k_1, the rate constant for transfer from the central to the tissue compartment; k_2, the rate constant for elimination by metabolism or excretion from the body; and V_2, the volume of the tissue compartment. From the standard deviations of the parameters, it can be seen that the data fit this model rather well. Discussions of the meaning of two-compartment distribution may be found in *References 4–6*. The central compartment is generally thought to consist of blood and highly perfused tissues such as heart, lung, liver, and kidney. The more poorly perfused tissue compartment includes muscle and skin. Because of the oily nature of ethchlorvynol, one would expect that it would be preferentially distributed into fat. Riegelman *et al.* (4) pointed out that, because of direct diffusion from tissues to fat, the effect of distribution of a drug into a fat compartment simply modifies the effective volume of the compartment from which the drug diffused. Thus the identity of the tissue compartment with any anatomical structure cannot be made.

The results point out very clearly that the slow decline of serum levels in the β-phase is not due to a low rate of metabolism but rather to extensive tissue localization of ethchlorvynol since k_2 is at least four times as large as β at each dose.

These data also demonstrate that ethchlorvynol is rapidly absorbed; from the k values, a half-life for absorption of approximately 0.3 hr. is calculated. Likewise the rate of metabolism is rather fast; a half-life of 5.6 hr. is seen. From serum levels in the β-phase, one may calculate f_c, the ratio of the amount of ethchlorvynol in the central compartment to the total amount in the body, and f_T, the similar value for the amount in the tissue compartment, from the following relations:

$$f_c = \frac{k_{-1} - \beta}{k_1 + k_2 - \beta} = 0.22 \qquad \text{(Eq. 2)}$$

$$f_T = 1.0 - f_c = 0.78 \qquad \text{(Eq. 3)}$$

$$f_T/f_c = 0.78/0.22 = 3.5 \qquad \text{(Eq. 4)}$$

This ratio is substantially higher than those for aspirin, griseofulvin, and spectinomycin which were reported by Gibaldi *et al.* (6) to be 1.1, 0.9, and 0.65, respectively.

CONCLUSIONS

Ethchlorvynol is extensively metabolized since only 0.025% of the dose is excreted unchanged or as the glucuronide.

Absorption of ethchlorvynol is very rapid, with an absorptive half-life of 0.3 hr.

The decline of serum levels is biphasic, which suggests a two-compartment model for distribution. The hybrid rate constants are 0.5 and 0.03 $hr.^{-1}$. From these the rate constant for elimination is calculated to be 0.13 $hr.^{-1}$. There is also evidence for extensive tissue localization of ethchlorvynol.

REFERENCES

(1) J. E. Wallace, W. J. Wilson, and E. V. Dahl, *J. Forensic Sci.*, **9**, 342(1964).

(2) D. W. Robinson, *J. Pharm. Sci.*, **57**, 185(1968).

(3) J. G. Wagner, "Pharmacokinetics," J. M. Richards Laboratory, Grosse Pointe Park, Mich., 1969, p. 135.

(4) S. Riegelman, J. C. K. Loo, and M. Rowland, *J. Pharm. Sci.*, **57**, 117(1968).

(5) P. A. Harris and S. Riegelman, *ibid.*, **58**, 93(1969).

(6) M. Gibaldi, R. Nagashima, and G. Levy, *ibid.*, **58**, 193(1969).

ACKNOWLEDGMENTS AND ADDRESSES

Received February 20, 1970, from the *Chemical Pharmacology Department, Scientific Divisions, Abbott Laboratories, North Chicago, IL 60065*

Accepted for publication August 26, 1970.

The technical assistance of Mary Jo Fourier is greatly appreciated.

Effect of Aging on Some Physical Properties of Hydrochlorothiazide Tablets

A. S. ALAM and E. L. PARROTT

Abstract □ Hydrochlorothiazide tablets were prepared using acacia, starch, and polyvinylpyrrolidone as granulating agents. The tablets were evaluated at room temperature and at elevated temperatures relative to changes in hardness, disintegration, and dissolution. Acacia is an unsatisfactory granulating agent because the values of the hardness, disintegration, and dissolution times are increased with aging; starch and polyvinylpyrrolidone are acceptable granulating agents because the physical properties of the tablets are essentially unchanged with aging. The changes in the physical properties of the tablets after short-term storage at elevated temperatures correlated with the changes upon aging for 1 year at room temperature. Thus, for the formulations used in this study, changes occurring after short-term storage at 37, 50, and 80° could be used to predict changes in physical properties during the normal shelf-life of the tablets at room temperature.

Keyphrases □ Hydrochlorothiazide tablets—age effect □ Aging, hydrochlorothiazide tablets—accelerated, physical stability □ Tablets, hardness, disintegration, dissolution—aging effect □ Granulating agents effect—physical stability, tablets

The compressed tablet is the most popular dosage form; for many pharmaceutical manufacturers, it comprises the majority of their products. As a part of research and development operations, the chemical stability of the medicinal compound in a tablet is routinely studied. Nevertheless, the manner in which medicinal compounds degrade in solid dosage forms is obscure, and the number of publications reporting degradation in solid dosage forms is not numerous (1–6).

In addition to demonstrating that the chemical nature of the medicinal compound will not change during the recommended life of the product, the manufacturer must consider possible changes in the physical properties of a tablet. A physically stable tablet should retain its original color, disintegration time, friability, hardness, shape, size, weight, and dissolution profile (7, 8).

If the dissolution of the medicinal compound from a tablet is slowed upon aging or storage of the tablet, the biological availability may be seriously affected because the medicinal compound would be less available for gastrointestinal absorption. It cannot be assumed that a rapid release of the medicinal compound from the tablet immediately after its production will be

Table I—Formulas in Milligrams per Tablet

Ingredients	I	II	III	IV
Hydrochlorothiazide	50.0	50.0	50.0	50.0
Lactose	295.0	282.5	282.5	282.5
Acacia	3.7	—	—	—
Starch	—	1.25	—	—
PVP K 29-32	—	—	7.0	17.5
Magnesium stearate	1.0	1.05	0.9	1.05

maintained upon aging (9). Since it is not economical to test clinically every product at various intervals of time during its storage, a dissolution profile is the best *in vitro* test to detect changes that might affect the release or dissolution of the medicinal compound from the tablet. In general, an unchanged dissolution profile with aging indicates no change of *in vivo* availability.

The purposes of this study were to compare the physical properties of hydrochlorothiazide tablets formulated with three granulating agents and to compare the effect of aging on the physical properties of these formulations. The effect of storage at elevated temperatures on physical properties of tablets was compared to aging at room temperature in order to explore the possibility that valid predictions of changes in physical properties could be made based on a short-term evaluation at elevated temperatures.

EXPERIMENTAL

Materials—Acacia, hydrochlorothiazide, hydrous lactose, and magnesium stearate were USP grade. Boric acid, potassium chloride, and potassium hydroxide were reagent grade. Polyvinylpyrrolidone (PVP)[1] had an average molecular weight of 40,000.

Preparation of Tablets—All tablets were prepared by a wet granulation method. The granulating liquids were 10% acacia, 5% starch paste, and 12.5 and 38.9% PVP in 95% ethanol. The formulas are given in Table I. The tablets were compressed on a Stokes model E single-punch tablet machine using a 1.03-cm. ($^{13}/_{32}$-in.) standard concave punch and die set. The tablet machine was adjusted to prepare satisfactorily appearing tablets, and no attempt was made to maintain a constant pressure during compression of the formulations.

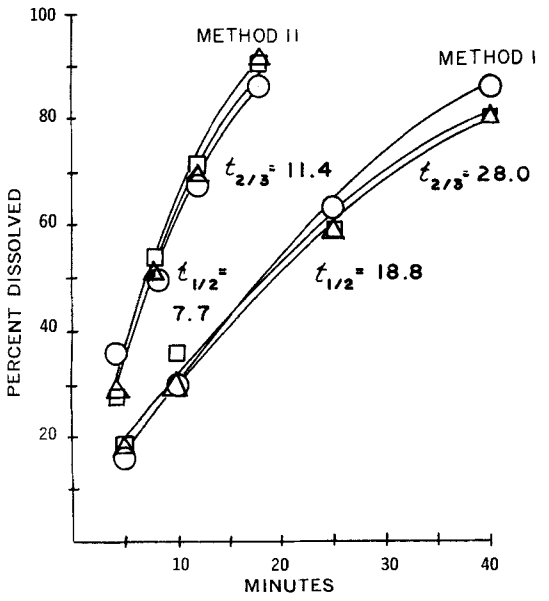

Figure 1—*Dissolution profiles of hydrochlorothiazide at room temperature as determined by dissolution Methods I and II. The symbols are for individual tablets and indicate the variation within a single batch of tablets.*

[1] Plasdone K 29-32, registered trademark of GAF Corporation, New York, N. Y.

Table II—Hardness, Disintegration, and Dissolution Profiles of Tablets of Hydrochlorothiazide Granulated with Acacia, Starch Paste, and PVP after Storage at 80°

Days	Hardness, kg.	Disintegration Time, min.	Dissolution Time, min. —Method I— $t_{1/2}$	—Method I— $t_{2/3}$	—Method II— $t_{1/2}$	—Method II— $t_{2/3}$
			Acacia			
0	5.3	10.8	15.0	20.1	7.0	9.7
1	5.8	20.1	18.3	19.8	10.8	15.9
2	6.8	17.8	11.7	22.1	11.3	15.6
3	6.9	21.9	16.0	22.9	10.7	15.1
4	8.3	18.4	19.8	26.6	10.5	14.4
5	6.8	16.7	22.5	30.8	10.0	13.8
6	6.7	17.0	20.4	28.1	10.0	14.1
7	7.0	16.3	18.8	26.0	10.0	14.1
14	7.8	15.5	21.0	28.3	8.3	12.0
			Starch			
0	5.5	3.5	9.7	11.3	5.3	7.3
1	5.4	3.8	10.3	13.6	4.3	6.3
2	5.3	3.8	11.6	16.0	5.0	6.7
3	5.3	3.2	10.3	12.3	5.7	7.3
4	5.3	4.0	12.3	16.6	5.3	7.3
5	5.5	4.0	9.7	14.2	4.6	6.7
6	5.0	4.4	8.2	10.2	4.9	6.6
7	5.4	3.3	7.0	8.0	6.0	7.7
			2% PVP K 29-32			
0	9.0	14.0	16.9	23.8	7.3	12.1
1	8.0	15.0	16.3	24.5	7.3	11.7
2	8.5	14.4	18.3	23.7	7.8	12.5
3	8.8	12.6	13.4	18.3	7.7	11.0
4	8.0	15.5	16.3	24.0	9.0	15.3
5	9.6	16.3	15.3	24.0	7.7	12.0
6	8.2	13.5	15.3	22.3	8.7	13.3
7	9.2	16.6	15.5	22.0	8.3	12.7
			5% PVP K 29-32			
0	7.2	17.0	19.5	28.8	8.5	13.3
1	7.1	17.3	17.8	22.0	11.7	12.0
3	7.5	17.0	15.5	22.3	9.0	12.5
4	7.0	16.0	14.7	21.7	8.7	12.0
7	7.2	17.3	18.3	25.8	8.7	13.3
14	8.0	19.0	18.8	29.3	7.7	13.7

Hardness—Hardness of the tablets was determined using a Pfizer hardness tester. Each hardness value reported is an average of six tablets.

Disintegration Time—The USP XVIII apparatus and procedure with disks were used to determine the disintegration time of the tablets in distilled water at 37°. The disintegration time reported is the time when all of the six tablets disintegrated and any particles had passed through the 10-mesh lower plate (10).

Dissolution Time—Method I employed in the study was the USP XVIII dissolution apparatus and method (11). The rate of rotation of the basket was 60 r.p.m. The dissolution fluid was a borate buffer at pH 10. The buffer solution was prepared by mixing 250 ml. of a 0.2 *M* boric acid and potassium chloride solution with 220 ml. of a 0.2 *M* sodium hydroxide solution and then adjusting to pH 10 by the addition of 28.0 ml. of the sodium hydroxide solution. The Hydrochlorothiazide Tablet Monograph, which became official after the completion of this study, specifies 150 r.p.m. in dilute hydrochloric acid (1 in 100).

Method II for determining the dissolution was Method II of NF XIII (12).

In determining the dissolution profile of hydrochlorothiazide from the tablet, a 1.0-ml. sample was withdrawn by a filtering pipet at various intervals of time and diluted to 10 ml. with borate buffer. The absorbance was determined by a Beckman DU spectrophotometer at 273 nm. against a blank of borate buffer (13).

Table III—Hardness, Disintegration, and Dissolution Profiles of Tablets of Hydrochlorothiazide Granulated with Acacia, Starch Paste, and PVP after Storage at 50°

Days	Hardness, kg.	Disintegration Time, min.	Dissolution Time, min. — Method I — $t_{1/2}$	Method I — $t_{2/3}$	Method II — $t_{1/2}$	Method II — $t_{2/3}$
			Acacia			
0	5.3	10.8	16.2	22.7	6.8	9.6
1	5.4	15.0	18.4	25.7	7.7	11.6
3	6.6	15.0	20.7	28.0	9.3	14.4
5	6.4	17.5	20.7	24.8	9.3	13.9
7	6.4	17.0	19.0	27.0	9.2	12.3
14	7.2	17.0	14.2	24.5	8.8	11.9
			Starch			
0	5.0	4.1	11.8	—	7.6	9.7
1	5.5	4.6	11.2	—	6.5	8.3
3	4.7	4.1	11.5	—	6.7	8.5
5	5.4	4.1	12.1	—	7.3	9.4
7	4.8	4.4	—	—	6.7	8.2
14	4.7	4.1	9.2	—	5.8	8.7
			PVP K 29-32			
0	7.7	14.2	18.6	26.0	5.4	10.0
1	6.9	14.3	18.0	25.3	7.0	10.8
3	8.7	14.3	15.9	25.0	8.0	12.1
5	8.1	14.1	15.6	25.1	6.7	10.6
7	6.6	13.3	16.4	25.4	6.3	10.3
14	7.3	12.7	15.5	24.8	7.5	11.6

By means of a standard absorption–concentration curve, the amount of hydrochlorothiazide in solution was calculated. Because a total of only 5.0 ml. was withdrawn during the dissolution, no correction was made for a change of volume and no additional dissolution fluid was added to replace the volume of the samples withdrawn.

RESULTS AND DISCUSSION

In determining the dissolution profile, it was realized that some weight variation of tablets was inherent in the tableting operation; therefore, the entire tablet was allowed to dissolve, and the solution was assayed for the total hydrochlorothiazide in each tablet. This procedure permitted the dissolution profile to be plotted in terms of the percent of the total assayed hydrochlorothiazide in each tablet. From the dissolution profile of each tablet, the time required for 50% of the hydrochlorothiazide to dissolve was read and designated as $t_{1/2}$. In a similar manner, the time required for 66.7% of the hydrochlorothiazide to dissolve from the tablet was read and designated at $t_{2/3}$. The value reported for the dissolution time represents the average dissolution time of three tablets. Dissolution profiles, which were obtained by both dissolution methods, are shown in Fig. 1. These are typical of the variation in dissolution of tablets from a single batch of tablets.

The initial values of the physical properties of the four formulations are given in Table II.

The tablets granulated with acacia and starch had the same hardness. The tablets granulated with 5% PVP were not as hard as those granulated with 2% PVP. With a smaller concentration of PVP, it seemed necessary to increase the hardness to form a satisfactory tablet. With a higher concentration of PVP, the polymer provided binding characteristics without as great a pressure during compression. There is no correlation between hardness and dissolution; thus, hardness is of the least significance in evaluating the release of a medicinal compound from a tablet.

The tablet prepared with starch had the fastest disintegration and dissolution. In these formulations, the disintegration and dissolution as determined by both methods followed rank correlation; that is, for both disintegration and dissolution times, the values according to the granulating agent in the formulation were: starch < acacia < 2% PVP < 5% PVP.

Table IV—Hardness, Disintegration, and Dissolution Profiles of Tablets of Hydrochlorothiazide Granulated with Acacia, Starch Paste, and PVP after Storage at 37°

Weeks	Hardness, kg.	Disintegration Time, min.	Dissolution Time, min. — Method I — $t_{1/2}$	Method I — $t_{2/3}$	Method II — $t_{1/2}$	Method II — $t_{2/3}$
			Acacia			
0	5.3	10.8	16.0	21.8	6.9	9.5
1	5.0	13.2	17.6	20.6	8.4	12.0
2	4.3	13.7	13.3	23.3	6.9	9.3
3	7.1	13.0	18.8	26.0	8.6	9.8
4	6.5	14.2	18.3	25.3	7.9	11.4
			Starch			
0	5.0	3.7	10.4	13.3	7.4	10.0
1	4.8	3.9	13.5	14.7	6.1	8.0
2	5.1	3.9	11.7	14.9	6.5	8.8
3	5.2	4.0	15.1	—	6.2	8.4
4	5.0	4.3	13.3	18.1	7.1	9.5
			PVP K 29-32			
0	7.7	13.6	18.7	24.9	6.1	9.8
1	5.9	12.9	16.0	23.7	5.9	11.7
2	7.0	11.9	17.7	25.5	8.3	11.9
3	7.6	14.0	17.9	26.1	8.4	12.5
4	7.4	13.5	15.9	23.1	8.4	12.0

Table V—Hardness, Disintegration, and Dissolution Profiles of Tablets of Hydrochlorothiazide Granulated with Acacia, Starch Paste, and PVP after Storage at Room Temperature

Months	Hardness, kg.	Disintegration Time, min.	Dissolution Time, min. — Method I — $t_{1/2}$	Method I — $t_{2/3}$	Method II — $t_{1/2}$	Method II — $t_{2/3}$
			Acacia			
0	5.3	10.8	14.8	20.2	6.9	9.7
1	5.5	12.7	14.6	24.1	7.3	11.0
2	5.5	12.7	20.3	28.6	7.3	10.3
3	5.9	12.7	19.3	27.1	7.6	10.8
4	5.4	15.0	17.4	24.7	6.9	9.6
5	6.9	16.5	17.5	24.4	8.0	10.9
6	5.8	14.2	22.4	32.9	8.1	12.3
7	5.2	14.7	22.0	31.3	8.5	12.1
8	6.3	14.5	16.8	23.6	7.7	10.8
9	5.4	11.8	16.1	22.4	7.6	11.1
10	8.6	15.0	17.1	24.5	9.0	12.4
11	7.2	14.4	18.9	26.9	6.6	9.1
12	9.1	18.0	19.6	27.8	7.5	10.4
			Starch			
0	6.0	3.7	10.4	—	7.1	—
1	7.0	3.2	6.1	8.8	6.1	7.6
2	8.0	5.0	6.0	8.6	2.4	7.6
3	6.4	4.0	9.8	13.7	2.5	5.2
4	6.5	4.0	8.2	12.2	3.2	4.9
5	8.1	3.6	7.4	10.9	3.5	4.8
6	7.9	3.6	8.5	12.1	3.0	4.5
7	7.8	2.8	7.3	10.4	4.1	6.3
8	8.5	3.4	8.9	12.7	3.8	5.4
9	8.5	3.7	8.4	12.3	4.0	6.1
10	6.8	4.3	5.0	7.7	3.7	5.6
11	9.8	3.5	8.8	13.0	3.9	5.8
12	8.9	3.3	6.6	10.2	3.6	5.3
			PVP K 29-32			
0	8.0	13.6	24.9	24.9	6.1	9.8
1	7.5	13.8	18.3	18.3	5.6	8.3
2	8.2	12.8	19.9	20.9	6.4	8.4
3	8.1	13.3	12.2	18.6	6.5	9.1
4	8.1	13.3	20.1	27.7	10.0	13.2
5	8.0	13.0	17.7	26.9	8.2	12.5
6	7.8	13.6	16.1	25.5	7.5	11.2
7	7.4	13.5	16.0	23.4	8.4	12.7
8	8.1	13.7	19.4	28.9	8.2	12.3
9	7.6	13.8	23.7	35.1	9.2	13.5
10	7.1	13.3	14.5	21.7	7.7	11.4
11	9.4	14.4	16.2	23.4	8.6	12.4
12	8.3	15.2	18.8	28.0	7.7	11.4

Although the values of the dissolution times are different as determined by Methods I and II, the relationship of $t_{1/2}$ and $t_{2/3}$ as determined by the two methods is almost constant. In this study the $t_{1/2}$ and $t_{2/3}$ as determined by Method II were approximately half the values obtained by Method I.

When formulating a new tablet, a quick estimate of the physical stability may be obtained by using the concept of chemical kinetics relating to rate and temperature. To obtain stability information in as short a time as possible, it is customary to evaluate samples stored at elevated temperatures for short periods. When using data obtained at elevated temperatures for short times to predict chemical and physical stability in solid dosage forms, one must realize that the mechanisms causing change can be different at higher temperatures than those functioning at room temperature (7). Yet such studies often are indicative of physical stability (14, 15).

Tablets were stored at 80° and their physical properties were measured at various intervals as shown in Table II. Under these conditions, the hardness of tablets granulated with starch and PVP was unchanged. There was no appreciable change in disintegration time of tablets granulated with starch and PVP.

Tablets containing 2 and 5% PVP were stored at 80° to show the influence of concentration of granulating agent on the physical properties of the tablet. The tablet containing 5% PVP had a slightly longer disintegration and dissolution time; however, the dissolution times were unchanged after storage for 14 days at 80°.

The effect of aging at 50 and 37° on the physical properties of hydrochlorothiazide tablets granulated with acacia, starch, and PVP is shown in Tables III and IV, respectively.

The dissolution time determined by Method I for tablets granulated with PVP and stored at 37 and 50° for 4 weeks and 14 days, respectively, appears to decrease slightly; however, the dissolution time as determined by Method II indicates a slight increase in dissolution time. Such data were interpreted as reflecting no change in dissolution time and were probably caused by a variation of a tablet used in the samples.

For tablets granulated with starch paste, the dissolution time after storage at 37 and 50° was unchanged as determined by Methods I and II, respectively. After storage at 37°, Method I indicated an increase in dissolution time; after storage at 50°, Method II indicated a decrease in dissolution time. These results were interpreted as no change in dissolution.

For tablets granulated with acacia, storage at 37 and 50° for 4 weeks and 7 days, respectively, resulted in an increase in dissolution time.

The physical properties of three tablet formulations were determined after storage at elevated temperatures, with the assumption that any changes in properties would occur more rapidly, but in the same manner, than changes would occur at room temperature. To test the validity of this assumption, tablets granulated with acacia, starch, and PVP were stored at room temperature for 1 year during which the physical properties were measured each month. The results are given in Table V.

For tablets granulated with acacia, the hardness, disintegration, and dissolution times were increased during 1 year of aging at room temperature. A similar increase in hardness, disintegration, and dissolution times was observed in tablets stored for 14 days at 50 and 80° and for 4 weeks at 37°.

For tablets granulated with starch, there was an increase in hardness during 1 year of storage at room temperature; no change in hardness was observed in tablets stored at elevated temperatures. For tablets granulated with starch, there was essentially no change in disintegration or dissolution during 1 year of storage at room temperature. Similarly, there was no change in disintegration or dissolution times for tablets stored for 14 days at 50 and 80° and for 4 weeks at 37°.

For tablets granulated with PVP, the hardness and disintegration were essentially unchanged after storage for 1 year at room temperature, for 14 days at 50 and 80°, and for 4 weeks at 37°. The dissolution was unchanged by storage at elevated temperatures, but at room temperature the dissolution time slightly increased after 1 year.

SUMMARY

In this report, changes in physical properties at elevated temperatures were qualitatively related to those at room temperature after 1 year of aging. Thus, one is able to predict from the changes in physical properties after a short time at 37, 50, and 80° that hydrochlorothiazide tablets granulated with acacia would have an increase in hardness, disintegration, and dissolution time as they aged at room temperature. The physical properties of hydrochlorothiazide tablets granulated with starch or PVP were essentially unchanged after short times at elevated temperatures. Based on these accelerated studies, it would be anticipated that starch or PVP would be a more suitable granulating agent for physically stable tablets than acacia. This projection is supported by the stability for tablets aged for 1 year at room temperature.

REFERENCES

(1) E. R. Garrett, in "Advances in Pharmaceutical Sciences," vol. 2, H. S. Bean, A. H. Beckett, and J. E. Carless, Eds., Academic, New York, N. Y., 1967, p. 77.

(2) J. T. Carstensen, M. Osadca, and S. H. Rubin, *J. Pharm. Sci.*, **58,** 549(1969).

(3) R. Tardif, *ibid.*, **54,** 281(1965).

(4) J. T. Carstensen, *ibid.*, **53,** 839(1964).

(5) J. T. Carstensen, E. Serenson Aron, D. Spera, and J. Vance, *ibid.*, **55,** 561(1966).

(6) J. T. Carstensen, J. Johnson, D. Spera, and M. Frank, *ibid.*, **57,** 23(1968).

(7) J. E. Tingstad, *ibid.*, **53,** 955(1964).

(8) L. Lachman, *ibid.*, **54,** 1519(1965).

(9) G. Levy, J. M. Antkowiak, J. A. Procknal, and D. C. White, *ibid.*, **52,** 1047(1963).

(10) "The United States Pharmacopeia," 18th rev., Mack Publishing Co., Easton, Pa., 1970, p. 932.

(11) *Ibid.*, p. 934.

(12) "The National Formulary," 13th ed., Mack Publishing Co., Easton, Pa., 1970, p. 803.

(13) C. R. Rehm and J. B. Smith, *J. Amer. Pharm. Ass., Sci. Ed.*, **49,** 386(1960).

(14) D. E. Cadwallader and Qamar-Ul-Islam, *J. Pharm. Sci.*, **58,** 238(1969).

(15) L. A. Bergman and F. J. Bandelin, *ibid.*, **54,** 445(1965).

ACKNOWLEDGMENTS AND ADDRESSES

Received August 11, 1970, from the *College of Pharmacy, University of Iowa, Iowa City, IA 52240*

Accepted for publication September 17, 1970.

Abstracted in part from a dissertation submitted by A. S. Alam to the Graduate College, University of Iowa, in partial fulfillment of Doctor of Philosophy degree requirements.

This project was supported in part by grants from GAF Corporation, New York, N. Y.