THE BIOPHARMACEUTICAL PROPERTIES OF SOLID DOSAGE FORMS

The In Vitro Characteristics of Phenylbutazone Tablets

by

RALPH OSWALD SEARL

B.Sc., University of British Columbia, 1960
B.S.P., University of British Columbia, 1963

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, 1966

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the Head of my Department or by his representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Ralph O Searl

Department of PHARMACY

The University of British Columbia
Vancouver 8, Canada

Date April 26th, 1966

ABSTRACT

Many researchers have attempted to resolve the problems associated with the claims that generic drugs are therapeutically inactive. The objective of this study was to investigate one drug - phenylbutazone - and to determine the overall quality of 23 brands of this drug on the Canadian market. Potency, content uniformity and availability of the drug from the dosage form were investigated.

A spectrophotometric method suitable for the analysis of individual phenylbutazone tablets was developed. This method involved the extraction of the drug from the tablets with alcohol, appropiate dilution with distilled water and spectrophotometric analysis of the aqueous solution. The dissolution and disintegration characteristics of twelve products were studied by two different methods. The official disintegration test described in the Food and Drugs Regulations and a stirrer method similar to that outlined by Levy and Hayes (31) were used.

The results of individual tablet assay showed that four products would be rejected on the basis of potency or content uniformity. Two other products, although complying with official requirements, would appear to show questionable characteristics. Two products would be rejected on the basis of disintegration times while six others demonstrated excessive variability in their disintegration characteristics.

The official disintegration apparatus was rejected for dissolution studies. A modified version of the apparatus described by Levy and Hayes (31) was considered adequate for this investigation.

The dissolution profiles indicated that one product would be classified as "excellent"; seven as "good" and four as "poor" with respect to drug release in vitro.

Preliminary studies indicate that there may be a definite correlation between in vitro dissolution and in vivo availability (as measured by drug content in the blood).

This abstract represents the true content of the thesis submitted.

M. Pernarowski, Ph.D.
Supervisor

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	LITERATURE SURVEY	4
	1. The Compressed Tablet	4
	a) Historical resume	4
	b) Essential qualities	5
	2. Tablet Variability	5
	a) Content uniformity	5
	b) Weight variation	6
	c) Potency tests	7
	d) Statistical tests	11
	3. In Vitro Testing	14
	a) Disintegration tests	14
	b) Dissolution tests	18
	4. In Vivo Methods	29
	a) Qualitative tests	30
	b) Quantitative tests	31
	5. In Vivo - In Vitro Correlations	33
III.	EXPERIMENTAL	37
	1. Spectrophotometric Determination of Phenylbutazone	37
	a) Spectral-absorbancy curves	37
	b) Calibration curves	41
	2. Assay of phenylbutazone tablets	46
	a) Equipment and reagents	46
	b) Procedure	46
	c) Results	47

3. Tablet Disintegration 47

a) Methodology 47

b) Results 52

4. Tablet Dissolution 52

a) Solubility of Phenylbutazone 52

b) Methodology 56

IV. DISCUSSION 66

1. Test Procedures and Results 66

a) Tablet assay 66

b) Disintegration tests 73

c) Dissolution tests 73

d) Disintegration - Dissolution correlation 81

2. Product Quality 82

a) Tablet assay 82

b) Tablet disintegration 82

c) Tablet dissolution 83

3. In Vivo Investigations 83

V. SUMMARY AND CONCLUSIONS 87

VI. BIBLIOGRAPHY 90

VII. APPENDIX 94

LIST OF TABLES

I.	The Effect of Increased Sample Size on Acceptability of Lots of Compressed Tablets	12A
II.	Disintegration Times and Availability of Prednisone from Clinically Active and Inactive Tablets	22A
III.	Wavelengths of Maximum Absorption and Absorptivity Values for Phenylbutazone in Different Media	45
IV.	Assay of Phenylbutazone Tablets from 23 Different Samples	48,49,50
V.	Disintegration Times of Phenylbutazone Tablets using Method II	51
VI.	Disintegration Times of Phenylbutazone Tablets using Method I	53
VII.	Disintegration Times of Phenylbutazone Tablets using Methods II and III	54
VIII.	Disintegration Times of Phenylbutazone Tablets using Methods IV and V	55
IX.	Disintegration Times and Dissolution Characteristics of Phenylbutazone Tablets using Methods IIA to VA inclusive	59
X.	Disintegration Times and Dissolution Characteristics of Phenylbutazone Tablets using Methods IIA and IVA	61
XI.	Disintegration Times and Dissolution Characteristics of Phenylbutazone Tablets using Methods VI and VII	65
XII.	Release Patterns of Phenylbutazone from Tablets using Methods IIA and VI	79A
XIII.	Release Patterns of Phenylbutazone from Tablets using Methods IVA and VII	80A

LIST OF FIGURES

1. Spectrophotometric Curves for (a) Phenylbutazone and (b) Phenylbutazone Tablet Extract, in Alcohol-water (1% v/v) Solution 38

2. Spectrophotometric Curve for Phenylbutazone in 0.1N HCl and Alcohol-Simulated Gastric Fluid Solution 39

3. Spectrophotometric Curve for Phenylbutazone in 0.1N NaOH and Alcohol-Simulated Intestinal Fluid solution 40

4. Calibration Curve for Phenylbutazone in Alcohol-Water (1% v/v) Solution 43

5. Calibration Curves for Phenylbutazone in (a) Simulated Gastric Fluid, U.S.P., (b) Simulated Intestinal Fluid, U.S.P. 44

6. Sampling Device 58

7. Dissolution Profiles of Phenylbutazone Tablets in Simulated Gastric Fluid using Method IIA 62

8. Dissolution Profiles of Phenylbutazone Tablets in Simulated Intestinal Fluid using Method IVA 63

9. Dissolution Profiles of Phenylbutazone Tablets in Simulated Gastric Fluid using Method VI 65A

10. Dissolution Profiles of Phenylbutazone Tablets in Simulated Intestinal Fluid using Method VII 65B

APPENDICES

APPENDIX A	Content Uniformity - Tablets (N.F.XII)	94
APPENDIX B	The Determination of the Disintegration Time of Tablets. (Food and Drug Laboratories, Ottawa; Official Method)	95

ACKNOWLEDGEMENTS

The author wishes to acknowledge the guidance and assistance given by Dr. M. Pernarowski during the course of this investigation. The author would also like to thank Mrs. E. Blackmore (nee Britten) for her technical assistance in the laboratory.

I. INTRODUCTION

Over the centuries man has attempted to overcome the unnatural conditions associated with disease by various means according to his ability and knowledge. To this end, drugs, whether derived from natural sources or the present day synthetic processes, have played an important role in the development of treatment methods.

Methods of drug administration developed slowly and, in fact, most solid dosage forms are a product of the technology associated with the industrial age. The compressed tablet and its modifications (that is, the coated and delayed release forms) are now the dosage forms of choice and, until recently, have been used with complete confidence.

Within the last ten years, scientists in industry and in the universities have begun to question the therapeutic effect of these dosage forms. In too many instances, the pharmacologist has been able to demonstrate the activity of the drug as such but the pharmacist has been unable to show that the effect of the dosage form parallels that of the pure substance. The competitiveness within the drug industry has further complicated the problem. The same drug may now be incorporated into a number of dosage forms and, depending on the drug, marketed by many manufacturers. There is now ample evidence that such dosage forms, although containing the same drug, may not behave in the same way in the body. This, then, has lead the pharmaceutical scientist into a new discipline - that of biopharmaceutics.

Biopharmaceutics may be defined as the study of the relationships between some of the physical and chemical properties of the

drug and its dosage forms and the biological effects observed following the administration of the drug in its various dosage forms. The discipline, therefore, deals with drug quality and the practitioner of this discipline must be able to answer at least four questions. These are:

1. Does the tablet contain the active ingredient specified on the label?
2. How much of the ingredient is present in the tablet?
3. Is the active ingredient affected by the adjuvants in the tablet and/or environment?
4. Is the active ingredient available to the patient?

This thesis deals with the first two and the last of these questions. The drug chosen for study was phenylbutazone and the reasons for this choice are two in number. First, phenylbutazone is marketed in tablet form by many manufacturers and a comparative study between products is, therefore, possible. Secondly, the drug itself is poorly soluble in gastric media but highly soluble in intestinal media. Drugs in this category have been known to be unavailable in vivo.

Most studies in this area have centered on a correlation between a physical testing process (either tablet disintegration or dissolution) and some in vivo parameter such as drug blood levels or metabolite in the urine. Coupled to this, pharmaceutical scientists have been critically re-evaluating their over-all approach to drug quality; the main emphasis being on content uniformity of tablets.

Until recently, the pharmacist has been satisfied with the average drug content in a lot of tablets, but because of the increased potency of many drugs, he is now more concerned with the amount of drug in each and every tablet. With this in mind, all brands of phenylbutazone tablets will be assayed in an appropriate manner and comments will be made on the quality of these products. Comments will also be made on the in vitro and in vivo availability of phenylbutazone from these products.

Investigations of this type enable the researcher to evaluate testing procedures for tablets. The inadequacy of such procedures is evident to the pharmaceutical scientist and, through research, better methods for evaluating the quality of tablets will be forthcoming.

II. LITERATURE SURVEY

1. The Compressed Tablet.

(a) Historical resume.

Tablets may be defined as solid dosage forms prepared by compressing or moulding. They have been in widespread use since the latter part of the nineteenth century and still remain the most popular of all medicinal preparations intended for oral use.

In Arabian manuscripts, written by al-Zahrawi during the latter half of the tenth century, tablet moulds and a process for controlling the weight of tablets are described. (25). However, the word "tablet" has only been in use since the early seventeenth century. This word was defined in 1775, in Samuel Johnson's first Dictionary of the English Language, as a "medicine in a square form" (22).

The modern compressed tablet dates from the invention of the tablet machine, in England, by William Brockedon for which he was granted a patent in 1843 under the title "Shaping Pills, Lozenges, and Black Lead by Pressure in Dies." A reference to bicarbonate of potash compressed into the form of a pill indicates that this process was put to early use (55).

The term "compressed tablet" had its origin in the United States and was coined by John Wyeth and Brother, to whom trade marks were issued in 1877. By 1894, tablets for almost every known disease were sold in the European and

American markets. However, no tablet received an official stamp of approval until the ninth edition of the United States Pharmacopeia (U.S.P. IX) was issued in 1916. Even in the 1926 edition of the U.S.P. only one tablet was officially recognised. The first really impressive entry of tablets into the U.S.P. occured in 1942 when 51 tablets were given official approval (22). Today, the United States Pharmacopeia (U.S.P.), British Pharmacopeia (B.P.) and the National Formulary (N.F.) recognise over 200 tablets as official preparations.

(b) Essential qualities.

The essential qualities of a good compressed tablet are the criteria which are used to determine the nature or excellence of tablets from a given lot. There is an implied warranty on the part of the manufacturer that such qualities do, in fact, exist in the tablet. Some of these qualities are:

1. Accurate and uniform weight.
2. Accurate and uniform dosage or potency.
3. Stability.
4. Ease of disintegration.
5. Availability of active ingredient for absorption.
6. Full therapeutic activity.

2. Tablet Variability

(a) Content uniformity.

The compressed tablet has become the most acceptable dosage form for the administration of therapeutic agents. It provides a convenient and, if well made, an efficient form of drug administration. Among the essential qualities of a well-made tablet, uniformity of dosage is considered to be of prime importance. In compressed tablets, this is dependent upon the uniform distribution of the active ingredient or ingredients throughout the tablet matrices and upon a consistent tablet weight (45).

The pharmacopeias list two general tests for the control of compressed tablets. These are:

1. The tablet disintegration test, and
2. The weight variation test.

In addition to these tests, the tablets must contain the labelled amount of active ingredient. This is measured by the potency tests in the individual monographs. The tablet disintegration test is not indicative of drug content but it may be a measure of drug availability. This test will be discussed more fully under in vitro testing.

(b) Weight variation.

Variation in individual weights within a batch of tablets may arise from many factors. To a large measure these factors are controllable; however, certain small deviations can always be expected. To protect the patient against excessive variability in drug dosage, weight tolerances have been established by the pharmacopeias.

Specific requirements were included in the B.P. (1948) and, after a careful study leading to a slight modification to increase the tolerance for the smallest tablets, similar requirements were adopted in the U.S.P. and N.F. The official weight variation test for tablets states that the weight of not more than two tablets out of twenty may vary from the average weight by more than the stated percentage and that no tablet may vary more than twice that percentage.

The function of the weight variation test is to control the variation in weight of tablets. It is designed for uncoated compressed tablets which must conform to the given tolerences unless otherwise specified. These tolerences vary from 5% to 15% depending on the average weight of the tablets. However, the test should not generally be used as a measure of potency since here one is assuming a completely homogeneous and uniform mix.

(c) Potency tests.

Although product dosage is expressed on an individual compressed tablet basis, potency testing utilizes an analytical sample which is a composite of many tablets. An assay procedure will often read - "Weigh and finely powder not less than 20 ---------- tablets. Weigh accurately a portion of the powder equivalent to about ----------." This procedure is followed even though one tablet might be more than sufficient for carrying out the analysis. Such procedures give information on the average tablet assay or mean potency of a batch of tablets.

They give no information on the individual tablets. For example, to take an extreme case, if half of the tablets tested were 50% high in potency and half 50% low, the composite sample would still assay satisfactorily. As pointed out by Train (62), it is the content of each and every dosage form which is of prime importance and not the mean content of a large number of these dosage forms.

Content uniformity has been investigated by Moskalyk, et al. (45), Garrett (16), Evers (15), and Smith, et al., (57). Suggestions were also made by the Pharmaceutical Manufacturers Association and others to change from the present sample assay to an individual tablet assay (4,52). One drawback to the latter, of course, is the large number of assays which would be required and also the lack of suitable assay methods.

Smith, et al., (57) attempted to define the nature of the distribution of dosage variation in commercially available compressed tablets. Of the 2198 tablets individually assayed, over 99% conformed to the then accepted composite limit of ± 10% and all tablets conformed to the wider limits of ± 15% which were suggested by the Committee on Inter-Tablet Dosage Variation of the Pharmaceutical Manufacturers Association (52).

In Smith's report, the average assays were very close to label claim, the standard deviations were small, 1.4% - 3.8% of label claim, and the curves obtained indicated essentially normal distribution. Examination of the data indicated a relationship between standard deviation and percent active

ingredient in the tablet. As the percent active ingredient increased, the variation in individual assays decreased. A correlation also existed between the tablet weight and tablet assay for ten of the twelve lots investigated. The correlation coefficients varied between 0.2 and 0.5. These excellent results were attributed to the good quality control procedures existing in the author's plant - Merck, Sharp and Dohme Ltd.

On the other hand, of the twelve products studied by Moskalyk, et al., (45), four failed the U.S.P. test for uniformity of tablet weight. In comparing their results with those obtained by Evers (15), Moskalyk, et al., (45) observed that the variation in assay for the larger tablets was also less than for the smaller tablets. However, they concluded that the actual variability of drug dosage was, as a rule, greater than could be apparent from the variation in individual tablet weight. These authors also reported that the dosage variation was greatest in the lightest weight tablets within a batch.

These results are to be expected since one of the main factors affecting the uniformity of a mixture is the relative proportions of the ingredients. The task of mixing becomes increasingly more difficult as the proportion of one ingredient relative to another decreases. Since tablets containing a relatively small proportion of active ingredient are usually those which contain a very potent drug, the need for more effective control over dosage variability in tablets was certainly indicated.

Data, presented to the Committee on Inter-Tablet Dosage Variation of the Quality Control Section of the Pharmaceutical Manufacturers Association (53), on 42 U.S.P. and 28 N.F. single drug component tablets demonstrated achievability of 85% - 115% of the purity rubric mean tolerance. At this meeting, the committee recommended that the compendia consider extending the drug content uniformity test (now applying to eight U.S.P. and six N.F. single drug component tablets) to all U.S.P. and N.F. single drug component tablets for which suitable individual tablet assay methods are available. Some multiple drug component tablets were also reported to have passed the test. These are: A.P.C. Tablets N.F., Trisulfapyrimidines Tablets U.S.P., Hexavitamin tablets N.F., and Sulfacetamide-Sulfadiazine-Sulfamerazine Tablets N.F.

As a result of the recommendations of the Pharmaceutical Manufacturers Association and previous studies cited, the N.F. XII (48) has adopted, for a selected group of tablets, a test for composition variation or content uniformity for compressed tablets. (Appendix A). Essentially this test allows for ten tablets of an initial sample of thirty tablets to be assayed individually as directed. The requirements of the test are fulfilled if all ten results fall within the limits of 85% to 115% of the labeled potency. However, if one result falls outside these limits, then the remaining twenty tablets are individually assayed. The requirements are met if not more than one of the thirty tablets is outside the limits of 85% - 115% of label claim.

The Quality Control Section of the Pharmaceutical Manufacturers Association (53) in September 1965 noted that: "As drug content uniformity tolerance requirements begin to be included in the monographs of an expanding number of official tablets, it is anticipated that the weight tolerance requirement test for such tablets will become superfluous and will probably be deleted."

At this time, Dr. E. G. Feldman, Director of Revision of the National Formulary and Dr. L. C. Miller, Director of Pharmacopeal Revision for the United States Pharmacopeia - also commented about the prospect that the weight variation test would be deleted where content variation is specified. Dr. Miller also commented on the economic aspects of multiple assays and the need for time-saving methods which might serve as adjuncts to the assay methods now specified in the compendia.

(d) Statistical tests.

The efficiency of any statistical test may be determined by its ability to differentiate between good batches which should be accepted and bad batches which should be rejected. Such tests should have a high probability of accepting the satisfactory batches and a low probability of accepting the unsatisfactory batches.

Dunnett and Crisafio (11) derived the Operating-Characteristic Curves for the official tablet weight variation test using sample sizes of 10, 20, 50 and 100 tablets. This data is represented in Table I. They found that there is an increased tendency to pass a batch if the sample size is

TABLE I.

The Effect of Increased Sample Size on Acceptability of Lots of Compressed Tablets.

	Lots Accepted	
	% Defective	
No of Tablets	5%	20%
10	93%	40%
20	95	23
50	98	4
100	99	0

See Reference (50).

increased and the percentage defectives is low (5% or less). On the other hand, an increase in sample size will result in a decreased tendency to pass batches with a high percentage of defectives (say of the order of 20%). In other words, an increase in sample size has the effect of considerably decreasing the probability of a non-uniform batch of tablets being accepted and slightly increasing the probability of a highly uniform batch passing the test (50).

From this they suggested that a two sample weight variation test is more valid, statistically, than the present one sample test in which twenty tablets are weighed individually and the allowable limits depend on the average tablet weight. In their test, 50 tablets are weighed and the mean weight calculated. Twenty tablets are examined, as in the official test, and the batch accepted if not more than one tablet deviates from the mean by $\pm$ 5%. If more than one tablet deviates from the mean by greater than $\pm$ 5% then the other 30 tablets are examined. The batch is then accepted if not more than five tablets deviate from the mean by $\pm$ 5% and no tablet deviates by more than $\pm$ 10%.

Grundman and Ecanow (18) suggested a "tablet acceptance by a double sampling plan" in which they tested 50 tablets and accepted the batch if all the tablets passed the test. If all tablets did not pass the test, they examined 100 more tablets and accepted the batch if not more than two tablets of the 150 tablets failed the test.

Brunning and King (4) utilized operating characteristic curves in their examination of an acceptance sampling plan for pharmaceuticals. They employed the plan used by the U.S. Army - MIL-STD-414 which calls for the establishment of four basic standards (42):

1. A.Q.L.- An acceptable quality level. A level of 10% means that the lot is satisfactory if it contains only 10% defectives.

2. U.Q.L.- An unacceptable quality level. A level of 40% means that the lot is unacceptable if it contains more than 40% defectives.

3. R_p - Producer's risk. This is the risk involved in misclassifying an acceptable lot.

4. R_c - Consumer's risk. This is the risk involved in misclassifying an unacceptable lot.

Once the values of these four standards have been decided upon, the corresponding sampling plan and hence the sample size is automatically determined.

If the A.Q.L. and U.Q.L. are quite far apart and a high risk of misclassification can be tolerated, as might well be the case with sodium chloride tablets, the plan will call for very few units in the sample. If the A.Q.L. and U.Q.L. are close together and a very small risk of misclassification must be maintained, as in the case of the potent steroids, a large sample will normally be required.

Using the four characteristic standards upon the corresponding sampling plan, - O.C. curves, sample size and acceptability criteria - may be obtained from tablets of the

MIL-STD-414 (42). The tablets in the sample are assayed individually and the percent defectives determined. If the percent defectives do not exceed the stated criteria, then the lot is accepted.

In comparing this variable plan to a two-step attribute plan, such as is now in the U.S.P. and N.F. for assay variation, it was found that the variable plan was superior for detecting cases of excessive variation and for excessive variation combined with a shift in mean. The two plans are about equal for cases of mean shift only. For example, it was found that for the U.S.P. plan, which cannot detect tablet to tablet variations, will accept a sample with 40% defectives 94% of the time while the statistical plan will accept this same sample only 8% of the time.

3. In-Vitro Testing

(a) Disintegration tests.

If compressed tablets are expected to provide effective medication, it is obvious that the tablet must dissolve or disintegrate within a reasonable time. This fact was recognised, studied and discussed, but official standards did not exist until relatively recent times. The lack of testing procedures was due, in large part, to an inability to standardize methodology and to the variations within the dosage forms being examined.

(i) Methods and Apparatus

Many methods have recently been developed for the

study of tablet disintegration though they vary in the complexity of the apparatus, liquid medium used, temperature, agitation and indicated end point. The temperature is either room temperature (22°C - 25°C) or body temperature (37°C). Elliot (12) found that this difference, a temperature increase of 10°C to 15°C, accounted for a two-fold increase in the solution rate of tablets.

The simplest apparatus for measuring the disintegration time of compressed tablets is a glass of water (69). Another method, suggested by Trunkel in 1931 and recommended for the retail pharmacist, utilizes an apparatus made by covering a small beaker with a screen, placing this in a larger beaker, and then adding water to cover the screen to a height of one centimeter. The tablets are placed on the screen and the time required for the disintegrated tablet to pass through the mesh is noted.**

Methods with definite end points include that proposed by Foote in 1928 in which a plate is supported by the tablet, the plate sinking to ring a bell by electrical contact. Brown in 1939 suggested the breaking of a tablet, both in air and in water, in a stirrup attached to one arm of a balance. Berry in 1944 suggested that the end point be determined by dropping a 20 Gm. weight attached to a wire loop as it cuts through the tablet.

** The material in this paragraph and the next two paragraphs was drawn from reference (55).

Several methods have been used to simulate peristaltic movement. An early method put foreward by Lewis in 1904 consisted of holding the tablet with a wire spiral on muslin stretched over a funnel and allowing water to drop on the tablet. One of the earliest methods which was developed and later adopted by the B.P. in 1945 consisted of rotating the tablets in test tubes of liquid. This method was criticized by Hoyle for having an indefinite end point because the cloudy solution obscures the final disintegration of the tablet center.

The passage of disintegrated tablets through a wire screen implies a definite end point and this technique, coupled to some form of movement of the tablet in the test fluids, has been utilized in several published methods. In most of these, the wire screen constitutes the bottom of a basket having glass or screen sides. Evanson and DeKay (14,48) introduced a rolling drum into their apparatus, which they claim provides a rolling wavelike action on the tablet similar to that of stomach contractions. This method was more reproducable than the Gershberg and Stoll method (17), in which tubes with mesh bottoms were moved up and down in simulated gastro-intestinal juices. The latter method was used in the early forties for testing tablets supplied to the U.S. Army (55). The Gershberg-Stoll method was modified and later accepted as official in the United States and Canada. However, no real attempt was made to reproduce physiological conditions in these tests.

(ii) Official Standards

Official standards for tablet disintegration were adopted first in Switzerland, France and England. The Swiss Pharmacopea of 1933 required that tablets for internal use (unless intended to dissolve slowly in the mouth) must disintegrate to a powder or dissolve within 15 minutes in water at 37°C. The French Codex of 1937 required the following test: Five tablets were placed in a flask with 100 ml of cold water. The flask was placed in a bath at 37°C and agitated frequently. To pass the test, the tablets must be completely disintegrated or dissolved at the end of ten minutes. The B.P. of 1953 also required a test on five tablets in water, but in this case five separate test tubes rotating in a bath held at 37°C were used. The tablets must dissolve or disintegrate within 15 minutes with exceptions as stated in the monographs. If not more than one of the five tablets fail the test, the test is repeated. No tablet must fail the second time (55).

The disintegration test for tablets in the U.S.P., N.F., and in Canada uses a basket-rack assembly consisting of six open end glass tubes which impinge at the bottom on a ten mesh stainless steel screen. Exact measurements are given for the test apparatus because a slight change in specifications can affect disintegration times. A more detailed description of this apparatus is given in Appendix B.

Tablets to be tested are placed in each of the six glass tubes and the apparatus assembled with plungers and discs over the tablets. The whole basket rack assembly is then raised and lowered through an 8 cm stroke, 30 times per minute, in a suitable liquid bath at 37°C. At the end of the prescribed time, as is specified in the individual tablet monographs or in Canada in the F and D Regulations (Appendix B), the basket is inspected. The tablets are considered to be completely disintegrated if no residue remains on the screen bottom. If more than two tablets fail to disintegrate, 12 more tablets must be tested. Of the 18 tablets then tested, 15 must have disintegrated within the given period of time.

Surveys by Murphey (46) in 1954 and Nuppenau (49) in 1964, comparing the requirements for disintegration of tablets in the various world pharmacopeias, shows the leniency of the U.S.P. standards for disintegration times. The range in most pharmacopeias is between five minutes and 15 minutes. In contrast, the U.S.P. allows disintegration times of from 15 minutes to one or more hours. In Canada the limits are 30 minutes in simulated gastric fluid and 30 minutes in simulated intestinal fluid for a total time of one hour.

(b) Dissolution Tests

In 1902 Hance (21) defined solubility with respect to compressed tablets as the power to disintegrate rather than the power to form solutions or to dissolve. While this definition

may be true for soluble compounds, it certainly will not be true for only slightly soluble drugs.

Today it is generally recognised that the in vitro tablet disintegration test does not necessarily bear a relationship to the in vivo action of the solid dosage form. During the past few years, several authors have proposed that the significant factor to consider is not tablet disintegration but dissolution of the drug fromthe tablet. Sperandio (59) in 1948 and Parrott (51) in 1955 realized that disintegration did not necessarily mean that the drug had dissolved, the tablet is merely broken up into smaller particles.

While the disintegration time does influence the rate of drug release to the body, the most important aspect is the rate of release from the primary drug particle. This is necessary because it is accepted that solution of the drug is essential if absorption is to take place. More recently, Levy and Hayes (31), and Yen (72) have reminded researchers that disintegration does not in itself imply dissolution. However, regardless of the lack of a significant relationship between disintegration and the tablet's in vivo activity, the test still provides a means of control in assuring that a given tablet formulation is the same from batch to batch, with regard to disintegration.

There is a mistaken belief among many that the active constituent as a chemical entity is the sole basis for the pharmacological effectiveness of a pharmaceutical product. However, the choice of dosage form and of brand can be just as important

as the choice of the actual therapeutic agent. In general, differences in therapeutic efficacy between generically identical drug products, while sometimes caused by instability or contamination, are most frequently due to differences in the rate at which the active ingredient or ingredients become available for absorption (35).

The first relationship between in vitro tablet disintegration and in vivo drug availability were established by the Food and Drug Directorate in Ottawa. Chapman, et al (8,9) in 1954-1956, using riboflavin and p-amino salicylic acid in separate studies, did show that the availability of the drug for absorption was predictable from disintegration times determined by the U.S.P. test. According to Schroeter, et al (54), these researchers were the first to determine rates of dissolution at the same time that the disintegration time was being determined.

Dissolution studies were not again emphasized until it became apparent that certain tablets, although complying with disintegration requirements, failed to demonstrate any therapeutic effects. Around 1960, papers began to appear in the literature indicating that adjuvants played an important role in the therapeutic effectiveness of the tablet. Levy and Nelson, (35), Delgado and Cosgrove (10), Wagner (67) and Gwilt, et al., (19) discussed many aspects of biopharmaceutics and indicated that added substances can have a pronounced effect on the in vivo availability of drugs such as tetracycline, tolbutamide and dicoumarol.

Parrot, et al., (51) found that the dissolution rate of benzoic acid was decreased when various concentrations of sodium chloride, sodium sulfate and dextrose were added to the dissolving medium. Sodium sulfate was most effective in decreasing the dissolution rate. When urea was used as an additive, an increase in the dissolution rate resulted.

Levy and Hayes (31), working with five different commercially available Acetylsalicylic Acid tablets found that the in vitro disintegration times for these tablets, which is often alluded to as an index of the rate at which the drug becomes available for absorption, is no criteria for availability or rate of solution. In fact the most rapidly dissolving products exhibited longer disintegration times than the slower dissolving products. It was also shown that disintegration times had no relation whatsoever to rate of absorption or to the biological availability of the drug in human subjects.

More recently, Campagna, et al., (6), together with Levy, Hall and Nelson (30) investigated independently, prednisone tablets which were reported to be inactive. A patient showed good clinical response when one brand of prednisone was administered. For unknown reasons, the brand was changed and the symptoms reappeared. When the original brand was again used, the response was good. These inactive prednisone tablets were tested against the active ones and it was found that the effective tablets released 50% of its contents 20 times as rapidly as the clinically ineffective ones. The official disintegration

time in both cases were less than six minutes as shown in Table II.

Wagner (67) reports that the nature and intensity of a biological response to a drug is often thought to be due only to the inherent activity of the molecular structure of the compound. Many factors contribute to this response: the drug itself, dissolution characteristics, dosage forms, formulation, method of manufacture, absorption and excretion. These same factors, as reported by Schroeter, et al., (54) will determine whether a correlation exists between in vitro disintegration-dissolution and in vivo availability and absorption. Consequently, it is possible to correlate dissolution and disintegration but this must be done for each product separately in order to be meaningful. At some stage, in vivo studies must be done in order to complete the correlation. If this is done and there is a good relationship between disintegration, dissolution and availability, then the disintegration test can be used routinely and would more or less imply dissolution and availability for a particular product.

On the basis of these and other reports, the Pharmaceutical Manufacturers' Association (53) appointed a committee to investigate the problem of dissolution of drugs from tablets. During the preliminary investigations of about 70 products, it was found that of those products containing drugs with solubilities of 1% or more, in almost every case, all of the drug was in solution when disintegration was completed. On the other hand, tablets containing drugswhose solubility was less than

TABLE II.

Disintegration Times and Availability of Prednisone from Clinically Active and Inactive Tablets

Prednisone Tablets	Disintegration Time (Minutes)		Average Time For 50% of the Drug to Dissolve (Minutes)
	Disks	No Disks	
Active *	< 6	6	4.3 ± 1.3
Inactive *	< 6	60 - 120	100 ± 53
Inactive **	2.5	180	173 ± 37

* See Reference (30).

** See Reference (6).

1%, dissolved in most instances, within one hour after the disintegration end point.

In April 1963, the committee suggested that the U.S.P. disintegration test was only useful as a tool to control batch to batch uniformity of tablets and to keep completely unsatisfactory products off the market. Much concern was also expressed about the need for obtaining blood level data to compare with any proposed dissolution test data if such a test is to be indicative of drug availability.

(i) Methods and Apparatus

The principle involved in dissolution studies is the same regardless of the apparatus used. Essentially the tablets are placed in a suitable liquid such as water, simulated gastric or intestinal fluid, and agitated. Aliquots of the liquid are then removed, at varying time intervals, for analysis.

It is generally felt that any procedure for in vitro tests should employ some device for agitating the eluant and product at a fixed speed. Since the Gershberg-Stoll apparatus is the only officially recognized tablet test apparatus on this continent, it has been widely used with various modifications. This is essentially the same apparatus described in the U.S.P. and by the Canadian Food and Drug Directorate for disintegration studies. This apparatus has been a starting point for many investigators because its basic parts consist of: a mechanical device

for agitating which may imitate the peristaltic movements, a thermostatic arrangement so that body temperature can be maintained, an immersion fluid such as simulated gastric and intestinal juice and a screen to support the tablets under investigation until they have disintegrated or released the active substance.

A more detailed description of this apparatus may be found in Appendix B. The main advantage of the apparatus is that disintegration times as well as dissolution rates may be observed at the same time on the same tablets. Schroeter, et al., (54) and Middleton, et al., (40) used the U.S.P. apparatus in their investigations on dissolution rates of drugs in tablets.

In his study on Acetylsalicylic Acid tablets, Levy (31) used a 400 ml. beaker, 0.1N HCl, a temperature of 37°C, and a controlled speed stirrer set at 59 r.p.m. which was fast enough for homogenous mixing but slow enough to keep solid particles at the bottom. Nash and Marcus (47) used a modified version consisting of a 600 ml. Buchner type funnel with a medium porosity fritted disk which was fitted into a 500 ml. suction flask with a stopcock at the bottom. The sample is placed in the funnel with 400 ml. of simulated gastric fluid and gently agitated by a stirrer. At fixed intervals, 200 ml. portions of fluid are drawn off for analysis and 200 ml. of fresh media added to the funnel. The process is repeated for the desired time interval. In

both cases the rate of stirring influences the rate of dissolution of the drug from the tablets.

Another method, suggested by Wiley (68), consisted of a stoppered cylindrical tube with a glass wool filter above the bottom outlet and a side arm for return of fluid to a reservoir. A pump was employed to circulate the fluid from the reservoir to the tube at a fixed rate. The sample is first eluted for one hour with 100 ml. of simulated gastric fluid at 37°C. At the end of this time, 50 ml. of fluid are removed and replaced with 50 ml. of simulated intestinal fluid. The procedure is repeated every hour for eight hours. This method was rejected as being too slow, cumbersome and complex and therefore, unsuitable for routine investigations.

The method developed in 1958 by Souder and Ellenbogen (58) to determine the release rate of sustained release granules contained in capsules consists of bottles (90 ml. capacity) fastened at their mid point to a horizontal axis in a water bath at 37°C. Samples are placed in the bottles, 60 ml. of fluid added and the bottles rotated (end over end at 40 r.p.m.). The bottles are removed at fixed intervals and the contents filtered immediately. Either the washed residue or the filtrate is assayed.

The limitations of this method are obvious:

1. The contents of the bottles must be filtered immediately upon their removal from the apparatus.

2. The small size of the bottles limits its use, especially in the case of sparingly soluble drugs.

3. The centrifugal force tends to press the solids against the bottom of the bottles allowing for little or no mechanical erosion.

However, this method has been successfully adapted by Smith Kline and French I.A.C. (Inter-American Corporation) for their spansules and is extensively used as a control tool. They, however, claim that this apparatus cannot be used to judge other products unless there is a definite correlation between this data and in vivo results or clinical response.

Vliet (65) compared the U.S.P., S.K.F. and Wiley methods and found that all methods, provided that the preparations contained freely soluble drugs, produced the same release patterns. The release was complete in 8 hours in all cases. On the other hand tablets containing sparingly soluble drugs gave different release patterns. For example:

S.K.F. method - 100% release in 8 hours

U.S.P. (no disks) - 35%-65% release in 8 hours

Wiley method - 10%-50% release in 8 hours

In a further attempt to standardize dissolution techniques, Simoons (56), in 1961-62, after considering all the advantages and disadvantages of the existing techniques, developed and worked with the ring apparatus as described in his book. From this he derived in vitro rate constants (K vitro) for various tablets and from urinary excretion

studies, in vivo rate constants (K vivo). He then correlated the two values and determined a ring constant (R) for any particular drug.

$$R = \frac{K \text{ vivo}}{K \text{ vitro}}$$

Thus, the in vivo behaviour for any particular drug could be predicted from in vitro studies, provided the ring constant R was previously determined. Wagner (67) has criticized this type of correlation claiming that it is spurious and artificial and should not be used.

(ii) Limitations

It is known that the release rate of a drug from a tablet depends on various factors other than those inherent in the tablet. Such factors as the flow of fluid around the tablet and the movement of the tablets in the container could influence the release rate. If these are inadequate, as in the Wiley method, the release rate is low.

In the modified Gershberg-Stoll apparatus, the tablets are subjected to up and down strokes which, together with the size of the mesh and weight of the tablets, determine the amount of mechanical erosion to which the tablets are subjected. It is also suggested that saturation with air as a result of the up and down strokes may cause oxidative processes in the substances under investigation. This in turn may lead to incorrect interpretation of the results especially when the assay used is spectrophotometric. Mixing and layering may also cause slight problems with this method.

As mentioned before, if a stirrer is used, as in the Levy method (31), the rate of stirring influences the rate of dissolution. Evaporation of fluid could also influence results. Schroeter, et al., (54) noticed that although excipients in tablets introduced an error of less than 1%, this is well within the error of the U.S.P. method. However loss of fluid due to evaporation or mechanical loss was up to 10% during tests of four hours or more. In the first half hour to one hour, 30ml.-40ml. or 4%-5% of a volume of 750 ml. were lost. However, on the basis of studies done on an aspirin, a steroid, and sulfonamide tablets, they concluded that, if the test was run for less than one hour, the error was not significant.

It was also suggested by Wagner that when all the drug has been released from the sample, the fluid should be only 25% or less of saturation with respect to the drug. The solution, under no circumstances, should be allowed to become saturated before all of the drug is released from the tablets. If this 25% or less saturation limit is maintained, then the effect of concentration in the solution on the rate of dissolution apparently is not significant.

To date, no one has come up with a satisfactory method or procedure for determining dissolution and dissolution rates of drugs from tablets which will meet exactly all the criteria and specifications for such determinations. There is valid criticism of all the methods discussed and the generally acc-

epted ones are accepted more for their ease of operation than for any other reason. The methods which seem to meet almost all the criteria do take anywhere up to eight hours or more for one evaluation. The only methods now used by the industry are the U.S.P., S K F and Levy methods.

There is a need for some simple method which can be applied routinely to dissolution studies. At present it is felt that disintegration tests are not enough to effectively evaluate a solid dosage form for its biological or therapeutic availability. Dissolution studies should be correlated with in vivo tests.

All researchers seem to use procedures adapted to their own purposes and, on the basis of their own results, are prepared to advocate general acceptance of their procedure. The situation today is similar to that of several years ago when claims were made that no one procedure would be able to adequately evaluate the disintegration characteristics of tablets. Today, one procedure, the Gershberg-Stoll method, is used throughout the world. A dissolution procedure will eventually evolve and gain the status of that now used for tablet disintegration.

4. In-Vivo Methods

The clinical effectiveness of tablets and other pharmaceutical dosage forms depends on at least two factors. The medication must be present in the labelled amount and it must also be available to the body. It is apparent, therefore, that in addition to in vitro examination of oral dosage forms for amount, identity, and purity, there must also be some evaluation

of the physiological availability of the active ingredients. In vivo methods used to determine physiological availability of drugs have ranged from simple qualitative procedures to sophisticated quantitative measurements of drug concentration in blood or urine.

(a) Qualitative Tests.

One of the earliest attempts to demonstrate the availability of drugs was carried out by Wruble (71), who administered enteric-coated tablets containing calcium sulfide and methylene blue to humans. If the tablet disintegrated in the stomach, the subject would eructate hydrogen sulfide; if it disintegrated in the intestinal tract, the urine would be blue in color. Clinical observations on Prednisone (6,30) and Tolbutamide (7) have been used as indications of drug availability.

(i) X-Rays

Early workers attempted to use x-ray findings as an indication of in vivo availability of drugs. Maney and Kuever (37) found that in vitro results generally agreed with in vivo findings. Abbott and Allport (1), on the other hand, concluded that x-rays were unsuitable for this type of work because of the variability between human subjects and the inability of x-rays to detect many drugs in the gastrointestinal tract. Actually, x-rays can only give information on disintegration and, furthermore, the pictures often are difficult to interpret and are not amenable to quantitative treatment.

More recently, Levy (28) has used x-rays to study the agitation intensities encountered in the human stomach by observing the disintegration of tablets containing radio opaque materials. Using the information obtained, he was able to develop dissolution rate tests which gave excellent correlation between in vitro and in vivo data (27,34). Steinberg, et al., (60) also used x-rays to study in vivo tablet disintegration and obtained results which substantiated Levy's previous observations. The general conclusion was that agitation in the stomach was of low intensity and the in vivo disintegration times were substantially longer than that obtained using the U.S.P. in vitro apparatus.

(b) Quantitative Tests.

(i) Urinary Excretion

The simplest of all in vivo procedures for obtaining quantitative data is probably the measurement of urinary excretion of the drug and/or its metabolites after the administration of a test dose. Melnick, et al., (38) used urinary excretion data in their study of the physiological availability of vitamins in pharmaceutical products. This concept of physiological availability was adopted and further developed by Chapman, et al., (9) and Morrison, et al., (44) who studied the relationship between in vitro disintegration time and physiological availability of riboflavin in sugar-coated tablets. These studies were the first attempts to correlate in vitro findings with quantitative

in vivo results. They formed the basis for the regulations in the Food and Drugs Act that require compressed or sugar-coated tablets to disintegrate within 60 minutes when tested by the official tablet disintegration method.

Levy and Jusko (33) employed urinary excretion data to study the effect of viscosity on drug absorption. They determined the total amount of salicylate in the urine of rats after administration of salicylic acid in methyl-cellulose solutions of varying viscosities. The urinary excretion technique was also used by Libby, et al., (36) to determine the availability of vitamins from preparations which failed to disintegrate in vitro. They found extreme individual variations in tests on the same product and several preparations were found to be totally unavailable to certain individuals.

(ii) Blood Levels.

The most popular of all in vivo procedures is the measurement of drug concentrations in the blood (serum, plasma). For many drugs, the measurement of blood concentration provides a good indication of physiological availability. However, it should be noted that for some drugs, such as certain antihistamines, which have a large distribution volume in vivo, this type of a correlation would be invalid.

Many workers have used blood levels as a criterion of drug availability. Juncher and Raaschov (23) found that two preparations of penicillin V tablets, which had

different in vitro disintegration times, also gave significantly different blood levels when tested in humans. Wood (70) used total salicylate serum levels to study the in vivo release rate of Acetylsalicylic Acid from hard gelatin capsules. Levy, et al., (26,32,33,34) used acetylsalicylic acid and salicylate as test drugs to study drug absorption and dissolution from dosage forms. In almost every case, they used blood levels and/or urine content of drug or metabolite as an indication of drug absorption. Middleton, et al., (41) used serum levels to investigate the absorption of orally administered iron from sustained release preparations.

5. In Vivo - In Vitro Correlations.

All in vitro tests have no intrinsic value per se but are useful only to the extent that they correlate with quantitative in vivo results. It has been emphasized repeatedly that in vitro disintegration times give no direct indication of the time required for a product to dissolve in vivo. However, despite the well-established nature of the relationship between in vitro and in vivo results, some authors still tend to equate in vitro disintegration times to in vivo availability.

As indicated previously, Chapman, et al., (8,9) found that the availability of riboflavin and p-aminosalicylate tablets to humans could be predicted from their in vitro disintegration times using a modified U.S.P. disintegration test. Tablets disintegrating in more than 60 minutes were not fully available in vivo. However, Endicott and Kirchmeyer (13)

reported that riboflavin and erythromycin tablets which took longer than 60 mins. to disintegrate in vitro were fully available in vivo.

Levy and Hayes (31), who conducted extensive studies with acetylsalicylic acid tablets, found that the faster dissolving tablets (short dissolution half-time) had longer disintegration times than tablets which dissolved more slowly. In subsequent work, Levy (27) suggested that the U.S.P. tablet disintegration test be replaced by a dissolution test for compressed tablets.

Schroeter, et al.,(54) determined in vitro dissolution rates and disintegration times for 76 lots of tablets, including a steroid, a sulfonamide, and oral antidiabetic agent, and an Aspirin-Phenacetin-Caffeine combination. Disintegration tests were carried out with and without the plastic disks. They found that there was a high degree of correlation between in vitro disintegration times (without disks) and dissolution rate for the steroid. No significant correlation was observed for the antidiabetic agent and the Aspirin-Phenacetin-Caffeine preparations. There was a tendency for the faster dissolving tablets to disintegrate more rapidly and the presence of sodium chloride in some of the sulfonamide preparations markedly influenced the results.

Campagna, et al., (6) observed that, in the case of Prednisone tablets, omission of disks in the U.S.P. Disintegration apparatus gave values which agreed with in vivo results and dissolution rate values. Carter (7) and Caminetsky (5)

reported similar observations with Tolbutamide tablets. Clinically ineffective tablets demonstrated substantially longer disintegration times than clinically effective ones. Levy (29) studied the two tablet brands used by Carter and found marked differences in their in vitro dissolution rates. Although many other workers have investigated tolbutamide, no in vivo data has been presented to show that tablets with different dissolution rates vary in clinical effectiveness (43).

Middleton, et al.,(40), examined the relationship between in vitro dissolution rate, disintegration time, and physiological availability of riboflavin in sugar-coated tablets. They found a close relationship between disintegration time and dissolution rate, and both in vitro procedures correlated reasonably well with physiological availability measured by urinary riboflavin excretion. It would appear that the results of in vitro tests in this instance were a useful indication of in vivo availability.

Quite recently, Levy, et al., (34), reported on an in vitro dissolution rate test which correlates quantitatively with the gastro-intestinal absorption of acetylsalicylic acid from three markedly different types of dosage forms. It was suggested that the in vitro conditions that yield such multiple correlation may be expected to be relatively similar to dissolution conditions found in vivo. The results obtained in this investigation would suggest that the apparent failure of some dissolution tests to reflect the results of in vivo studies may be due to improper test conditions. It was found that a change of only 20% in

stirring rate, from 60 r.p.m. to 50 r.p.m., resulted in a successful correlation.

In spite of these encouraging results and the fundamental relationships existing between in vivo availability and dissolution rates, there still remains the problem of finding a dissolution test than can be applied to all drugs.

III. EXPERIMENTAL

1. Spectrophotometric Determination of Phenylbutazone.

Phenylbutazone (1,2 - Diphenyl-4-butyl-3,4-Pyrazolidinedione), a weak organic acid, pKa 4.4, is very slightly soluble in water (less than 0.7 mg. per ml.) and freely soluble in alcohol (50 mg. per ml.), acetone, ether and ethyl acetate (39). A solubility of 2.2 mg. per ml. at pH 7.5 was reported by Brodie (2,3).

After a number of trials, alcohol appeared to be the solvent of choice for the extraction of phenylbutazone from tablets. Since large quantities of solvent are required for spectrophotometric determinations, and because dissolution media are aqueous, alcohol was rejected as a diluting solvent.

(a) Spectral - Absorbancy (S-A) curves.

Spectrophotometric curves were determined in distilled water, 0.1N HCl solution, simulated gastric fluid U.S.P. (without enzyme), 0.1N NaOH solution and simulated intestinal fluid U.S.P. (without enzyme). All spectral-absorbancy curves were run on a Bausch and Lomb Spectronic 505 recording spectrophotometer and examples of such curves are shown in Figures 1, 2 and 3.

(i) Procedure

The general procedure for preparing spectral-absorbancy curves is as follows:

> Dissolve 100 mg. of phenylbutazone in 250.0 ml. of alcohol. Dilute a 25.0 ml. aliquot of the alcohol solution to 1000.0 ml. with the solvent specified. Prepare S-A curves over the 210 mu. to 280 mu. range using 1% v/v alcohol in the specified solvent as the

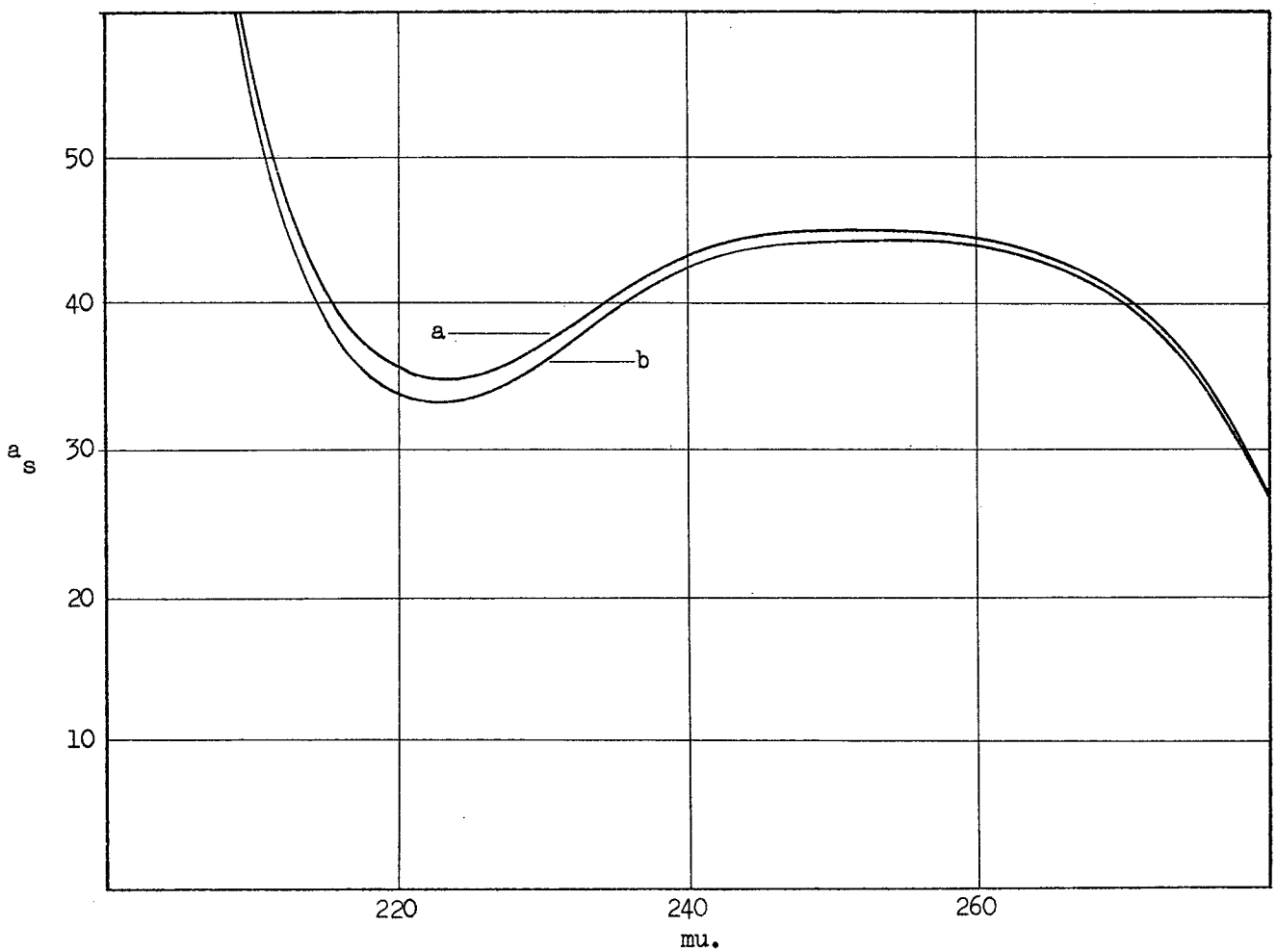


FIGURE 1. Spectrophotometric Curves for (a) Phenylbutazone and (b) Phenylbutazone Tablet Extract in Alcohol-Water (1% v/v) Solution.

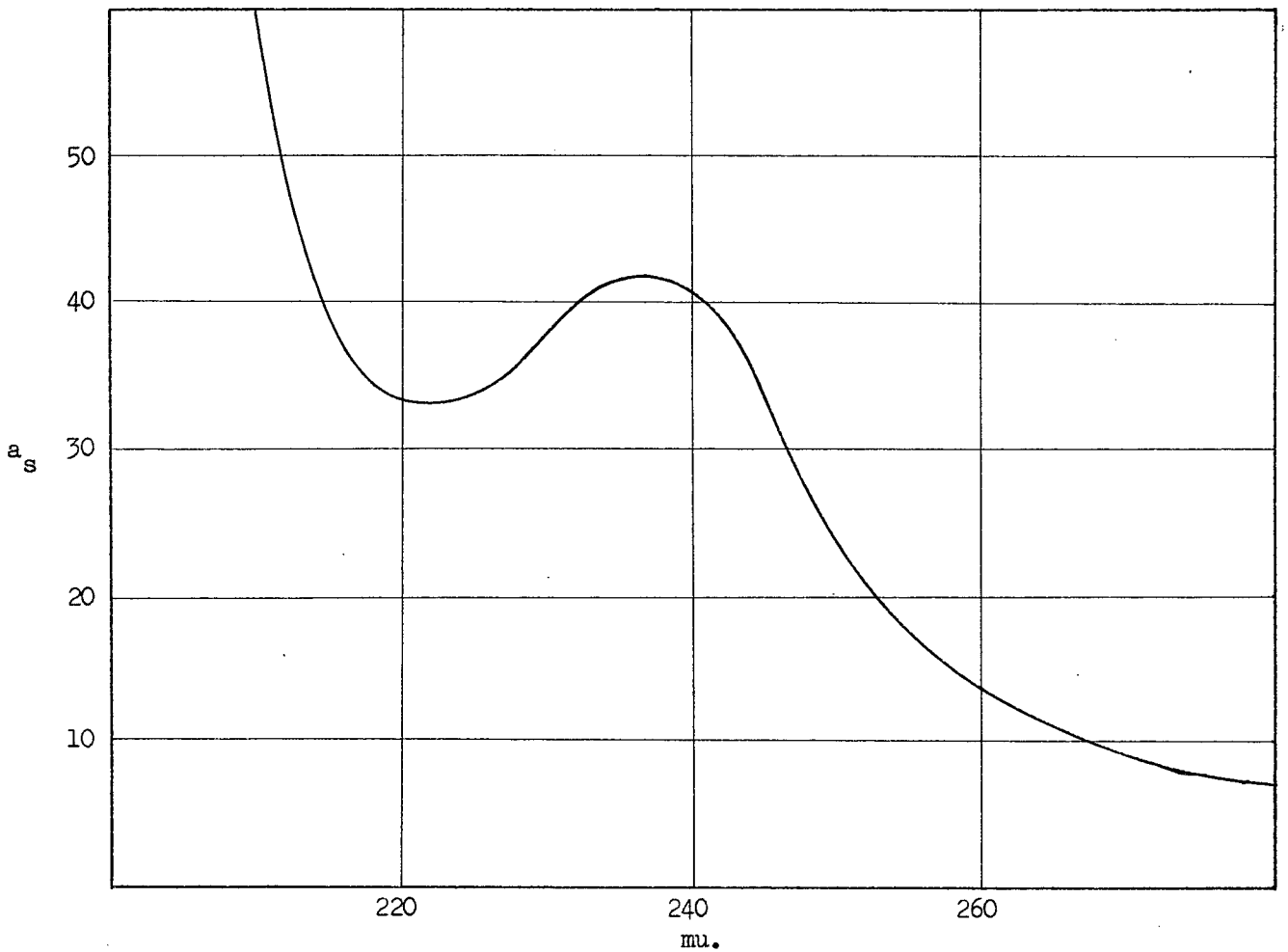


FIGURE 2. Spectrophotometric Curve for Phenylbutazone in 0.1N HCl and Alcohol-Simulated Gastric Fluid Solutions.

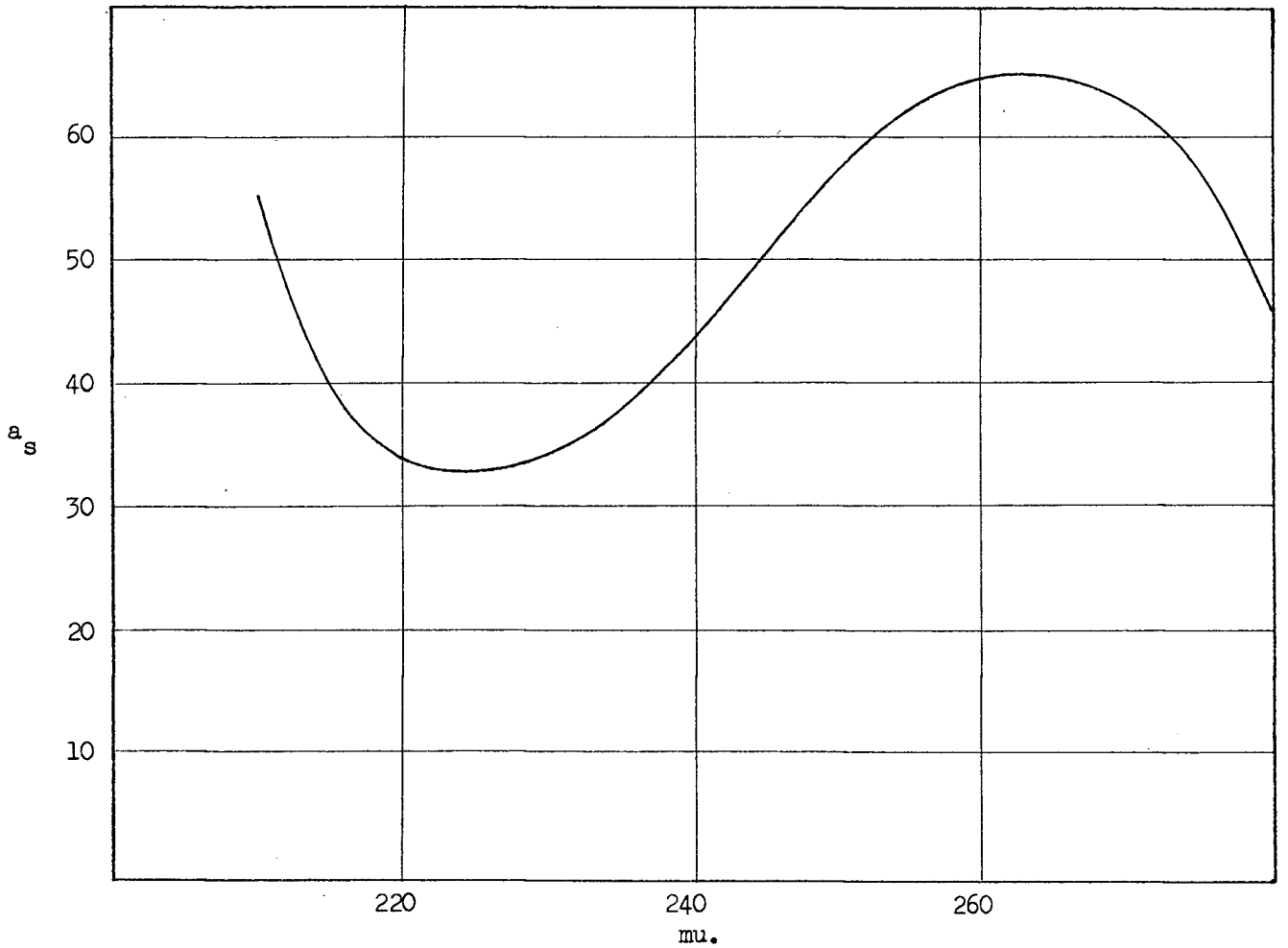


FIGURE 3. Spectrophotometric Curve for Phenylbutazone in 0.1N NaOH and Alcohol - Simulated Intestinal Fluid Solutions.

blank.

The wavelength of maximum absorption in each solvent was determined from each graph and used in subsequent assay procedures.

(ii) Results

Figure 1, Curve A, represents the S-A curve for phenylbutazone in alcohol-water, 1% v/v, solution. Curve B is the S-A curve for phenylbutazone tablet extract in alcohol-water, 1% v/v solution. These two curves are identical except for effects due to concentration differences. There is no sharp absorption maximum but the plateau region, from 245 mu. to 265 mu., can be used analytically. All subsequent measurements were carried out midway between these two wavelengths, that is at 255 mu.

Figure 2 represents the S-A curve for phenylbutazone in simulated gastric fluid U.S.P. (without enzyme). This curve is the same as that for phenylbutazone in 0.1N HCl solution. Here the wavelength of maximum absorption is 237 mu. The wavelength of maximum absorption for phenylbutazone in simulated intestinal fluid U.S.P. (without enzyme) and in 0.1N NaOH solution was found to be 265 mu. These curves, represented by Figures 2 and 3, correspond to those reported by Sunshine and Gerber (61) for phenylbutazone in 0.1N H_2SO_4 solution and 0.1N NaOH solution.

(b) Calibration Curves

A calibration curve indicates the validity of Beer's Law and, in order to check such validity, absorbancy-concentration

curves were prepared for phenylbutazone in distilled water, simulated gastric fluid U.S.P. (Without enzyme) and simulated intestinal fluid U.S.P. (without enzyme.) These curves are shown in Figures 4 and 5.

(i) Procedure

The general method for the preparation of such curves is given below:

Dissolve 100 mg. of phenylbutazone, accurately weighed, in 250.0 ml. of alcohol. Dilute aliquots, from 23.0 ml. to 27.0 ml., to 1000.0 ml. with the specified solvent. Record the absorbancy (A_s) of each solution at the wavelength of maximum absorption using 1% v/v alcohol in the specified solvent as the blank.

(ii) Results

All curves were found to be straight lines and, on this basis, the absorptivities (a_s) in various media and at the wavelength of maximum absorption were calculated using the equation

$$a_s = \frac{A_s}{b\ c}$$

where a_s is the absorptivity, b the cell length (1 cm.), c the concentration (Gm./L.), and A_s the absorbancy.

The wavelengths of maximum absorption and the absorptivity values for phenylbutazone in the various media are summarized in Table III.

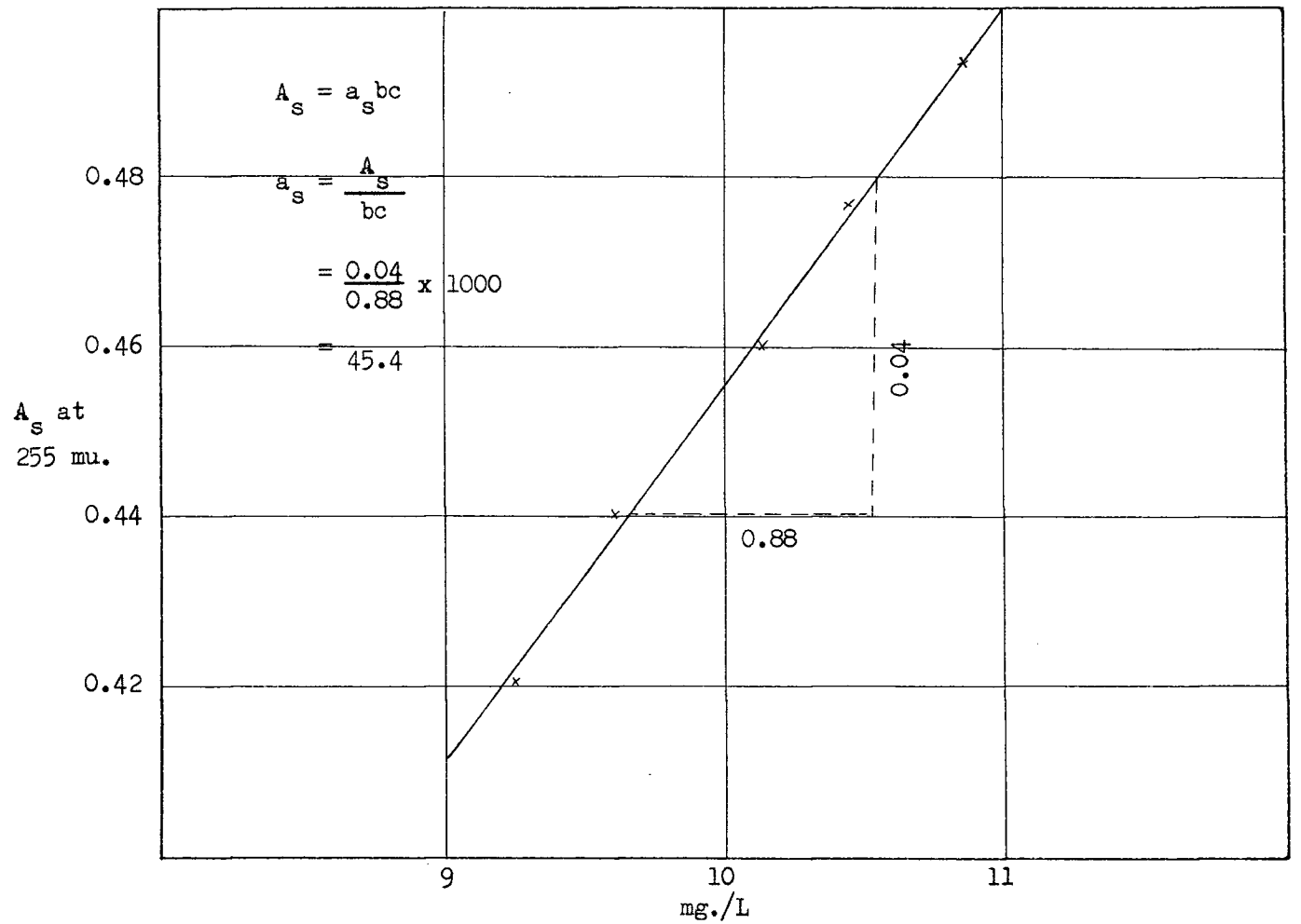


FIGURE 4. Calibration Curve for Phenylbutazone in (1% v/v) Alcohol-Water Solution.

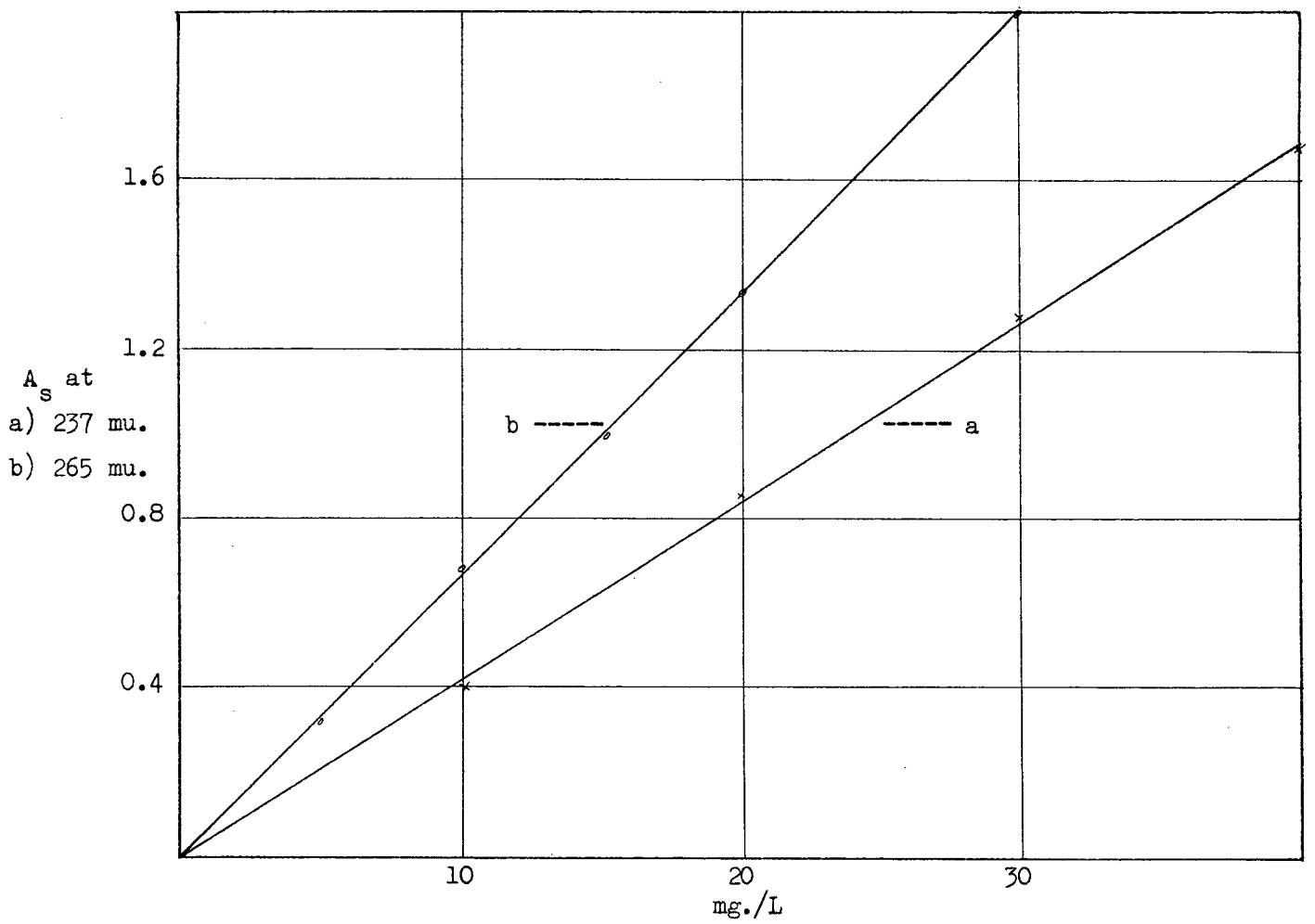


FIGURE 5. Calibration Curves for Phenylbutazone in (a) Simulated Gastric Fluid and (b) Simulated Intestinal Fluid, U.S.P.

TABLE III.

Wavelength of Maximum Absorption and Absorptivity Values for Phenylbutazone in Different Media*

Medium	Wavelength of maximum absorption	Absorptivity
Distilled water	255 mu	45.1
0.1N HCl solution	237	42.0
0.1N NaOH solution	265	65.4
Simulated gastric fluid U.S.P. (without enzyme)	237	42.3
Simulated intestinal fluid U.S.P. (without enzyme)	265	66.5

* Average of five determinations

2. Assay of Phenylbutazone Tablets

(a) Equipment and Reagents

Glass mortar and pestle.

Sintered glass funnel (medium porosity).

Suction flasks (150 ml.).

Volumetric flasks (100 ml. and 1000 ml.).

Pipette (10 ml.).

Spectrophotometer.

Alcohol (95%).

Distilled water.

(b) Procedure

Weigh ten tablets individually. Crush each tablet separately in a mortar. Add 25 ml. of alcohol and extract. Filter the alcoholic solution through the sintered glass funnel inserted into the suction flask. Apply suction if necessary. Repeat with an additional 25 ml. of alcohol. Rinse the mortar and pestle with a further 25 ml. portion of alcohol, and filter, at the same time washing the residue in the funnel. Quantitatively transfer the alcohol solution to a 100 ml. volumetric flask and dilute to volume with alcohol. Mix well. Transfer 10.0 ml. (pipette) of the alcohol solution to a 1000 ml. volumetric flask and dilute to volume with distilled water. Mix well. Read the absorbancy of the aqueous-alcoholic solution at 255 mu. using a 1% v/v alcohol-water solution as a blank. Calculate the concentration of phenylbutazone in the sample and hence the amount per tablet.

$$\text{Gm. per tablet} = \frac{10 \times A_s}{45.4 \times 1}$$

(c) Results

A spectral-absorbancy curve was prepared from a tablet sample and is shown in Figure 1B. This curve compares favourably with that (for pure drug) in Figure 1A. The implication here is that no other substances are being extracted and assayed when this procedure is used. Using this spectrophotometric method, ten tablets, from each of 23 different brands of phenylbutazone tablets, were assayed individually. The results are shown in Table IV.

3. Tablet Disintegration

Disintegration tests were carried out on 23 brands of sugar-coated and two brands of enteric coated phenylbutazone tablets. The results are shown in Table V. Approximately one half of these tablets disintegrated quickly, uniformly, and complied with the regulations in the Food and Drugs Act. Except for use as controls, there appeared to be no need to study these products in depth. Some of these and most of the products which had longer disintegration times or did not disintegrate uniformly were, therefore, singled out for further investigation. The official tablet disintegration method and four modifications were used in studying these twelve products.

(a) Methodology

Method I: This is the official method specified in the regulations to the Food and Drugs Act. The method is described in detail in Appendix B.

TABLE IV

Assay Values for 23 Brands of Phenylbutazone Tablets*

	Mg. of phenylbutazone per tablet						
Sample Code	A	B[a]	C	D	E	F	G
Tablet No.							
1	95.5	98.5	100.0	102.5	97.5	100.0	100.5
2	98.5	99.0	102.0	100.0	99.0	102.0	100.0
3	100.0	98.0	100.0	103.0	98.5	105.0	98.5
4	101.0	101.0	103.0	101.0	99.0	102.0	96.5
5	99.0	81.5[a]	98.5	102.0	96.0	100.0	97.0
6	102.5	103.5	100.5	104.5	96.5	102.5	98.0
7	99.0	80.0[a]	102.0	102.0	96.0	104.0	104.0
8	103.0	99.0	96.0	103.0	99.0	104.0	101.0
9	102.0	91.0[b]	100.0	103.0	95.5	103.5	103.0
10	101.0	102.5	102.0	102.5	97.5	100.5	99.5
Average (mg./tab)	100.2	95.4	100.0	102.2	97.5	102.0	99.8
Standard deviation	2.29	8.36	2.09	1.25	1.38	1.82	2.84

* Label claim = 100 mg./tablet

a Outside the acceptable potency range of 85% to 115% for individual tablets. (N.F.XII)

b Outside the acceptable potency range of 93% to 107% for composite samples. (N.F.XII)

Table IV Continued

	Mg. of phenylbutazone per tablet							
	H	I	J[b]	K	L	M	N	O
1	99.0	95.0	95.5	94.5	96.7	96.1	98.5	96.7
2	101.5	100.0	92.0[b]	98.5	96.9	96.5	100.0	99.8
3	101.0	95.0	98.0	103.0	101.0	94.3	100.0	99.1
4	98.5	101.5	93.5	96.0	101.3	94.1	103.5	98.4
5	99.0	104.0	94.0	98.5	101.5	92.1[b]	99.0	97.5
6	98.0	99.5	94.5	99.5	96.9	95.0	104.0	95.0
7	101.0	94.0	90.5[b]	99.0	101.3	99.4	103.7	98.4
8	99.0	96.0	88.0[b]	97.5	102.1	98.5	101.2	97.5
9	98.5	100.5	95.0	94.5	104.1	99.8	97.0	98.0
10	96.5	98.0	87.5[b]	102.5	96.7	90.6[b]	105.5	98.0
Average (mg./tab.)	99.2	98.3	92.8[b]	98.3	99.9	95.6	101.2	97.8
Standard deviation	1.55	3.29	3.35	2.92	2.77	3.04	2.80	1.32

b Outside the acceptable potency range of 93% to 107% for composite samples. (N.F.XII)

Table IV Continued

	Mg. of phenylbutazone per tablet							
	P[b]	Q	R	S	T	W	X	Y
1	91.7[b]	102.7	101.1	101.5	101.3	106.5	102.2	96.9
2	89.7[b]	101.8	107.7[b]	99.8	100.7	101.5	107.3[b]	97.8
3	87.8[b]	100.8	104.5	97.8	100.2	99.8	111.5[b]	98.8
4	86.0[b]	96.7	104.2	100.0	105.2	104.2	108.4[b]	99.2
5	92.1[b]	106.1	101.1	99.8	104.7	104.9	104.0	98.2
6	87.3[b]	102.0	99.4	104.8	101.2	105.7	86.8[b]	99.4
7	90.8[b]	99.8	101.1	100.0	99.6	102.2	89.3[b]	97.2
8	86.0[b]	103.8	98.1	103.1	100.0	106.1	106.7	99.6
9	86.8[b]	100.0	103.5	102.0	101.5	103.7	103.2	98.7
10	90.8[b]	102.0	102.7	101.5	101.2	101.2	103.0	98.4
Average (mg./tab)	88.9[b]	101.5	102.3	101.0	101.6	103.6	102.2	98.4
Standard deviation	2.38	2.47	2.78	1.99	1.88	2.30	8.01	0.29

b Outside the acceptable potency range of 93% to 107% for composite samples. (N.F.XII)

TABLE V

Disintegration Times of Phenylbutazone Using Method II*

Sample Code	Average Disintegration Time* (Minutes)	Range (Minutes)
A	18	11
B	12	8
C	4	1
D	20	2
E	41	65
F	32	5
G	51	58
H	39	29
I	9	5
J	10	4
K	17	14
L	41	24
M	24	7
N	18	9
O	14	3
P	43	61
Q	37	24
R	20	4
S	4	0
T	21	10
U	Enteric coated	
V	Enteric coated	
W	71	74
X	56	71
Y	6	1

* Average of six tablets.

Method II: Method I was modified to utilize only simulated gastric fluid.

Method III: Method II was modified by omitting the discs described in the official procedure.

Method IV: Method I was modified to utilize only simulated intestinal fluid.

Method V: Method IV was modified by omitting the discs described in the official procedure.

An Erweka tablet disintegration tester (Type ZT2) and a Fisher thermostatically controlled immersion heater were used in the above methods. This equipment complies with the specifications in the U.S.P. All test media were prepared without enzymes.

(b) Results

Tablet disintegration results are shown in Tables V, VI, VII and VIII.

4. Tablet Dissolution

(a) Solubility of phenylbutazone.

Dissolution studies are usually carried out in water, simulated gastric fluid, or in simulated intestinal fluid. Preliminary investigations showed that phenylbutazone was relatively insoluble in all these media. The general procedure used to determine such solubilities was as follows:

> Add 100 mg. of phenylbutazone to 1000 ml. of media (500 mg. to 100 ml. in the case of simulated intestinal fluid.) Maintain at 37^{0}C, with constant

TABLE VI

Disintegration Times of Phenylbutazone Tablets Using Method I

Tablet No.	1	2	3	4	5	6	Mean Time (Minutes)	Standard Deviation
Sample Code	Time in minutes							
A	11	13	17	21	21	22	17	4.7
B	8	8	13	13	14	16	12	3.3
C	3	3	4	4	4	4	4	0.5
D	19	19	20	21	20	21	20	0.9
E	28	18	83*	37	39	41	41	22.3
G	45	45	45	30	45	45	43	6.3
H	48	45	45	30	25	20	35	12
L	28	36	48	42	52	40	41	8.6
P	55	55	28	40	38	45	42	10.6
Q	39	39	53	39	52	41	44	6.8
W	59	46	71*	72*	a	59	61*	28.9
X	52	59	58	23	62*	53	51	14.3

* Disintegration time in excess of 60 minutes

a Did not disintegrate within 120 minutes

TABLE VII

Disintegration Times of Phenylbutazone Tablets using Methods II and III.

Sample Code	Method II*		Method III*	
	Time (Minutes)	Range	Time (Minutes)	Range
A	17	13	58	b
B	14	5	a	a
C	4	2	4	2
D	19	3	19	8
E	35	8	a	a
G	51	45	57	b
H	36	16	43	28
L	38	9	38	13
P	36	22	68	b
Q	39	8	61	73
W	80	b	a	a
X	70	80	51	b

* Average of twelve tablets
a More than two hours for all tablets tested
b More than two hours for one to three tablets

TABLE VIII

Disintegration Times of Phenylbutazone Tablets Using Methods IV and V.

Sample Code	Method IV*		Method V*	
	Time (Minutes)	Range	Time (Minutes)	Range
A	17	5	19	16
B	13	4	a	a
C	4	2	5	3
D	27	7	34	17
E	38	48	a	a
G	41	70	54	60
H	40	5	50	13
L	28	15	72	b
P	37	13	25	29
Q	79	55	a	a
W	a	a	a	a
X	62	43	a	a

* Average of twelve tablets
a More than two hours for all tablets tested
b More than two hours for one to three tablets

agitation, for 24 hours. Filter and assay the filtrate spectrophotometrically.

The results of these investigations indicated that 0.025 mg. of the drug dissolved in one ml. of water, 0.018 mg. in one ml. of simulated gastric fluid (pH 1.2), and 3.2 mg. in one ml. of simulated intestinal fluid (pH 7.5).

It is customary in investigations of this type to determine the time required for 50% of the drug to dissolve in a certain quantity of medium. From the above results, it was evident that this would not be possible when simulated gastric fluid was used as test medium. However, the time required for 10% and 20% of the drug to dissolve together with mg. of drug dissolved at various time intervals can easily be determined.

(b) Methodology

The twelve products selected for intensive disintegration studies were also chosen for the dissolution investigations. Most of the methodology is the same as that outlined in the previous section. The numbering system is consistent with that previously used and the necessary modifications are outlined below:

Method I was not used in these investigations.

Method II A: This is the same as Method II except that aliquots of dissolution medium are taken, at varying time intervals, for analysis. These samples are taken through a sampling device, a diagram of which is shown in Figure 6.

(i) Sampling Device

A sampling device was assembled using a sintered glass funnel of course porosity and a sintered disk sampling tube of medium porosity. This was then connected to vacuum and compressed air outlets as shown in Figure 6. Before a sample was withdrawn, clamp A was opened and clamp B closed. All the liquid in the device was then blown out into the bulk solution. Clamp A was then closed and clamp B opened. A sample was then drawn up into the funnel by suction and a 10 ml. aliquot pipetted off for analysis. The remaining sample in the funnel was immediately put back into the bulk solution by closing clamp B, opening clamp A, and turning on the compressed air. This procedure was followed for all samples taken for analysis during the course of this investigation.

Method IIIA: This is the same as Method III. As described above, samples were withdrawn for analysis.

Method IVA: This is the same as Method IV. As described above, samples were withdrawn for analysis.

Method VA: This is the same as Method V. As described above, samples were withdrawn for analysis.

Using the above four methods, disintegration and dissolution data was obtained for six tablets from each of the twelve products. Dissolution samples were taken after one and two hours. The results are listed in Table IX.

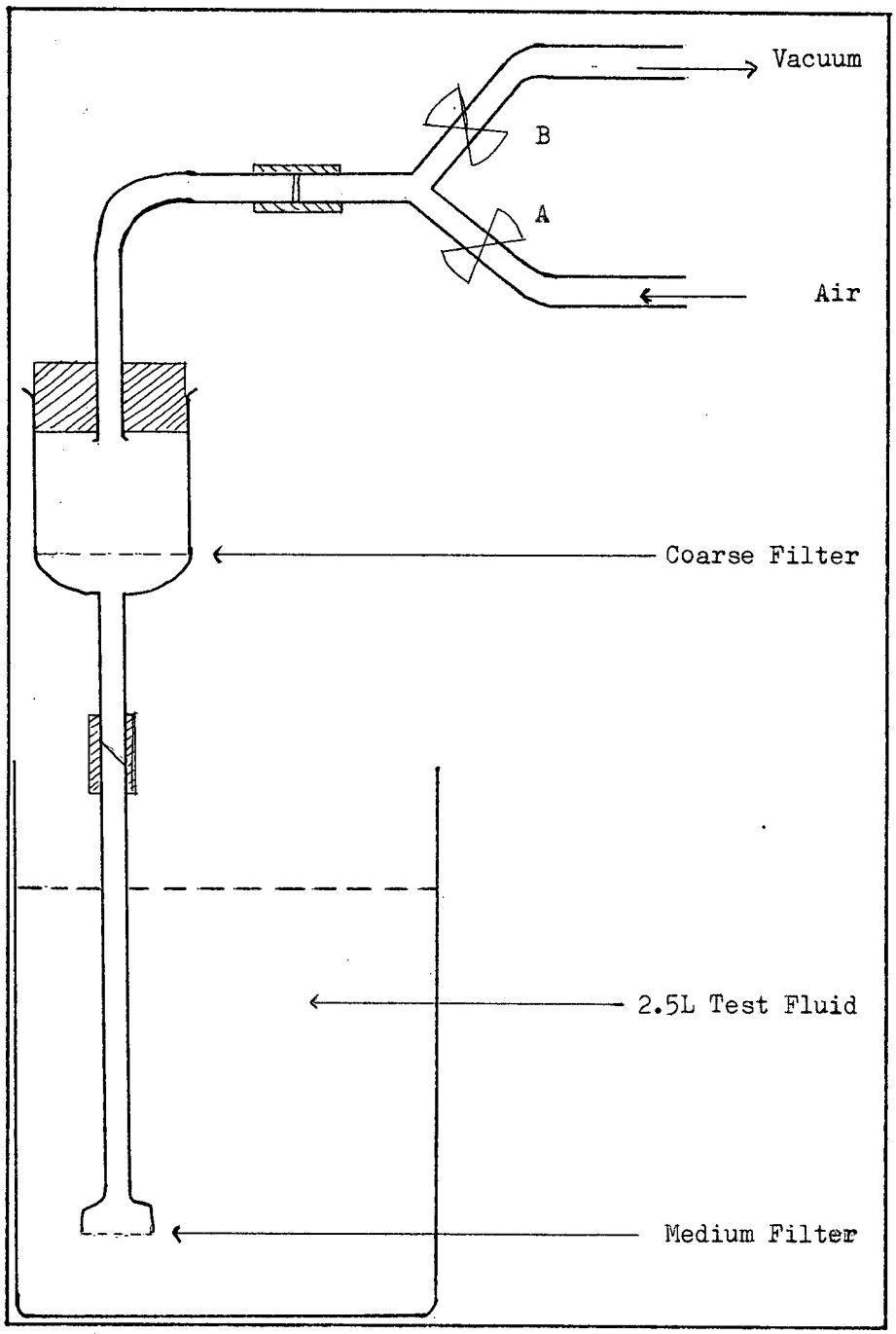


FIGURE 6. Sampling Device.

TABLE IX

Disintegration Times and Dissolution Characteristics of Phenylbutazone Tablets Using Methods II to V Inclusive*

Sample Code	Disintegration Time (Minutes)				Dissolution Mg. in solution**							
	Methods											
	II	III	IV	V	IIA		IIIA		IVA		VA	
					1	2	1	2	1	2	1	2
A	17	52[b]	17	19	3	4	2	4	28	44	32	51
B	16	a	13	a	3	5	1	1	30	38	26	41
C	4	4	4	5	5	6	3	4	80	89	74	85
D	17	19	27	34	2	3	2	5	50	68	41	60
E	29	a	38	a	6	9	4	8	70	77	10	29
G	62	57[b]	41	54	4	5	3	4	50	72	38	64
H	32	43	40	50	4	5	3	4	49	68	33	55
L	35	38	28	72	4	5	5	7	51	66	37	49
P	28	68	37	25	9	11	3	5	69	78	65	75
Q	40	61	79	a	3	4	2	3	24	56	13	38
W	56[b]	a	a	a	5	9	1	2	30	44	6	21
X	83	51[b]	62	a	2	3	2	3	24	48	4	11
Pure Drug (Percent)					30	34			98	100		

* Average of six tablets
** Mg. in solution after one and two hours.
a More than two hours for all tablets tested.
b More than two hours for one to two tablets.

Dissolution tests were repeated on individual tablets using Methods IIA and IVA. One tablet was placed in a tube of the basket-rack assembly and the apparatus operated in the usual manner. This test was repeated twice for each product. Sample aliquots were obtained for analysis after 15 minutes, 30 minutes, 60 minutes, 90 minutes, 120 minutes and every hour thereafter for seven hours. The results are shown in Table X and illustrated in Figures 7 and 8.

Methods VI and VII

(i) Apparatus

The apparatus used in this method is similar to that used by Levy and Hayes (31). It consists of a constand temperature water bath, a Fisher Stedi-Speed adjustable stirrer (Model 12), a teflon coated three blade impeller (5 cm. in diameter), a cylindrical wire basket with a hinged top, made from 10 mesh stainless steel wire cloth (2.2 cm. in diameter and 2.8 cm. in length) and a three liter glass container similar to that used in the previous methods. The wire basket dimensions were similar to those of the tubes used in the tablet disintegration apparatus. The length of this basket was approximately the same as that from the wire screen to the bottom of the plunger in the official apparatus.

(ii) Test procedure

The three liter glass jar containing 2.5 liters of test medium was allowed to equilibrate in the constant temperature water bath at 37°C ± 1°C. A single

TABLE X

Disintegration Time and Dissolution Characteristics of Phenylbutazone Tablets using Methods IIA and IVA*

Sample Code	Disintegration Time (minutes)		Dissolution Mg. in solution**					
	IIA	IVA	IIA			IVA		
			2	4	6	2	4	6
A	15	17	10	17	24	58	74	81
B	8	8	11	20	24	51	68	74
C	4	5	30	32	33	99	102	102
D	15	32	5	9	13	67	85	93
E	30	37	16	18	19	92	96	98
G	42	40	13	21	28	97	106	110
H	35	47	9	14	19	76	92	99
L	37	40	6	10	14	65	84	95
P	40	30	15	18	22	90	92	92
Q	23	58	6	9	15	67	84	88
W	63	b	14	21	28	53	84	99
X	75	70	12	17	21	57	86	95
Pure Drug (Percent)			34	35	36	100	100	100

* Average of two tablets.
** Mg. in solution after two, four and six hours
b Tablet slowly dissolves.

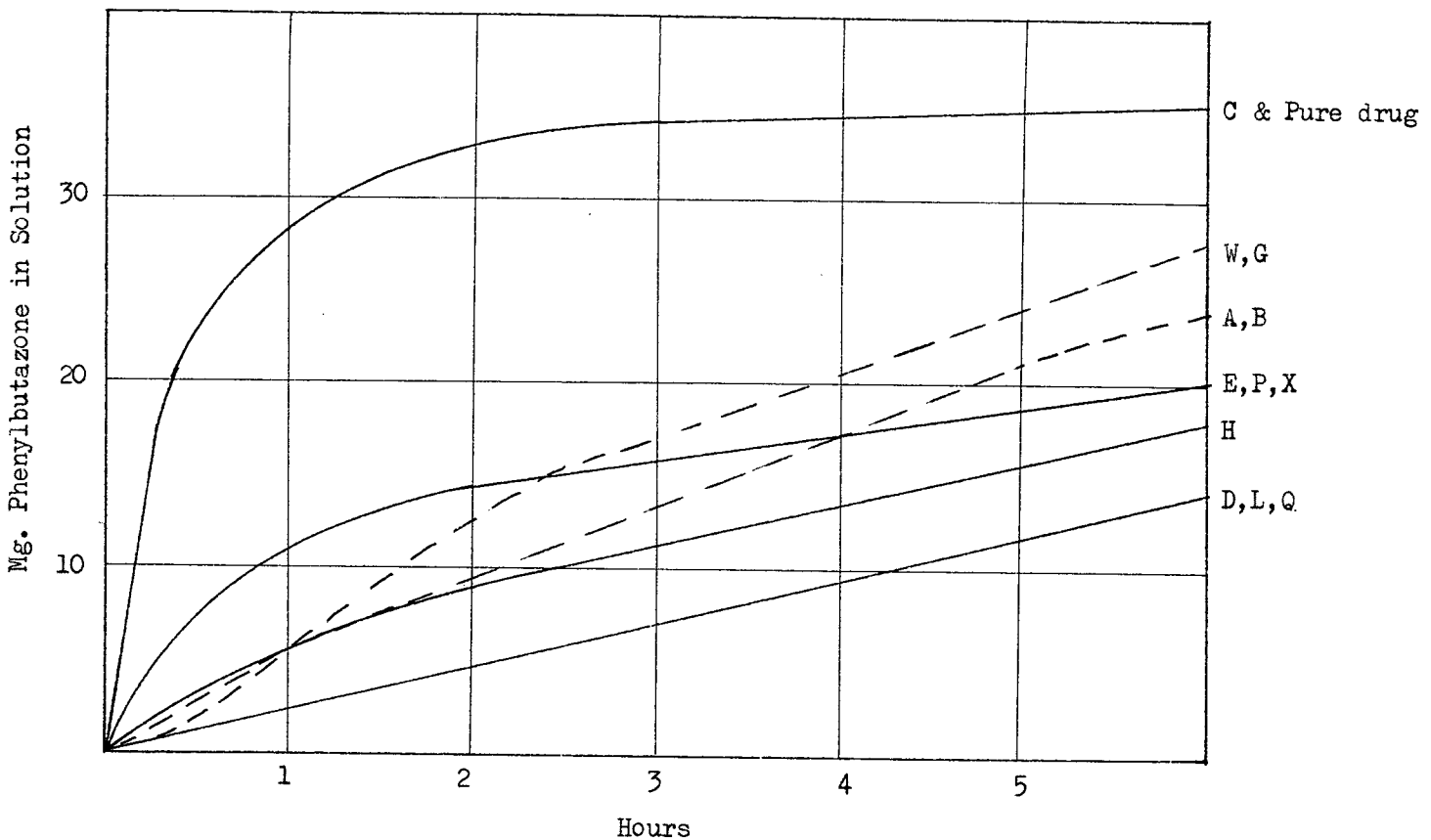


FIGURE 7. Dissolution Profiles of Phenylbutazone Tablets in Simulated Gastric Fluid using Method II.A.

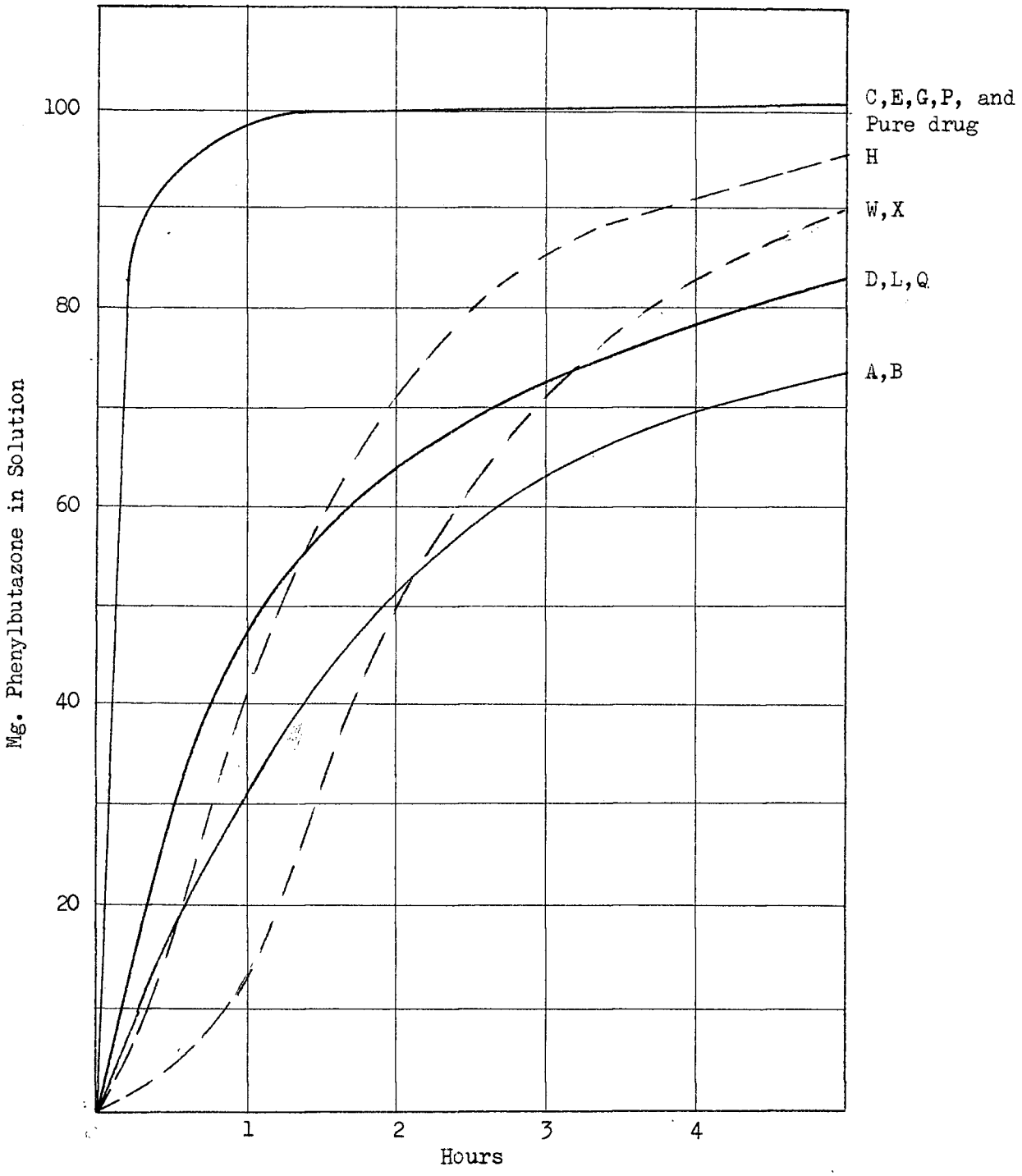


FIGURE 8. Dissolution Profiles of Phenylbutazone Tablets in Simulated Intestinal Fluid using Method IV A.

phenylbutazone tablet was placed into the cylindrical wire basket which is hung below the impeller of the stirring shaft. The stirrer is then inserted into the liquid to a depth of 10 cm. below the surface. The speed of agitation in all cases was 100 r.p.m. in a foreward (clockwise) direction. Sample aliquots were taken at 15 minute intervals for the first hour, 30 minute intervals for the second hour, and, thereafter, at hourly intervals for seven hours. The sampling procedure has already been described.

Disintegration times, that is, the time required for tablet residue to fall through the bottom of the basket, were also determined during these dissolution studies. Two tablets from each of the twelve phenylbutazone samples were tested individually in both gastric fluid (Method VI) and intestinal fluid (Method VII) without enzymes. The results are tabulated in Table XI and illustrated in Figures 9 and 10.

TABLE XI

Disintegration Times and Dissolution Characteristics of Phenylbutazone Tablets using Methods VI and VII. *

Sample Code	Disintegration Time (minutes)		Dissolution Mg. in solution**					
	VI	VII	VI			VII		
			2	4	6	2	4	6
A	20	30	6	11	14	80	94	99
B	a	30	2	3	4	60	83	93
C	4	5	29	31	33	99	99	99
D	20	30	5	9	12	78	98	104
E	a	b	0.5	1.5	2	21	56	76
G	45	25	10	18	22	98	100	100
H	45	45	7	11	15	75	96	99
L	30	35	11	14	18	80	94	99
P	25	35	12	18	22	86	87	88
Q	45	60	6	12	16	39	59	70
W	a	b	0.2	0.8	1.2	29	64	88
X	c	c	3	11	17	0.5	7	48
Pure Drug (Percent)			26	28	29	99	100	100

* Average of two tablets
** Mg. in solution after two, four and six hours
a More than seven hours
b Tablet slowly dissolves
c Tablet coating intact for three to four hours

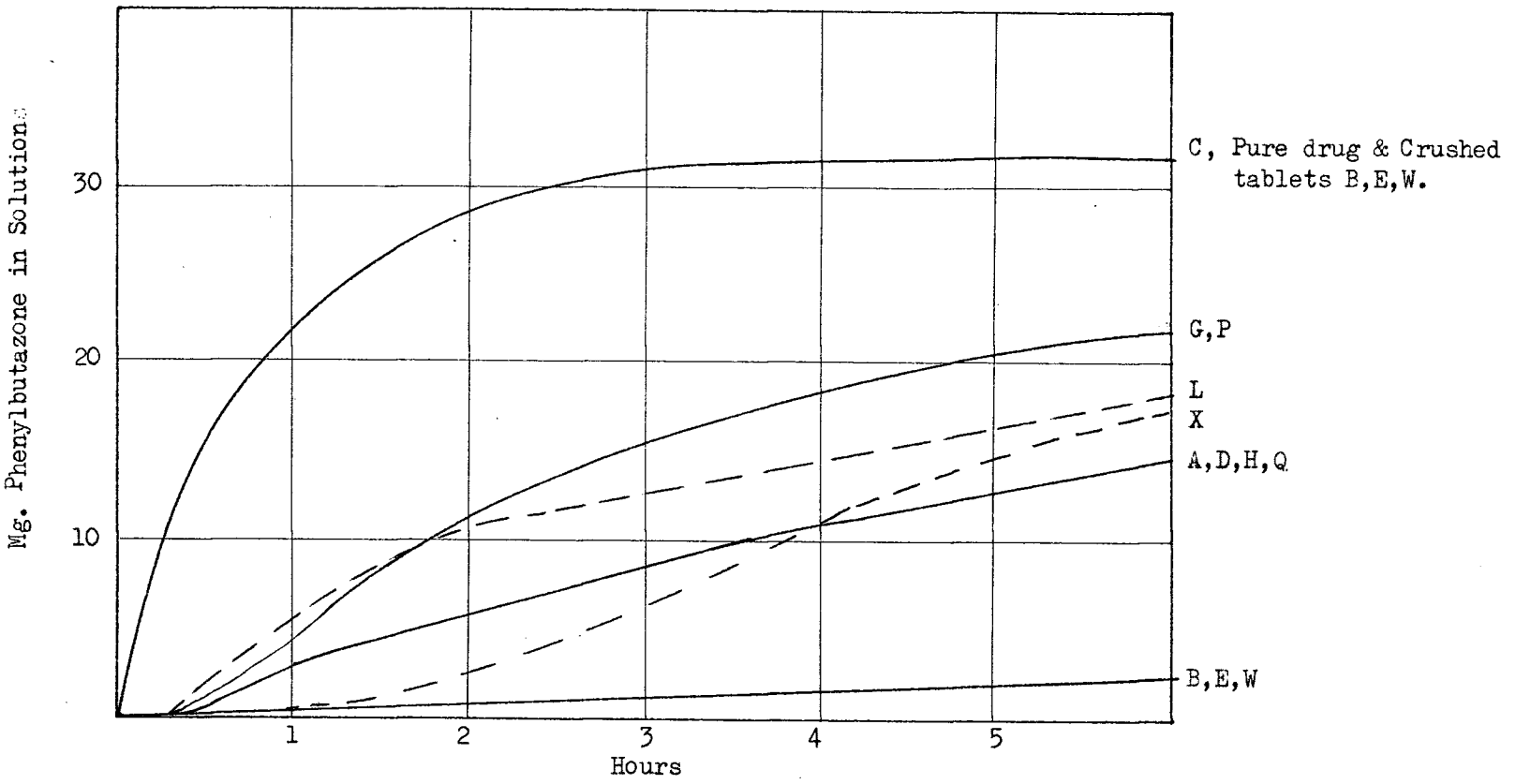


FIGURE 9. Dissolution Profiles of Phenylbutazone Tablets in Simulated Gastric Fluid using Method VI.

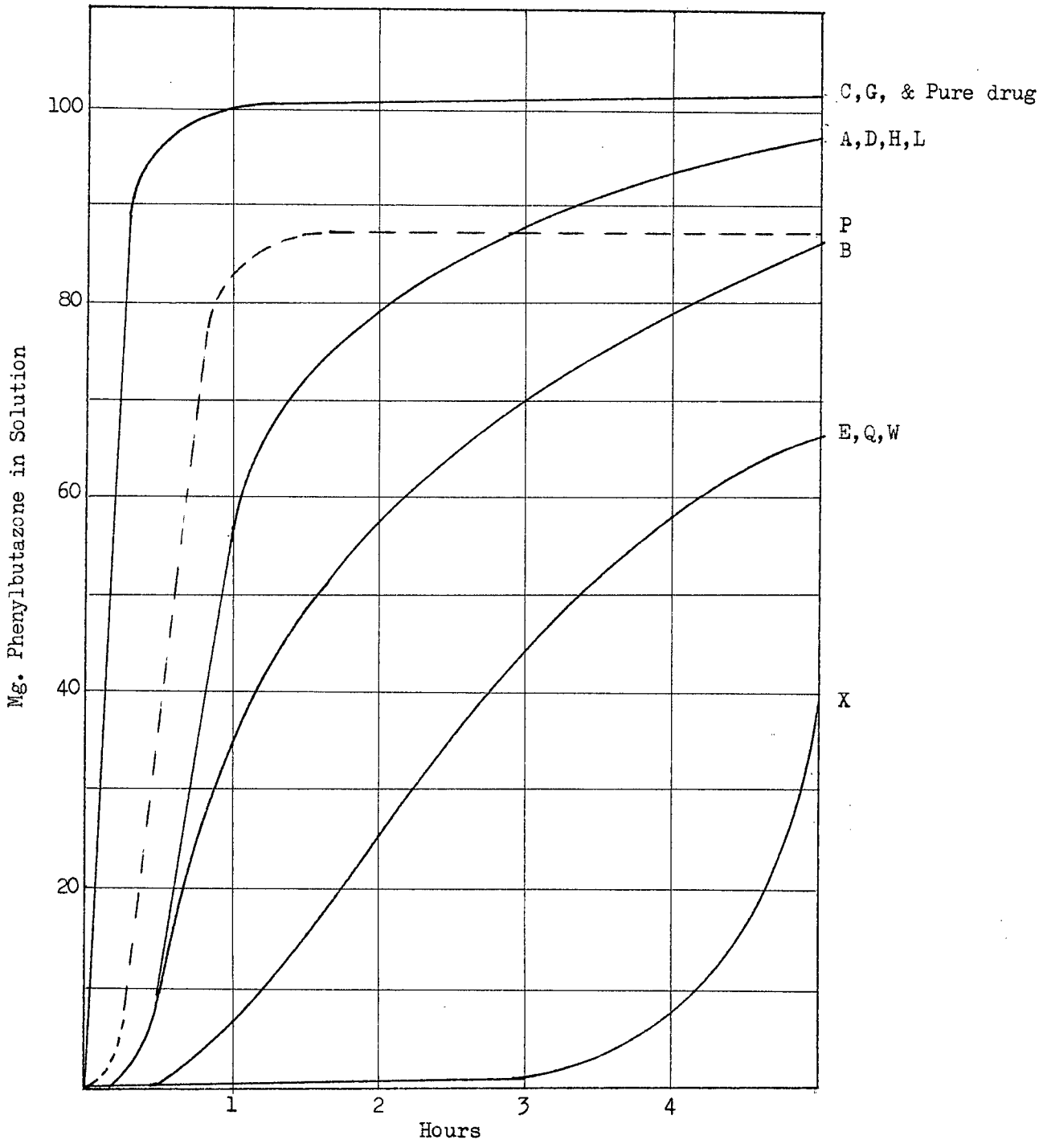


FIGURE 10. Dissolution Profiles of Phenylbutazone Tablets in Simulated Intestinal Fluid using Method VII.

IV. DISCUSSION

Three topics will be discussed in this section - the test procedures, the quality of the products investigated, and the preliminary release characteristics of phenylbutazone and phenylbutazone in tablet form.

1. Test Procedures and Results.

(a) Tablet Assay.

All assay procedures for tablets in the official compendia specify that not less than twenty tablets should be ground up, thoroughly mixed, and suitable samples taken for analysis. This procedure generally tends to give results which fail to indicate any tablet to tablet content variation. Since tablets are usually administered singly, or at least in quantities somewhat less than that specified in an assay, it is important that the drug content of each and every tablet comply with the label claim.

The N.F. XII (48) has introduced a test for uniformity of drug content in tablets. This test states that not more than one out of thirty tablets may assay outside the limits of $\pm$ 15% of labelled potency. Although this is a step in the right direction, the problem of excessive variability still remains. Products which fall just within the extremes of these limits may be therapeutically tolerable; however, such results would indicate poor manufacturing procedures and this should not be encouraged. In addition to the present requirements, a more stringent test should be applied. Either a standard deviation

or range limit should be included in the test. As the test now stands, a range of 30% may well be acceptable.

The results of this investigation indicate that a suitable test for uniformity of drug content in tablets should read:

> Assay ten tablets individually. The average content of these ten tablets should fall within ± 7% of labelled potency. The standard deviation for the ten individual assays should be not more than 4% and no tablet should assay less than 85% or more than 115% of labelled potency.

The assay procedure for phenylbutazone tablets in the N.F. XII (48) calls for samples containing 600 mg. of drug (that is, the equivalent of six tablets). An attempt was made to assay individual tablets by this titrimetric procedure. The results were inconsistant primarily because of the small quantity of drug in each tablet and for this reason a spectrophotometric procedure was developed. This method of analysis was described in the previous section. This procedure, on the basis of results on pure drug and tablets containing phenylbutazone, was found to be accurate and was therefore used in all single tablet assays.

(i) Results.

The N.F. XII sets limits of ± 7% of label claim for the average assay of phenylbutazone tablets. Of the 23 samples tested, two samples, J and P, assayed 92.8% and 88.9% respectively as shown in Table IV. If individual tablet assay

is considered (the N.F. allows ± 15% of labelled potency), one other sample, B, contained tablets assaying less than 85% and, therefore, would be rejected although the average assay was within the limits of 93% to 107% of label claim. However, if the suggested criteria of a 4% standard deviation is applied, one other product, X, would be rejected. Two other samples, M and R, contained tablets which, on an individual basis, were outside the limits set for average assay and it is doubtful if these tablets could be considered adequate. These results would tend to substantiate the observations made by Brunning and King (4) that the present official attribute methods of tablet testing cannot differentiate or detect excessive tablet to tablet variation.

It was also noted that although the labelled potency of all products was 100 mg. of phenylbutazone per tablet, six samples, E,J,M,O,P and Y contained tablets which assayed less than this amount. However, sample Y showed the least variability (a standard deviation of 0.29) in tablet potency indicating good control procedures during manufacture. This may be compared with the variability shown by samples B and X (standard deviations of 8.36 and 8.01 respectively) which was more than the 4% limit suggested and would indicate poor quality control.

All tablets studied are available commercially in Canada and were purchased through regular drug outlets.

(b) Disintegration Tests.

(i) Initial Investigations

Initial investigations using Method II showed that the disintegration times of the 23 products varied from four to 71 minutes as shown in Table V. The times for four products were less than ten minutes and for nine products were greater than thirty minutes. However, only one product failed to comply with the regulations in the Food and Drugs Act. Even though most products complied with existing regulations, there was much in-product variation.

Sample C is an example of a good product, the minimum disintegration time being three minutes and the maximum being four minutes. On the other hand, many other products showed extreme variability. For example, sample W, with a disintegration time of 71 minutes, showed a minimum time of 46 minutes and a maximum time of more than 120 minutes. These results would indicate poor quality control. A reasonable spread of values would be approximately fifteen minutes. Using this arbitrary limit as a base, eight of the 23 products would show excessive variability.

Of the twelve products chosen for more intensive study, one disintegrated in less than ten minutes, three had disintegration times between ten minutes and thirty minutes, seven disintegrated between thirty minutes and sixty minutes and one showed a disintegration time of more than sixty minutes.

(ii) Investigations On Twelve Products.

The official disintegration test (Method I) on the twelve products indicates that sample W fails to comply with the time limit requirement of sixty minutes (see Table VI). This product, and sample E, contained individual tablets which showed disintegration times in excess of 75 minutes. The variability (measured by one standard deviation) in disintegration times from tablet to tablet for these two products was 80% - 100% greater than for the product with the next highest time. This would indicate non-uniform tablet production.

Disintegration tests by Methods II and IV showed no appreciable differences in average disintegration times for eleven of the twelve products tested as shown in Tables VII and VIII. One product, Q, had an average disintegration time of 39 minutes by Method II compared to 79 minutes by Method IV. However, within a test, some products showed a high degree of variability. Sample G. by Method II, contained tablets ranging from 30 minutes to 75 minutes and by Method IV, from 20 minutes to 90 minutes. Samples E and Q, by Method IV also showed ranges of 48 minutes and 55 minutes respectively. Sample W did not disintegrate by either method. Sample X had a long disintegration time coupled with a high variability under the same test conditions.

A comparison of the disintegration times by Methods I, II and IV, for the twelve products, showed that sample Q had a disintegration time which was 100% longer by Method

IV than by either of the other two methods. Sample X, when tested by Methods II and IV, showed disintegration times of 70 minutes and 62 minutes respectively as compared to 51 minutes obtained by Method I. The results would also indicate that two products, W and X, demonstrate prolonged disintegration times under all test conditions. For ten of the twelve products, the disintegration times obtain-by these methods utilizing discs, were within fifteen minutes of each other.

Three products C, D, and L, demonstrated identical disintegration times when tested by Methods II and III. The other nine products showed distinctly longer disintegration times with Method III. By this method, no tablets from products B, E and W disintegrated within two hours. Products A, G, P and X contained one to three tablets which also failed to disintegrate within this time.

The disintegration times for two products, A and C, were relatively unaffected by changing from Method IV to Method V. All tablets of the five products B, E. Q, W and X, failed to disintegrate within two hours when tested by Method V. Product P disintegrated faster by Method V while products D, G, H and L disintegrated faster by Method IV. Tablets from products B, E, W and X failed to disintegrate within two hours when tested by Methods III and V as shown in Tables VII and VIII.

It should be noted that one product, C, showed a consistantly low disintegration time of four minutes when tested by any of the five methods.

(iii) Summary of Results

The results obtained in this investigation would indicate that the present disintegration test does not discriminate sufficiently when excessive variability is a factor. There is an obvious need for a more stringent test, one which would include some measure of variability such as range or standard deviation. A practical limit might be a fifteen minute spread in disintegration times between tablets in any one test.

The results, obtained with and without discs, suggest that the discs were necessary to keep the disintegration times within reasonable limits for all tablets tested. Without the discs, 50% of the tablets tested would have disintegration times in excess of two hours. The absence of discs made no difference for the other 50%. In most cases, there were no significant differences in disintegration times when gastric fluid or intestinal fluid was used as test medium.

The discs were originally included in the test procedure in order to exert gentle physical force on the tablets. This was supposed to simulate forces encountered in the gastrointestinal system. Early investigators in the Food and Drugs Laboratories indicated that this procedure was valid for the products tested. However, subsequent investigations by several workers (28,60) indicated that in vivo conditions were such that tablets were not subjected to much physical force while in the stomach.

The results of this investigation would indicate that tablets could be formulated to disintegrate (without discs) under in vitro conditions which may be more indicative of an in vivo climate. This test may have some merit if an in vitro - in vivo relationship is to be implied from the disintegration test. However, the present disintegration test should not be used as an indication of drug availability unless in vivo data is obtained and correlated to the in vitro results.

(c) Dissolution Tests.

(i) Tests on Six Tablets.

The amount of phenylbutazone in solution after two hours ranged from 3 - 11 mg. and from 1 - 8 mg. when the tablets were tested by Methods IIA and IIIA respectively. For most products, the results indicated that the amount of drug in solution was lower by Method IIIA than by Method IIA. However, two products, A and X, showed no change in dissolution rates. Two other products, D and L, showed higher results by Method IIIA. It was also noted that tablets which did not disintegrate fully within the time limit of two hours showed lower levels of dissolution. Product E, when tested by Method IIIA, seemed to be an exception.

The dissolution levels were, as expected, higher by Methods IVA and VA than by Methods IIA and IIIA. The maximum amount of drug in solution in two hours ranged from 38 - 89 mg. and from 11 - 85 mg. as determined by Methods IVA and VA respectively. Two products, A and B, showed

higher levels by Method VA than by Method IVA. This result seems to be reasonable for product A since disintegration of these tablets was relatively rapid. However, the tablets of product B did not disintegrate within two hours. The other products E, Q, W and X, which also did not disintegrate, showed low dissolution rates. It was also noted that for product W, whose disintegration was poor by all methods, the presence of the discs in Methods IIA and IVA seemed to aid in the dissolution process.

Many investigators have used the Gershberg-Stoll apparatus to study dissolution of various tablets. The results of the present investigation shows that tests conducted with discs generally gave higher dissolution rates than tests without discs. They also show that rapid disintegration aided in the dissolution process. From the previous discussion on disintegration studies, it was suggested that the presence of the discs may tend to mask the true characteristics of the tablets. Therefore, although the discs may be expedient in disintegration tests, they should be omitted if this apparatus is used for dissolution studies. In this case, the disintegration and dissolution of the tablets would better reflect the true inherent characteristics of the products.

(ii) Tests on Individual Tablets.

Dissolution profiles of single tablets from each of the twelve products were obtained using Methods IIA and IVA. The results are tabulated in Table X and illustrated in

Figures 7 and 8. The disintegration times listed are for the individual tablets tested. After six hours, the maximum amount of pure powdered drug dissolved from a gelatin capsule in gastric fluid was 36 mg. One product, C, approached this limit with 33 mg. in solution after six hours. In general, the results indicate that there were at least three different patterns of drug release from these tablets.

Product C and the pure drug dissolved rapidly during the first 30 minutes, more slowly during the next 90 minutes and showed no additional solution after about two hours. At the other extreme, products such as D, L and Q seemed to release the drug at a constant rate over a six hour period at a level which was about 60% lower than that for product C. All other products fell between these extremes.

Initial dissolution rates during the first 90 minutes appeared to depend upon the disintegration time. The faster disintegrating tablets showing the highest rates. After this initial period, the rate of release of drug from all products was observed to fall into three patterns. The rate of release from products D, L, Q and H were almost identical. The same may be said of products (A,B,X) and (W,G); and Products (E,P) and C. The differences in initial disintegration times could account for the differences in dissolution levels attained by these products in six hours. It should be noted that although the disintegration times of products W and X were in excess of 60 minutes, the drug

release patterns, after disintegration had occured, were better than those obtained for products with shorter disintegration times.

Since phenylbutazone is more soluble in intestinal fluid than in gastric fluid, the dissolution levels attained by Method IVA (Figure 8), were much higher than those obtained by Method IIA. Within 30 minutes, 85% of the drug from products A, E, G. P, and a pure drug sample had dissolved and 100% was in solution after 90 minutes. Products (A,B) and (D,L.Q) showed a much more gradual rate of release reaching levels of about 75% and 85% respectively after five hours. Disintegration times seemed to affect the release of drug from products such as H and X. However, after disintegration, the rate of release was fairly rapid. Product W did not disintegrate but slowly dissolved after the outer coat had broken away.

The release pattern for a good phenylbutazone tablet, using Method IIA, appears to be as follows: 20% released in 15 minutes, 25% in 30 minutes, 27% in 60 minutes, 30% in 90 minutes, and 33% between three and six hours. This may be compared with approximately 34% dissolution for pure in three hours. In intestinal fluid (Method IVA), 75% of the drug should be in solution within 15 minutes and 100% between 60 and 90 minutes.

The performance of the tablet preparations when tested by Methods IIA and IVA could be rated as follows: Product C demonstrated good dissolution characteristics by

both methods. Products E, G and P showed good release by Method IVA only. Products L, D, and Q showed poor release patterns by both methods.

Stirrer method.

Previous investigators have determined that factors such as rate of agitation (r.p.m.), depth of stirrer, and medium used can influence the rate of drug release from solid dosage forms. With this in mind, preliminary studies to determine the effect of stirring rate and depth of stirrer on dissolution rate were carried out using one brand of phenylbutazone tablets. It was found that a stirring speed of 100 r.p.m. (with the stirrer blade set 10 cm. below the surface of the liquid) was fast enough to allow for homogenous mixing of the dissolved drug but slow enough to avoid any turbulent action. The coarse tablet particles were observed to be gently swirled around the bottom of the container forming a mound below the stirrer.

Methods VI and VII were used to study the dissolution characteristics of individual tablets from each of the twelve samples. The disintegration times listed in Table XI are for the individual tablets tested. The maximum amount of drug in solution after six hours ranged from 1.2 - 33 mg. as determined by Method VI. Tablets B, E and W, which did not disintegrate, showed very low dissolution levels.

The release patterns obtained by Method VI (Figure 9) were similar to those obtained by Method IIA (Figure 7),

except that the products at the various levels may be interchanged. The presence of the disks in Method IIA may have been responsible for the difference between the release patterns obtained for products B, E and W by this method and those obtained by Method VI. When sample tablets from these products were crushed before testing, the dissolution patterns obtained were identical to those of tablets from product C and of the pure drug sample. These results would indicate that the drug was available from the formulation. Tablets from product X contained a coating which remained intact for three to four hours and this would affect the dissolution rate as seen from the curve.

Dissolution profiles obtained by Method VII are depicted in Figure 10. The trends may be illustrated by three release patterns: tablets such as those from samples C, G and P show initial rapid dissolution to a maximum of 100% within the first hour; tablets from samples E, Q and W do not completely disintegrate and hence release their drug content at a more gradual rate; the other samples fall somewhere between these two extremes.

Product X is exceptional in that it contains a coating material which is resistant to disintegration by either of these test methods. It also showed some resistance when tested by Methods IIIA and VA. However, once this coating was removed, the drug dissolved rapidly. Tablets from samples E and W slowly dissolved but did not disintegrate into fine particles. Sample P is a good example of a product

which is well formulated and releases its active ingredient. However, it is poorly controlled with respect to its drug content.

Disintegration, as observed by this test method, does not automatically imply dissolution. Five products tested in simulated gastric fluid disintegrated but showed poor release patterns. Two products, tested in simulated intestinal fluid, also disintegrated and showed low levels of dissolution.

(iii) The Stirrer Apparatus (Methods VI and VII) v.s. the F.D.D. Apparatus (Methods IIA and IVA).

The release pattern for a good tablet tested by the stirrer method appears to be very similar to that obtained by the F.D.D. apparatus. For product C, using Method IIA, the time for 10% release (T10%) was ten minutes and for 20% release (T20%) was 24 minutes. By Method VI, T10% was also ten minutes and T20% was 28 minutes. These results may be compared with that for pure drug when T10% was 15 minutes and T20% was 31 minutes, as shown in Table XII.

Using Method IIA, four products, L, P. Q and X failed to attain 20% dissolution in five hours. Product Q did not even attain a T10% level in more than five hours. Therefore eight products attained 20% dissolution in five hours or less. On the other hand, with Method VI, only three products C, G and P showed a T20% of five hours or less. Two of these, G and P, were 300 and 288 minutes respectively. Hence nine products tested by this method failed to attain 20% dissolution in five hours. Three of these products,

TABLE XII

Release Patterns for Phenylbutazone from Tablets using Methods IIA and VI.*

Sample Code	Method IIA		Method VI	
	T 10% (Minutes)	T 20%	T 10% (Minutes)**	T 20%
A	132	278	240	a
B	132	297	a[b]	a[b]
C	10	24	10	28
D	169	282	294	a
E	25	178	a[b]	a[b]
G	96	289	120	300
H	135	288	219	a
L	255	a	177	a
P	40	313	99	288
Q	330	390	198	a
W	72	226	a[b]	a[b]
X	95	332	174[c]	372[c]
Pure Drug	15	31	21	60

* Average of two tablets
** Time for 10% and 20% of the drug to be in solution
a More than seven hours
b Tablet essentially intact after seven hours
c Tablet coating intact for three to four hours

B, E and W, also failed to have a T10% of less than five hours. The tablets of these three products were essentially intact after seven hours. However, the tablets of five products, A, D, H. L and Q, although they disintegrated, did not release 20% of their active ingredient in seven hours.

Tests by Method IVA showed that only one product, B, had a T75% in excess of five hours. With Method VII four products, E, Q, W and X, had a T75% of more than five hours. Products E and W again failed to disintegrate, however, they dissolved slowly. These results are shown in Table XIII.

Methods IIA and IVA would appear to give more favourable results which may or may not represent the true dissolution characteristics of the products. However, these two methods were rejected for dissolution studies since the presence of the discs seemed to overly influence the dissolution rate of the drug from the tablet. Previous authors (8,54) have suggested that a test without discs might be a more acceptable procedure. However, insufficient data was collected in this investigation to warrent any definite conclusions on the merits of this system at this time.

All methods give essentially the same type of dissolution curves in gastric and intestinal fluids. The discs in the F.D.D. apparatus tend to produce a more rapid disintegration of the tablets than would normally occur without discs. Significant differences in dissolution rates may not then show up on dissolution testing using this apparatus. This was obvious in the case of products B, E and

TABLE XIII

Release Patterns for Phenylbutazone from Tablets using Methods IVA and VII.*

Sample Code	Method IVA		Method VII	
	T 50% (Minutes)**	T 75%	T 50% (Minutes)**	T 75%
A	83	268	54	96
B	124	369	86	188
C	9	20	9	13
D	69	165	57	108
E	36	54	210[b]	352[b]
G	36	57	31	42
H	65	122	80	120
L	77	169	54	97
P	27	40	36	49
Q	86	165	174	a
W	113	207	188[b]	308[b]
X	72	165	369[c]	a
Pure Drug	6	10	5	10

* Average of two tablets
** Time for 50% and 75% of the drug to be in solution
a More than seven hours
b Tablet slowly dissolves
c Tablet coating intact for three to four hours

W which were shown to release the drug only after being crushed.

Products D and Q remained at about the same low dissolution level with all methods although their tablets did disintegrate (at the time of the test) within the official time limit of 60 minutes. Conversely, product C remained at the same high level with all methods and systems used.

In general, the Stirrer method tended to give dissolution results which probably would be more consistent with the actual inherent behavior of the individual tablets. Here the dissolution characteristics were not marked by disintegration forces which may or may not aid in the dissolution process. It is therefore suggested that for dissolution tests, the official disintegration apparatus should be discarded and some other method, such as the Stirrer method, used in its place.

(d) Disintegration - Dissolution Correlations.

No specific correlations could be found between disintegration times and dissolution rates of phenylbutazone from compressed tablets. It was observed that tablets which disintegrated slowly always showed lower dissolution rates. However, tablets which disintegrated rapidly did not necessarily show higher dissolution rates. One product consistently exhibited short disintegration times and high dissolution rates. However, in the majority of cases the availability of the drug from the tablets could not be predicted from their disintegration behavior. These observations have also been reported in the literature (43, 54,67).

2. Product Quality

(a) Tablet Assay.

(i) Two of the 23 products tested, J and P, would be rejected on the basis of average content.

(ii) One other product, B, would be rejected on the basis of individual tablet assay.

(iii) Product X would also be rejected if the suggested criteria of a 4% standard deviation was applied.

(iv) On the basis of (i), (ii) and (iii) above, four of the 23 products tested (approximately 17%) would be rejected.

(v) Two products, I and M, although complying with official requirements, had standard deviations between 3 and 4 and therefore would appear to show questionable characteristics with respect to potency variation.

(b) Tablet disintegration.

(i) By the official procedure (Method I), two products (W and E) would fail to comply with current regulations.

(ii) Allowing for a fifteen minute spread in values, six products (E, G, H, P, W and X) would show excessive in-product variability when tested by Methods I, II or IV.

(iii) Considering individual products, only two (Q and X) would show between-methods variability.

(iv) Two products (W and X) showed prolonged disintegration times by all methods.

(v) Fifty per cent of the products tested would fail to comply either with current regulations or the proposed in-product variability criteris of $\pm$ 15 minutes.

(c) Tablet Dissolution.

(i) The release of phenylbutazone from sugar-coated tablets fell into three distinct patterns when tested by Methods VI and VII.

(ii) Three products (C, G and P) demonstrated an initial rapid dissolution rate which produced a maximum of 100% dissolution within the first hour when tested by Method VII.

(iii)Three products (E, Q and W) released the drug at a more gradual rate and attained maximum levels of about 75% in five hours.

(iv) One product, C, consistently showed excellent dissolution characteristics which were comparable to that found for pure drug.

(v) Two products, E and W, may be classified as having questionable dissolution patterns.

(vi) It is difficult to judge the merrits of the majority of products on the basis of the limited information obtained by these in vitro methods. For a proper evaluation, in vivo data should be obtained for correlations with these in vitro findings.

3. In Vivo Investigations

This investigation concerned itself with the in vitro characteristics of phenylbutazone tablets. However, in vivo studies were begun in this laboratory and some of the results of these investigations are reported herein.

Burns, et al.(73) reported that peak plasma levels for phenylbutazone are reached in about two hours. In this same publication

they claimed that a large portion of administered phenylbutazone is found in the plasma. It was decided, therefore, to investigate serum concentrations after administration of the products exhibiting specific dissolution characteristics. The procedure followed is outlined below.

> "Administer 200 mg. of drug (or two 100 mg. tablets). At the same time, withdraw 15 ml. of blood, allow to stand for two hours, centrifuge at 1500 r.p.m., and remove the serum. This is the blood blank. Blood samples are then taken at approximately two, five, seven and 24 hours after drug administration."

The amount of phenylbutazone in the serum is determined by the procedure outlined below.

> "Add 0.5 ml. of 3 N HCl and 20.0 ml. of heptane to 2.0 ml. of serum. Shake for thirty minutes. Extract 15.0 ml. of the heptane solution with 5.0 ml. of 2.5 N NaOH. Record the absorbancy of this solution at 265 mu."

The drug (or drug in tablet form) was administered to three healthy males.

The first subject received 200 mg. of phenylbutazone in capsule form. A peak concentration of approximately 30 mg./ L. was observed five hours after administration. Twenty-nine hours after administration, the concentration of phenylbutazone in the serum had fallen to approximately 12 mg. / L.

This same subject received 200 mg. of phenylbutazone in tablet form (Product Q). The serum concentration was approximately 7 mg. / L. five hours after administration. Twenty-seven hours after administration, serum concentration had risen to approximately 15 mg. / L.

A second subject received the same product and the results were almost identical.

A third subject was given 200 mg. of phenylbutazone in tablet form (Product A) daily for three days. The serum level after 12 hours was approximately 16 mg. / L., after 36 hours, 30 mg. / L., and after 60 hours, 45 mg. / L.

The results obtained with phenylbutazone powder would appear to contradict literature observations. Peak levels were obtained in five rather than in two hours as reported by Burns, et al. (73) Furthermore, these authors stated that the rate of metabolic transformation ranged from 10 to 35 per cent per day. The value calculated in this preliminary experiment was of the order of 60 per cent. On the other hand, this was not confirmed for Product Q. Serum levels continued to increase (even though these were depressed below those found for pure drug) and showed no indication of decrease over the 24 hour investigational period.

It is difficult to relate these in vivo findings to the in vitro dissolution characteristics of the tablets investigated. These studies covered only two extremes - pure phenylbutazone and a tablet with very low dissolution characteristics. One observation can be made. This particular tablet (Product Q) does not produce immediate blood levels. On the basis of the results obtained with Product A (serum levels increased over a 60 hour period), it is

probable that Product Q would also exhibit similar characteristics. The implication here is that, with time, both products would produce identical serum levels. For long term therapy, therefore, this product might well be satisfactory. On the other hand, conditions such as acute gout would not respond to treatment with this particular product. It is interesting to note that the 24 hour concentration for both the pure drug and Product Q are about the same - approximately 15 mg. / L.

It would be unwise to attempt any correlation with in vitro findings at this point. However, the general trends would indicate that such correlations are feasible. The researcher would expect a peak blood level shortly after the administration of phenylbutazone powder. Such is the case. Similarly, the researcher would expect that this level would be much less after the administration of Product Q. This was also observed. Other products would be expected to fall between these two extremes. If they do, and if these levels increase in the same manner as the in vitro concentrations of the respective products in the dissolution medium, then an in vitro - in vivo correlation can be made.

V. SUMMARY AND CONCLUSIONS

1. The assay procedure in the N.F. XII for phenylbutazone was found to be unsatisfactory for individual tablet assays and for subsequent dissolution studies.

2. A spectrophotometric method was developed and found suitable for the purposes of this investigation.

3. The limits set in the N.F. XII for content uniformity do not encompass all cases of excessive variability. Consequently, the following test criterion is suggested:

> Assay ten tablets individually. The average content of these ten tablets should fall within ± 7% of the labelled potency. The standard deviation for the ten individual assays should be not more than 4% and no tablet should assay less than 85% or more than 115% of the labelled potency.

4. Four of the 23 products tested would be rejected on the basis of drug content or uniformity of content. Two other products, although complying with official requirements, would appear to show questionable characteristics.

5. The official tablet disintegration test apparatus was found to be adequate for disintegration studies.

6. The official requirements for tablet disintegration were inadequate with respect to in - product variability. It is, therefore, suggested that a range of fifteen minutes is a reasonable limit for a variability test.

7. Two products would be rejected on the basis of the present disintegration requirements. However, six products would fail to comply with the suggested variability test.

8. The official disintegration apparatus was found to be unsuitable for dissolution studies.

9. A modified version of the Levy and Hayes method (31) was used for dissolution tests.

10. The release pattern, in simulated gastric fluid, for pure phenylbutazone is as follows: 11% released in 15 minutes; 16% in 30 minutes; 22.5% in 60 minutes; 27.5% in two hours and 30% - 33% in four to six hours. One of the twelve products was observed to follow this pattern. On the other hand, three products released approximately 2% - 5% of their drug content in six hours.

11. The release pattern for pure phenylbutazone in simulated intestinal fluid is as follows: 30% release in five minutes; 60% in ten minutes; 87% in 15 minutes; 98% in 30 minutes and 100% in 60 minutes. Three products followed this pattern.

12. Five products (in simulated intestinal fluid) showed 50% dissolution in approximately 50 minutes, 75% in 96 minutes, 90% in 192 minutes and 100% in five to six hours.

13. Three products dissolved at a steady rate to reach 30% dissolution in two hours and 60% dissolution in four hours.

14. The twelve products that were tested intensively may be rated as follows:

1. One product showed excellent characteristics in all tests.
2. Four products demonstrated good characteristics in all tests.

3. Two products showed good characteristics in all but one test.
4. One product showed fair dissolution characteristics.
5. Four products would be rated as showing poor disintegration and dissolution characteristics. Two of these could also be questioned on the basis of content uniformity.

VI. BIBLIOGRAPHY

1. Abbott, A.H.A. and Allport, N.L., Quart.J.Pharm. 16,183(1943) through Morrison and Campbell (43)

2. Brodie, B.B., "Absorption and Distribution of Drugs", p.16. ed. T.B.Binns, E and S Livingstone Ltd., Edinburg and London, (1964)

3. Brodie, B.B. and Hogben, A.M., J.Pharm.Pharmacol 9,345(1957)

4. Brunning, H.L. and King, E.P., J.Pharm.Sci., 51,1187(1962)

5. Caminetski, S., Can. Med. Assoc. J., 88,950(1963)

6. Campagna, F.A., Cureton, G., Miriginan, R.A. and Nelson, E., J.Pharm.Sci., 52,605(1963)

7. Carter, A.K., Can.Med.Assoc.J., 88,98)1963)

8. Chapman, D.G. J.Pharm.Sci., 45,374(1956)

9. Chapman, D.G., Crisafio, R and Campbell, J.A., J.Pharm.Sci., 43,297(1954)

10. Delgado, J.N. and Cosgrove, F.P., Texas State J. Med., 59,1106 (1963)

11. Dunnett, C.W. and Crisafio, R., J.Pharm.Pharmacol, 7,314(1955)

12. Elliott, T. Pharm.J., 131,514(1933) through Scoville's - The Art of Compounding, p.81 (55).

13. Endicott, C.J. and Kirchmeyer, F.J., Drug Standards, 24,193(1956)

14. Evanson, R.V. and Dekay, H.G., Bull.Natl.Formulary Commun. 18, 45(1950) through Morrison and Campbell (43)

15. Evers, N., J.Pharm.Pharmacol., 21,205(1948)

16. Garrett, E.R., J.Pharm.Sci., 51,672(1962)

17. Gershberg, S. and Stoll, F.D., J.Pharm.Sci., 35,284(1946)

18. Grundman, R.A. and Ecanow, B., J.Pharm.Sci., 53,1526(1964)

19. Gwilt, J.R., Robertson, A., Goldman, L. and Blanchard, A.W., J. Pharm. Pharmacol., 15,445(1963)

20. Hamarneh, K., J.Am.Pharm.Assoc., Pract.ed., 21,90(1960) through King, R.E. (25)

21. Hance, A.M., Am.J.Pharm. 74,80(1902)

22. Husa's Pharmaceutical Dispensing, Ch. 5., Mack Publishing Co. (1959)

23. Juncher, H. and Raaschov, F., Antibiot.Med., 4,497(1957)

24. Kebler, N., J.Am.Pharm.Assoc., 3,820(1914) through Scoville's The Art of Compounding, p. 81 (55)

25. King, R.E., Remington's Pharmaceutical Sciences Ch. 39, Mack Publishing Company, Easton, Penn. (1965)

26. Leonards, J.R. and Levy, G., J.A.M.A., 193,99(1965)

27. Levy, G., J.Pharm.Sci., 50,388(1961)

28. Levy, G., J.Pharm.Sci., 52,1039(1963)

29. Levy, G., Can.Med.Assoc.J., 90,978(1964)

30. Levy, G., Hall, N.A. and Nelson, E., Am.J.Hosp.Pharm. 21,402 (1964)

31. Levy, G., and Hayes, B.A., New.Eng.J.Med. 262,1053(1960)

32. Levy, G. and Hollister, L.E., J.Pharm.Sci., 54,1121(1965)

33. Levy, G., and Jusko, W.J., J.Pharm.Sci. 54,219(1965)

34. Levy G., Leonards, J.R. and Procknal, J.A., J.Pharm.Sci. 54, 1719(1965)

35. Levy, G. and Nelson, E., J.A.M.A., 177,689(1961)

36. Libby, D.A., Schertel, M.E. and Loy, H.W., J.A.O.A.C. 48,961 (1965)

37. Maney, P.V. and Kuever, R.A., J.Pharm.Sci. 30,276(1941) through Morrison and Campbell (43)

38. Melnick, D., Hochberg, M. and Oser, B.L., J.Nutr. 30,67(1945) through Morrison and Campbell (43)

39. Merck Index (The) of Chemicals and Drugs, 7th Ed. Merck and Co., Inc., Rahway, N.J., U.S.A. (1960)

40. Middleton, E.J., Davie, S.J. and Morrison, A.B., J.Pharm.Sci. 53,1378(1964)

41. Middleton, E.J., Nagy, E. and Morrison, A.B., New Eng.J.Med. 274,136(1966)

42. "Military Standard Sampling Procedure and Tables for Inspection by Variables for Percent Deviation (MIL-STD-414)". Superintendent of Documents, U.S. Government Printing Office, Washington, 25, D.C. April 1963 - through Olson and Lee (50)

43. Morrison, A.B. and Campbell, J.A., J.Pharm.Sci. 54,1(1965)

44. Morrison, A.B., Chapman, D.G. and Campbell, J.A. J.Pharm.Sci. 48,634(1959)

45. Moskalyk, R.E., Chatten, L.G., Cox, C.E. and Pernarowski, M., J.Pharm.Sci., 50,651(1961)

46. Murphey, P., Bull.Am.Soc.Hosp.Pharm., 11,397(1954)

47. Nash, R.A. and Marcus, A.D., Drug Standards, 28,1(1960)

48. National Formulary, XII Rev. The American Pharmaceutical Association, (1965)

49. Nuppenau, H., Ardiv. for Pharmaci. og. Chemi., 71,607(1964)

50. Olson, T.N.T., and Lee, I., J.Pharm.Sci., 55,1(1966)

51. Parrott, E.L., Wurster, D.E. and Higuchi, T., J.Pharm.Sci. 44, 269(1955)

52. Pharmaceutical Manufacturers Association - "Proceedings of the Sub-Committee on Inter-tablet dosage variation". Quality Control section, March (1963)

53. P.M.A. - Minutes of the 85th Meeting of the Quality Control section - The Greenbrier, White Sulphur Springs, W.Va. - Sept. 27-29 (1965)

54. Schroeter, L.C., Tingstad, J.E., Knoechel, E.L. and Wagner, J.C., J.Pharm.Sci., 51,865(1962)

55. Scoville's - The Art of Compounding, p. 81, McGraw-Hill Book Co. Inc., New York, (1957)

56. Simoons, J.R.A., "Formulation and Experimental Evaluation of oral sustained release medication based on the principle of delayed diffusion". Drukkerij Wed. G.Van Soeste N.V. Amsterdam (1962).

57. Smith, C.D., Michaels, T.P. Chertkoff, N.J. and Sinotte, L.P. J.Pharmsci., 52,1182(1963)

58. Souder, J.C. and Ellenbogen, W.C., Drug Standards 26,77(1958)

59. Sperandio, G.J., Evanson, R.V. and DeKay, H.G., J.Am.Pharm.Assoc. Sci. Ed., 37,71(1948)

60. Steinberg, W.H., Frey, G.H., Masci, J.N. and Hutchins, H.H., J.Pharm.Sci. 54,747(1965)

61. Sunshine, I. and Gerber, S.R. "Spectrophotometric analysis of drugs including atlas of spectra". Charles C. Thomas, Publisher, Springfield, Illinois, U.S.A.

62. Train, D., J.Pharm.Sci., 49,265(1960)

63. United States Pharmacopea (U.S.P.) 17th Rev. Mack Printing Co., Easton, Pa. (1965)

64. Vliet, E.B., Drug Standards 27,97(1959)

65. Vliet, E.B., Drug Standards 28,113(1960)

66. Vliet, E.B., and Krulger, E.O., J.Pharm.Sci., 51,181(1962)

67. Wagner, J.G., J.Pharm.Sci. 50,359(1961)

68. Wiley, F., Communications to the chairman of the tablet sub-committee of the contact section of the Pharm. Manufacturers Ass., August (1957) - through simoons (56)

69. Wood, J.H., Am. Druggist, 44,105(1904), through Scoville's The Art of Compounding (55)

70. Wood, J.H., J.Pharm.Sci., 54,1207(1965)

71. Wruble, M.S., Am.J.Pharm., 102,318(1930) through Morrison and Campbell (43)

72. Yen, J.K.C., Can.Pharm.J., 97,25 - 493(1964)

73. Burns, J.J., Rose, K.R., Chenkin, T., Goldman, A., Schulert, A. and Brodie, B., J.Pharmacol and Expt.Therap., 109(346)(1953)

APPENDIX A

Content Uniformity - Tablets

Where directed in the individual monographs, select a representative sample of 30 tablets. Assay 10 of these individually using the Assay procedure as directed in the monograph. When the amount of drug in a single tablet is less than that required in the assay method, the degree of dilution of the solutions and/or the volume of aliquots may be adjusted so that the concentration of the drug in the final solution will be of the same order as that obtained in the official assay method. The requirements are met if all 10 results fall within the limits of 85 per cent to 115 per cent of the mean of the tolerances specified in the official monograph. If one, but not more than one, result falls outside these limits, assay the remaining 20 tablets individually. The requirement is met if not more than one of the 30 results is outside the limits of 85 per cent to 115 per cent.

* The National Formulary (N.F. XII), Mack Printing Company, Easton, Pa. page 449

DO-25

Official Method

December 1962.
(reprinted January 1965)

FOOD AND DRUG LABORATORIES

OTTAWA

The Determination of the Disintegration Time of Tablets

Scope: This method is applicable to all tablets intended to be swallowed whole except those which release their medicament at timed intervals or in sustaining quantities over a specified period of time.

Apparatus: (a) A device for raising and lowering the basket-rack assembly in the immersion fluid at a constant frequency rate between 28 and 32 cycles per minute through a distance of not less than 5 cm and not more than 6 cm.

(b) A basket-rack assembly consisting of six open-end glass tubes, each 7.75 ± 0.25 cm long and having an inside diameter of not less than 21.0 mm and not more than 22.5 mm and a wall approximately 2 mm thick. The tubes are held in a vertical position by two plastic plates, each about 9 cm in diameter and 6 mm in thickness, with six holes, each about 24 mm in diameter, equidistant from the centre of the plate and equally spaced from one another. Attached by screws to the under surface of the lower plate is a piece of 10-mesh No. 23 (0.025-inch) gauge woven stainless steel wire cloth, of the same diameter as the lower plate. The glass tubes and the upper plastic plate are secured in position at the top by means of a stainless steel plate, about 9 cm in diameter and 1 mm in thickness, having six perforations, each about 20 mm in diameter, which coincide with those of the upper plastic plate and the upper open ends of the glass tubes. A central shaft about 8 cm in length, the upper end of which terminates in an eye through which a string or wire may be inserted, is attached to the stainless steel plate. The parts of the apparatus

...

are assembled and rigidly held by means of three bolts passing through the two plastic plates and the steel plate.

(c) Each tube is provided with a slotted and perforated cylindrical disk 9.5 ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. The disk is made of a suitable transparent plastic material having a specific gravity of between 1.18 and 1.20. Five 2 mm holes extend between the ends of the cylinder, one of the holes being through the cylinder axis and the others parallel with it, equally spaced on a 6 mm radius from it. Equally spaced on the sides of the cylinder are four notches that form V-shaped planes so arranged that their edges are uniformly 2.55 mm from the cylinder's surface. Each notch creates a 1.60 mm square opening on the end of the cylinder to be placed downward in the tube and widens to 8.5 mm on the top of the cylinder along a chord of the top surface. All surfaces of the disk are smooth. The disks described meet the specifications outlined in the U.S.P. XVI.

(d) Each tube is provided with a plunger made by separating two plastic disks with a 1/8 inch stainless steel rod approximately 3 1/2 inches in length. The lower disk is cylindrical and smooth, 7.5 ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. Six holes, 5/32 of an inch in diameter, are bored symmetrically in one circle around the axis of the disk. The stainless steel rod is permanently embedded in the centre of the disk. The upper disk is cylindrical, smooth and approximately 7.5 mm thick. The lower half of this disk has a diameter of 20.7 ± 0.15 mm and the upper half has a diameter of approximately 24 mm. This provides for an indent to enable the seating of the plunger in the glass tube. Twelve holes, 3/32 of an inch in diameter, are bored symmetrically in two circles around the axis of the disk. A hole is bored in the centre of the disk, the stainless steel rod inserted through the centre of it and the two disks permanently positioned with respect to each other so that the lower disk is 2.8 ± 0.1 cm from the bottom edge of the glass tube when the apparatus is assembled.

...

(e) A cylindrical jar, Pyrex-type glass, having an outside diameter of 6 inches and a height of 8 to 8 1/2 inches.

(f) A knife-edge heater and thermostat or similar apparatus to maintain constant temperature.

(g) A diagram of the assembled apparatus is shown in Appendix I. The assembly design may be varied somewhat provided that the basic specifications are maintained.

(h) A diagram of a glass tube, disk and plunger is shown in Appendix II.

Reagents:

(a) Hydrochloric Acid, U.S.P. XVI.
(b) Sodium Chloride, U.S.P. XVI.
(c) Pepsin, N.F. XI.
(d) Potassium Phosphate, Monobasic U.S.P. XVI.
(e) Sodium Hydroxide, U.S.P. XVI.
(f) Pancreatin, N.F. XI.
(g) Simulated Gastric Juice. Dissolve 2.0 g of sodium chloride and 3.2 g of pepsin in 500 ml of water, add 7.0 ml of hydrochloric acid and sufficient water to make 1000 ml of simulated gastric juice. The pH is approximately 1.2.
(h) Simulated Intestinal Juice. Dissolve 6.8 g of monobasic potassium phosphate in 250 ml of water. Mix with 190 ml of 0.2 N sodium hydroxide solution and 400 ml of water. Add 10.0 g of pancreatin, mix and adjust the resulting solution with 0.2 N sodium hydroxide solution to a pH of 7.5 ± 0.1. Add sufficient water to make 1000 ml.
(i) Fresh media shall be used for every six tablets. The enzymes shall be omitted in the preparation of stock solutions of the digestive fluids to avoid decomposition. The pepsin and pancreatin can be conveniently added to an aliquot of the respective stock solutions in the proper quantity just before use.

Procedure: Uncoated and Plain Coated Tablets

Assemble the apparatus when the device for raising and lowering the basket-rack assembly is at rest and the cylinder of the device is in the down position. With 2.5 L of media in the cylindrical jar, adjust the apparatus until the level of liquid in the jar coincides approximately with the mid-line of the upper plastic plate. Maintain the temperature of the media at 37°C ± 2°C by means of a knife-edge heater and thermostat or other suitable means.

Remove the basket-rack assembly from the media and disassemble. Select at random six tablets from the sample and place one in each of the tubes of the basket-rack assembly. Place a plastic disk on each tablet in the manner specified under Apparatus (c) and then a plunger as specified under (d). (See also diagram of assembled apparatus Appendix II). Insert the assembly in 2.5 L of simulated gastric juice and set the machine in motion. The plastic disks should travel up and down freely, exerting a gentle rubbing action on each tablet.

At the end of one-half hour of operation, if any tablets or remnants remain on the screens, gently rinse the basket with water. Replace the gastric juice with 2.5 L of simulated intestinal juice and operate the apparatus until no particles remain above the screen except empty coating shells which cannot pass through. Disintegration is then considered to be complete. The tablets pass the test if the mean disintegration time of the six tablets is not more than that specified in paragraph C.01.015 and D.01.015 of the Regulations under the Food and Drugs Act.

Enteric Coated Tablets

Assemble the apparatus as described in the first paragraph under "Uncoated and Plain Coated Tablets".

Remove the basket-rack assembly from the media and disassemble. Select at random six tablets from the sample and place one in each

...

of the tubes of the basket-rack assembly. Place in a plunger in each tube as specified under Apparatus (d) and as shown in Appendix II. Insert the assembly in 2.5 L of simulated gastric juice and set the machine in motion.

At the end of 60 minutes of operation, remove the basket-rack assembly from the medium and gently rinse with water. There should be no distinct evidence of disintegration. Replace the simulated gastric juice in the jar with 2.5 L of simulated intestinal juice. Remove the plungers, place a plastic disk on each tablet in the manner specified under Apparatus (c), reinsert the plunger as specified under (d) and continue the test until no particles remain above the screen except empty coating shells which cannot pass through. Disintegration is then considered to be complete. The tablets pass the test if the mean disintegration time of the six tablets is not more than that specified in paragraph C.01.016 or D.01.016 of the Regulations under the Food and Drugs Act.

Test Criterion The test criterion listed herein apply to all tablets subject to the Regulations under the Food and Drugs Act.

The disintegration endpoint is considered to be the point at which no particles remain above the screen except empty coating shells. In certain instances, however, sticky tenacious masses may occur. Under such circumstances, disintegration is considered to be complete if these masses contain no palpably firm core. This latter endpoint definition shall apply only to those tablets which, because of the active ingredient or because of special coating requirements for the active ingredient, form these sticky masses. Examples of such substances are choline, its derivatives and salts, bile salts and botanical extracts.

The mean disintegration time of six tablets shall be not more than 60 minutes and not more than one tablet shall disintegrate in more

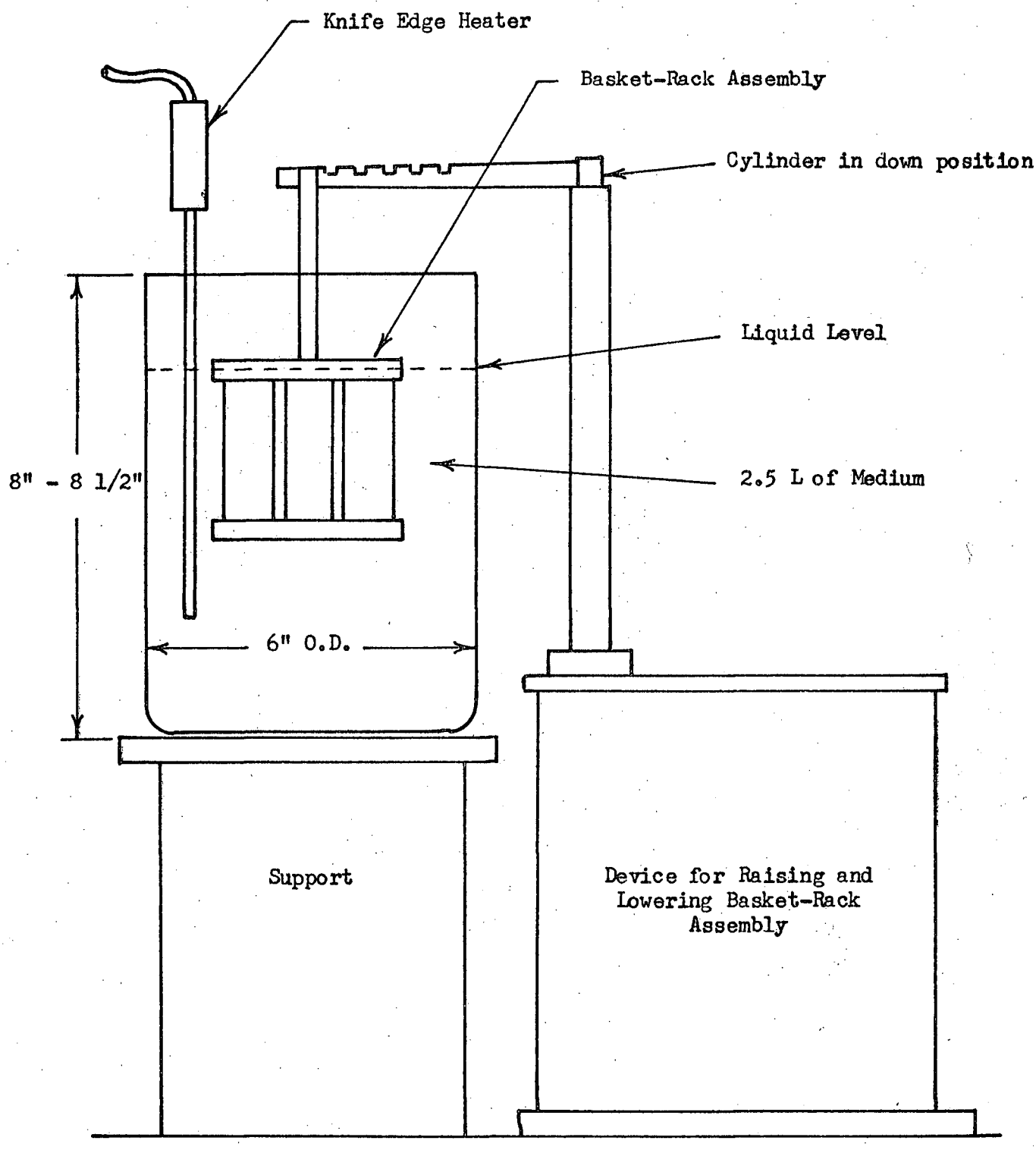
...

than 75 minutes. If one of the six tablets disintegrates in more than 75 minutes, repeat the test with an additional 12 tablets. The average disintegration time of the 18 tablets shall be not more than 60 minutes and not more than one tablet shall disintegrate in more than 75 minutes.

In the case of enteric coated vitamin preparations, the mean disintegration time of six tablets shall be not more than 30 minutes and not more than one tablet shall disintegrate in more than 40 minutes. If one of the six tablets disintegrates in more than 40 minutes, repeat the test with an additional 12 tablets. The average disintegration time of the 18 tablets shall be not more than 30 minutes and not more than one tablet shall disintegrate in more than 40 minutes.

APPENDIX I

Diagram of Assembled Apparatus



APPENDIX II

Diagram of Glass Tube, Plastic Disk and Plunger