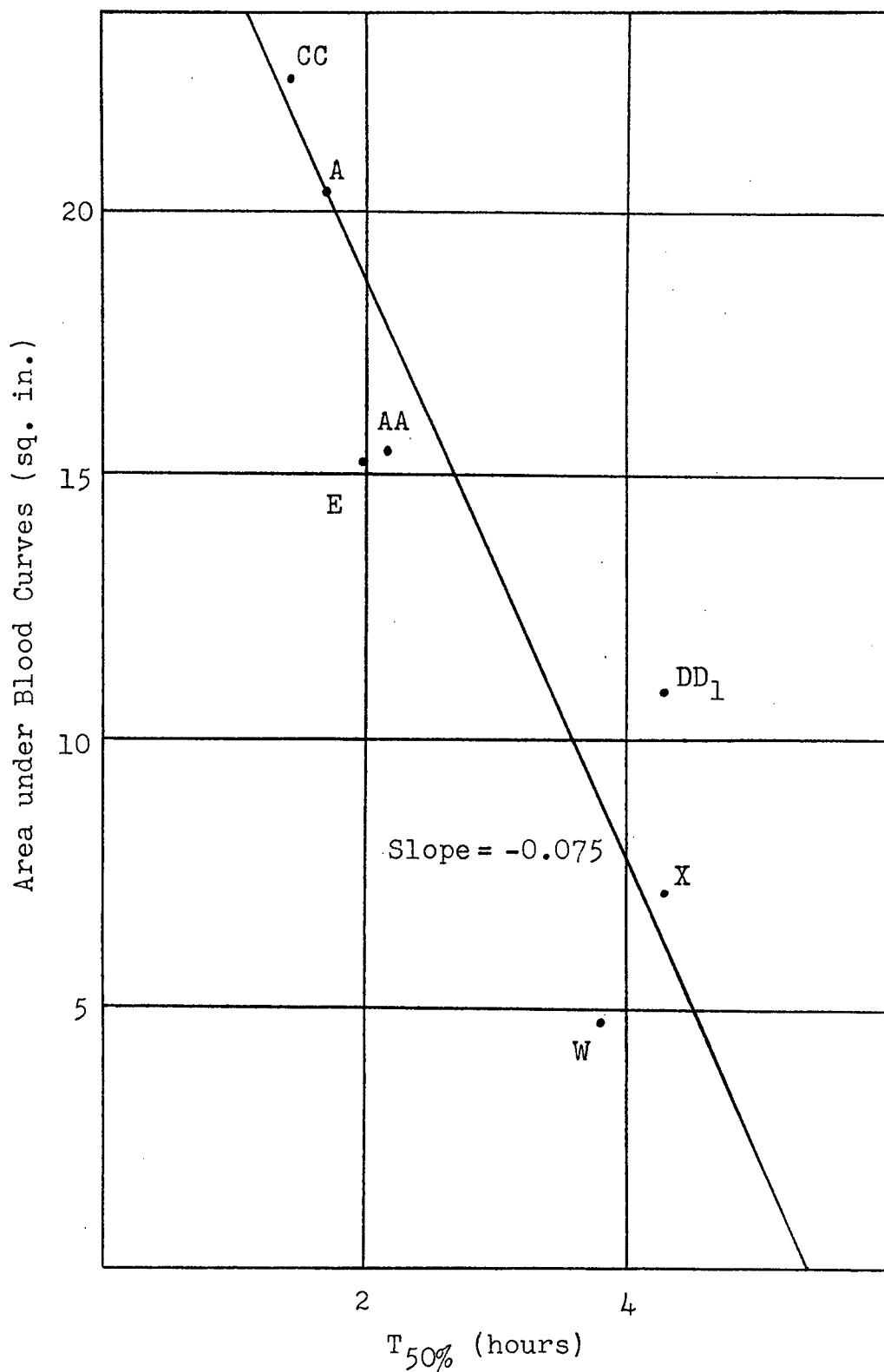for Subject 1

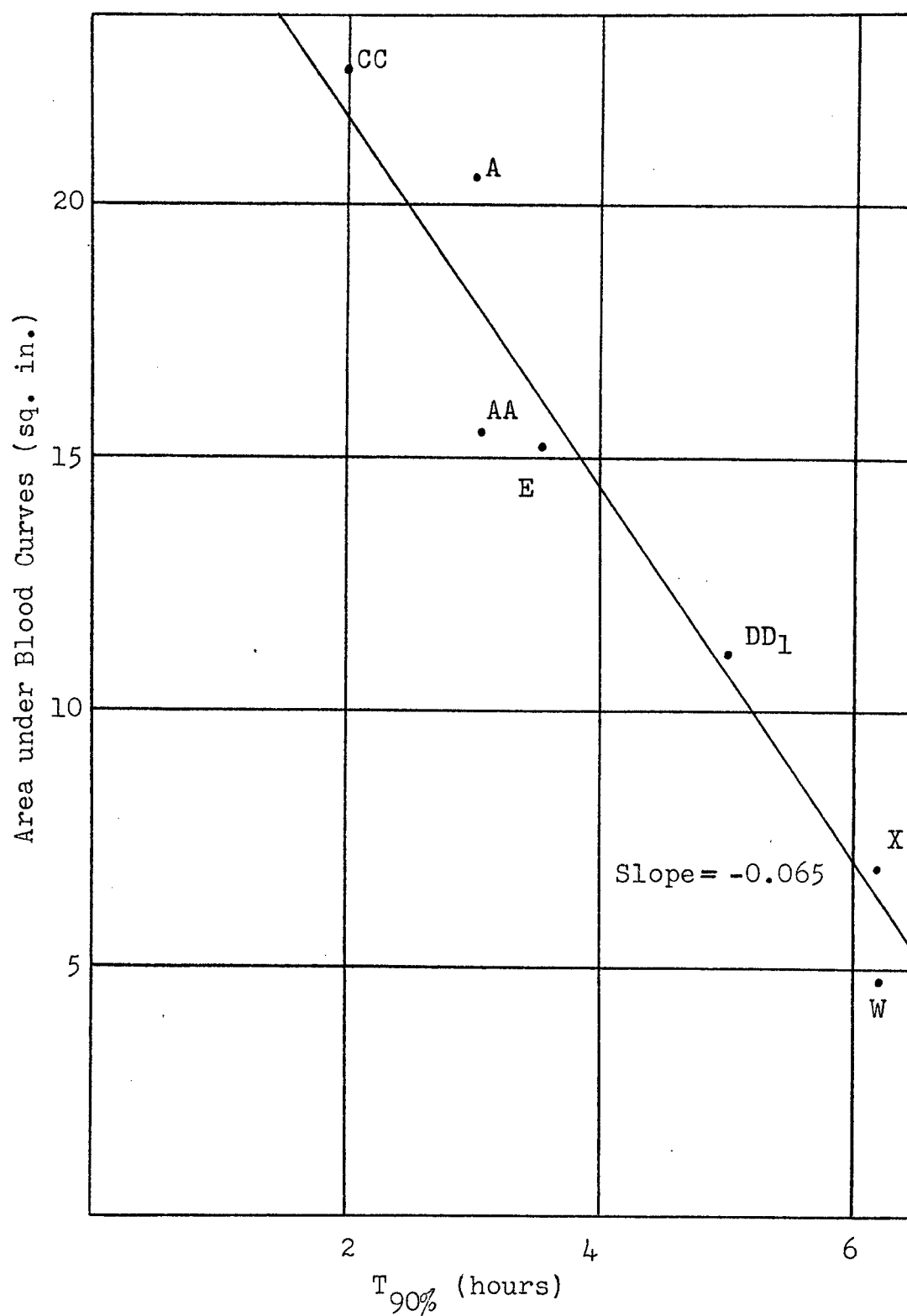Figure 11. Correlation of $T_{50\%}$ Values with "In Vivo" Data
for Subject 2

Figure 12. Correlation of $T_{90\%}$ Values with "_In Vivo_" Data for Subject 2

VII. DISCUSSION

The dissolution procedure described herein is
completely automatic. No routine analysis of the medium is
required, because a complete recording of the amount of the
active ingredient released from the tablet throughout the
dissolution process is obtained on the recorder. Determination
of the total area under the recorded curve will give the
total amount of drug released. At the same time, a complete
recording of the pH changes in the dissolution medium can
be obtained on a recording potentiometer. This recording
enables one to see how the dissolution process is affected
by the changing pH of the dissolution medium.

A single analysis of the collected medium will
also give the total amount of drug released in a period of
time but it will not give the dissolution time for a spec-
ified amount of drug to go into solution. Further, this
final analysis does not give the dissolution profile which
can be seen to vary from product to product.

Even though the apparatus set-up seems to involve
many components, the basic parts required for the continuous
flow system are the reservoirs of dissolution medium, the
dissolution vessel, the pump and the collecting vessel. The
recording potentiometer and the spectrophotometer with its
attached recorder are accessories that furnish more inform-
ation and avoid manual analysis of the medium. These

accessories are not necessary if one is interested in the total amount of drug released in a certain period of time. The basic parts of this dissolution apparatus are relatively easy to obtain and assemble and provide a good reproducible method of checking on product quality.

The inverse relationship established between the "in vivo" and the "in vitro" data obtained by this test procedure tends to indicate that this procedure may possibly be used in the prediction of the "in vivo" availability of the active ingredient from the solid dosage form. A $T_{50\%}$ value of 120 minutes as the limit of acceptance for the products seems reasonable on the basis of both the "in vivo" and the "in vitro" data. From the "least squares" lines, it would seem that products with a $T_{50\%}$ value of more than five hours would not be absorbed into the blood stream at all.

From both the "in vivo" and the "in vitro" data, only four of the seven products tested, namely A, E, AA and CC, can be accepted as products that will be effective when administered to patients. Products W and X give such low serum levels and long $T_{50\%}$ values that one can conclude that these products are unsatisfactory and should not be administered to patients. Product DD_1 with slightly higher serum levels is still unsatisfactory. The poor "in vivo" release from these products is most probably due to poor formulation, which is revealed by their poor disintegration.

characteristics. Product W and X do not disintegrate while the disintegration time of Product DD_1 is abnormally long.

VIII. SUMMARY

In this investigation, a completely automatic continuous flow dissolution procedure was developed and tested. Pertinent conditions of dissolution were studied and chosen to test seven brands of commericially available phenylbutazone tablets. "In vivo" studies were carried out on these products by determining serum levels after the administration of the products to nine subjects.

From the "in vitro" data obtained by the test dissolution procedure, a $T_{50\%}$ value of 120 minutes was chosen as the limit of acceptance for the test products. Of the seven test products, only four were acceptable on the basis of both the "in vivo" and the "in vitro" data.

Correlation of the "in vivo" and the "in vitro" data resulted in "least squares" lines with negative slopes. This correlation indicated the possibility of using this "in vitro" dissolution procedure in the prediction of the "in vivo" availability of phenylbutazone from the solid dosage form.

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