Keyphrases

Emulsion stabilization—polymers
Hexadecane-water emulsion—high mol. wt. polymers, stabilization
Particle-size distribution—emulsions
Polymers, effect—emulsion particle size
Stability, emulsions—aging, polymer effect

Evaluation of Physical and Pharmaceutical Factors Involved in Drug Release and Availability from Chloramphenicol Capsules

By A. J. AGUIAR, L. M. WHEELER, S. FUSARI, and J. E. ZELMER

The importance of physical and pharmaceutical factors involved in chloramphenicol release and availability from four commercial lots of chloramphenicol was evaluated. The study was carried out in three parts: (*a*) deaggregation or dispersion determinations, (*b*) dissolution studies, and (*c*) *in vitro* gut permeation using an everted sac technique. A correlation between drug release as reflected by the deaggregation and dissolution rates and chloramphenicol plasma levels in humans is demonstrated. In this specific instance the results of the study demonstrate that, although the products tested contain analytically the same quantity of chloramphenicol, the rate of release of the antibiotic, and hence its availability from the capsules differs significantly. The commonly accepted scheme which defines drug absorption from dosage forms is modified to include the deaggregation rate.

THE IMPORTANCE of physical properties of drugs in relation to their pharmacological availability and activity has been demonstrated and emphasized repeatedly in the past. Until recently, proportionally little attention was paid to studies related to drug release from pharmaceutical dosage forms. For example, there has been a vast amount of research done to evaluate dissolution rates of drugs from tablets where the geometry of the dissolving surface is kept constant during the dissolution process. However, most tablets and capsules of drugs used in clinical therapy are intended to disintegrate in the gastrointestinal environment after oral administration.

If the tablets or capsules disintegrate, the surface area and the geometry of the dissolving surface will change continuously with time. The dissolution rate which is dependent on the surface area will also change. Therefore, studies in which the dispersion (or deaggregation) as well as the dissolution rates are measured are of greater value in assessing the optimum formula for a capsule or tablet of a drug than simple dissolution measurements. The studies would also allow a closer correlation of drug availability from the dosage forms with plasma levels or other pharmacological criteria of drug efficacy.

The present work is an evaluation of the availability of chloramphenicol from four commercial lots of chloramphenicol capsules. Specifically the study is an attempt to relate pharmaceutical and physical factors with the differences in plasma levels observed when the four capsules were tested in adult human volunteers. The human absorption studies are reported elsewhere (1, 2).

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The authors thank Dr. A. W. Kinkel and Dr. E. Holmes for the human absorption data shown in Fig. 5; Miss B. Shawler for assistance in the dissolution measurements; and Dr. J. F. Sadusk and Dr. L. M. Lueck for their constructive suggestions during the course of this work.

EXPERIMENTAL

The capsules tested were four commercial lots of chloramphenicol capsules produced by different manufacturers and were purchased from a local

pharmacy. For purposes of these studies, they were labeled as A,[1] B, C, and D.

The study was carried out in three parts: (*a*) deaggregation or dispersion determinations, (*b*) dissolution studies, and (*c*) *in vitro* gut permeation using an everted sac technique.

The method employed to measure the deaggregation rates was essentially the one reported earlier (3). In the present study the simulated gastric fluid T.S. (USP XVI) was presaturated with chloramphenicol to minimize the dissolution of the drug particles as they appeared in the medium.

Five hundred milliliters of simulated gastric fluid T.S. presaturated with chloramphenicol was added to an 800-ml. beaker placed in a constant-temperature bath set at 30 ± 0.5°. The solution was stirred at 100 r.p.m. and allowed to come to temperature. The design of the all-glass stirrer used was such that it provided random agitation throughout the depth of the liquid without creating a vortex.

Two capsules from each lot were added to the gastric fluid for each determination. A stopwatch was started as soon as the gelatin shell of the capsule dissolved and first traces of the drug appeared, generally in about 2 min.

The percent transmittance (from which the absorbance was calculated) was measured at 650 mμ using a Coleman Junior spectrophotometer. A pump circulated the fluid *via* a 3-mm. diameter Tygon tubing from the beaker through a flow-through cell located in the spectrophotometer. The force necessary to deaggregate the drug was provided by the shearing action of the stirred liquid.

The dissolution rates of the capsules were measured by two different methods. In the first, a USP tablet disintegration apparatus of the Vanderkamp[2] design was employed, and the dissolution was carried out in simulated gastric fluid T.S. (USP XVI). One capsule was placed in each of the six tubes of the basket-rack assembly, omitting the plastic disks. The assembly was immersed in 800 ml. of simulated gastric fluid T.S. contained in a 1,000-ml. beaker, and held at 37° ± 0.5°. The assembly was put in operation at a constant frequency rate of 30 c.p.m. and 5-ml. aliquots of the solution were withdrawn after 10, 20, and 30 min. Each aliquot was centrifuged at 2,000 r.p.m. for 2 min., and the supernatant diluted and assayed spectrophotometrically for chloramphenicol at 278 mμ.

The other method used for measuring the dissolution rates was as follows. One capsule was dropped into 400 ml. of simulated gastric fluid T.S. (without pepsin) held in a beaker maintained at 30 ± 0.5°. The solution was stirred at 11 r.p.m. using an electronic-controlled laboratory stirrer[3] designed with three parallel prongs facing down. Five-milliliter samples were removed at 2-min. intervals initially and 5-min. intervals after the first hour. The samples were filtered through a 0.45-μ Millipore filter disk using a Swinney syringe adapter and assayed spectrophotometricly at 278 mμ after appropriate dilution with the gastric fluid.

The *in vitro* gut permeation of chloramphenicol was studied using a modified Crane and Wilson everted sac technique (4).

The excised small intestine from Holtzman rats weighing 120–150 g. was everted so that the mucosa faced outward. A 10-cm. segment taken 1 cm. from the stomach was tied tightly at the lower end, 1 cm. from the tip, and trimmed. The upper portion was attached 1 cm. from the top to a blunt cannula supported by a rubber stopper, leaving 8 cm. of the everted sac free and available for absorption. The segment supported by the cannula and rubber stopper was suspended in an 80-ml. glass tube containing 70 ml. of buffer–chloramphenicol mixture maintained at 37 ± 0.5° in a constant-temperature bath. One and six-tenths milliliters (1.6) of buffer without drug at 37° was introduced into the sac through the cannula.

A mixture of 95% oxygen and 5% carbon dioxide was bubbled through the solution through a longer cannula extending from the rubber stopper to the bottom of the glass tube.

At predetermined time intervals the solution inside the sac was removed, the sac was rinsed with a further 1.6 ml. of buffer which was also removed, and the combined solutions were assayed for chloramphenicol. The rinse solution was replaced with 1.6 ml. of fresh buffer.

The buffer solution used was Krebs-Ringer bicarbonate solution (5) (pH 7.2) with 0.3% glucose. The solutions were prepared in distilled water, 0.3% glucose was added, and the final solution was gassed for 10 min. with 95% oxygen–5% carbon dioxode. The gut segment was considered to be viable for 2 hr.

In order to measure the chloramphenicol bound by the gut tissue, the everted sac was removed from the apparatus at the end of the run, washed on the inner and outer surfaces with distilled water, and dried at 65°. The dried material remaining was extracted with ethanol and assayed.

The solutions were assayed spectrophotometrically for chloramphenicol at 278 mμ.

RESULTS AND DISCUSSION

The purchased capsules were subjected to various analytical tests, and the results are summarized in Table I.

Deaggregation Studies—The deaggregation profiles of the four commercial lots of chloramphenicol capsules tested are shown in Fig. 1. This plot of percent transmittance *versus* time provides a convenient comparison of the rates. It is readily apparent from the plot that Capsule A has the fastest deaggregation rate, and reaches the steady state in approximately 10 min. On the other hand, Capsule D has a very poor deaggregation rate. In fact, after 3 hr., Product D maintains its capsular appearance (Fig. 2). The initial increase in turbidity with Capsule D can perhaps be partly ascribed to the presence of additives in the capsule.

Capsules B and C have faster deaggregation rates than Capsule D, but the rates were slower than that of Capsule A.

The theoretical concepts developed earlier (3) to quantify the deaggregation rates were based on the premises that the deaggregation rate followed a first-order process and that the species present in the media were either the large aggregates and/or small aggregates. This implied that the large aggregates were broken down into small aggregates without

[1] Product A Chloromycetin Kapseals, Lot P 13542A, Parke, Davis & Co.
[2] Van-Kel Industries, Livingston, N. J.
[3] Gerald K. Heller Co., Las Vegas, Nev.

TABLE I—ANALYSIS AND COMPARISON OF FOUR COMMERCIAL LOTS OF CHLORAMPHENICOL CAPSULES

Analytical Test	Capsule A	Capsule B	Capsule C	Capsule D
Uniformity of capsule fill				
Average capsule fill, mg.	351.3	462.8	343.4	355.1
Range of capsule fill, mg.	339.6–369.8	379.9–504.8	333.0–352.1	318.6–371.7
Assay Uniformity				
Average assay, mg. chloramphenicol/capsule	248.3	261.9	249.1	244.6
Average percent of label claim	99.3	104.8	99.7	97.8
Range of assays in percent of label claim	96.2–104.8	86.6–114.4	96.6–101.6	88.1–102.0

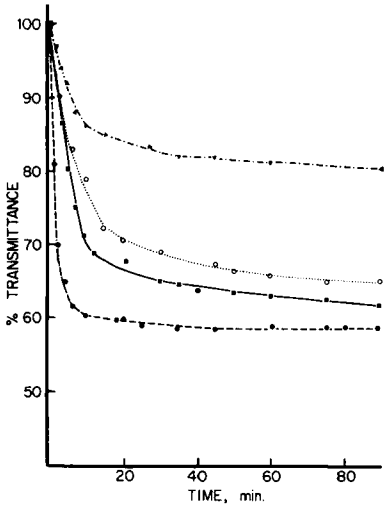

Fig. 1—Plot of percent transmittance versus *time showing the relative deaggregation rates of the four capsules in simulated gastric fluid T.S. Key: ●, Capsule A; ■, Capsule B; ○, Capsule C; ▲, Capsule D.*

going through the intermediate states, or if these were formed they were extremely short lived.

Based on these premises, equations were developed which described the deaggregation process. In the final form the equation was written as:

$$\log \frac{A_s}{A_s - A_t} = \frac{k}{2.303} t \qquad \text{(Eq. 1)}$$

Fig. 2—Chloramphenicol Capsule D after 3 hr. in simulated gastric fluid (deaggregation rates determination).

where A_s is the absorbance at the final state and A_t the absorbance at time t.

If the deaggregation process follows Eq. 1, a plot of $\log A_s/(A_s - A_t)$ *versus* t should be linear. From the slopes, the relative deaggregation rates can be evaluated.

In Figs. 3 and 4, the deaggregation rates of the four commercial lots of chloramphenicol capsules are plotted in accordance with Eq. 1. It is readily evident that the deaggregation rate of Capsule A follows Eq. 1. The deaggregation rates of the other three capsules are more complex.

In the case of Capsule D (Fig. 4), during the first 60 min. the deaggregation rate is indeterminate, possibly due to the appearance of additives in the medium. After the first hour, the rate appears to follow a first-order process, but it is extremely slow.

The deaggregation rates of Capsules B and C are intermediate between A and D and are nonlinear. The nonlinearity is possibly due to the reaggregation of the particles after they appear in the test medium. If the dispersed particles reaggregate, then the mechanism for the reverse reaction must also be taken into account, and the equation describing the phenomena would be much more complex than that shown in Eq. 1.

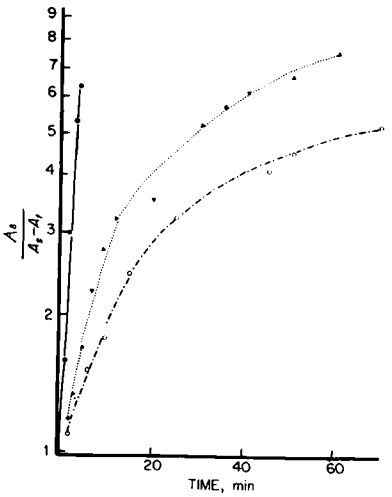

Fig. 3—Deaggregation rates of Capsules A, B, and C in simulated gastric fluid T.S. plotted according to Eq. 1. Key: ●, Capsule A; ▲, Capsule B; ○, Capsule C.

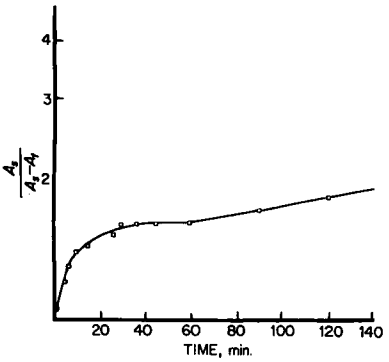

Fig. 4—Deaggregation rate of Capsule D in simulated gastric fluid T.S. plotted according to Eq. 1.

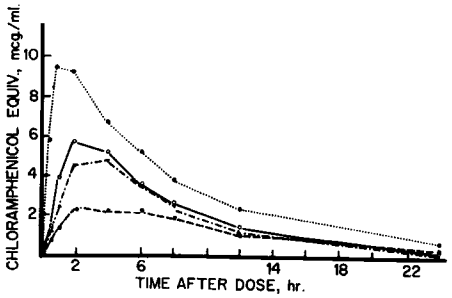

Fig. 5—Mean plasma levels in human volunteers of nitro compounds (chloramphenicol equivalents) following single oral doses of chloramphenicol capsules. [Dose 0.5 g. (2 capsules), 10 subjects] (see Reference 2*). Key: ●, Capsule A; △, Capsule B; ○, Capsule C; ■, Capsule D.*

Furthermore, the turbidity of the deaggregation medium is dependent on the particle size of the drug and in the present case also on the additives in the capsule such as fillers and lubricants. Equation 1 describes a situation (3) in which the particle size of the drug tested was uniform. If the particle size of the chloramphenicol in the capsules is different, or if the nature and amount of additives are dissimilar, the application of Eq. 1 in the present study would serve only as a qualitative comparison of the deaggregation rate rather than a quantitative measurement.

Figure 3 shows that there is at least a fivefold difference in the initial slopes of the lines between Capsules A and B and at least a sevenfold difference between A and C. The differences in the initial slopes of the lines emphasize the earlier and greater release of chloramphenicol from Capsule A in contrast to the other three capsules.

A qualitative correlation exists between the deaggregation rates of the four commercial lots of chloramphenicol capsules and the plasma levels shown in Fig. 5.[4] Capsule A shows a higher and earlier mean chloramphenicol peak plasma level in comparison with the others, and the deaggregation rate of Capsule A is also much faster. The mean peak plasma level observed with Capsule D is much lower and delayed while the deaggregation rate of the capsule is also very slow. Capsules B and C show intermediate deaggregation rates and intermediate mean plasma levels, although the order is reversed.

The apparent faster deaggregation rate of Capsule B in comparison to C can possibly be ascribed to the larger amount of additives present in B, as the turbidity is a function of the total quantity of particles present in the medium. Since the capsules were purchased it was not possible to ascertain definitively the composition and quantity of the additives present in Capsules B, C, and D.

A few of the D capsules were then emptied, and an equivalent weight of the powder was packed into a larger (No. 1) capsule to determine if the packing force would affect the rate. Packing into a larger capsule increased the initial dispersion. However, the particles quickly formed two or three large aggregates and further deaggregation was very slow indicating that the nature of the adjuvants was more important than the packing density or force.

Dissolution Studies—The results of the dissolution studies carried out with the Vanderkamp disintegration apparatus according to USP specifications are summarized in Table II.

The data presented in Table II show that about 90% of the chloramphenicol in Capsule A is in solution within the first 10 min. and emphasizes the rapidity of the dissolution of the product. Capsule C shows only about 50% of the drug in solution within this period while Capsules B and D have less than 10% in solution.

The rapid dissolution of Capsule A correlates well the rapid absorption and high plasma levels observed with the product.

The data presented in Table II also show that Capsules B and D have the lowest rates of solution. The mean plasma level obtained with Capsule D is also the lowest. The mean plasma level observed for Capsule B is higher than that with Capsule D, although their dissolution rates appear to be the same.

The results of the dissolution studies carried out with the electronic stirrer shown in Fig. 6 indicate the rapid dissolution rate of Capsule A in comparison with the others. With the experimental procedure that was used, there appears to be no significant difference between the rates of solution of the other three capsules.

The rapid dissolution of Capsule A again correlates well with the rapid absorption and high chloramphenicol plasma level shown in Fig. 5. The dissolution rates (as determined) do not differentiate between the blood levels of the three other capsules tested.

The particle-size distribution of chloramphenicol in the four capsules was approximated by sieve analysis. About 10 g. of the powder blend obtained by emptying 30 capsules from each lot was passed through a series of screens with progressively decreasing mesh size. The powder retained on the sieve was weighed, and an aliquot assayed spectrophotometrically for chloramphenicol content. The percent chloramphenicol retained on each sieve was computed and the data are shown in Fig. 7.

Admittedly there are some errors involved in determining the particle-size distribution by screen-

[4] Figure 5 is presented to facilitate the discussions and comparisons in this paper. For details and other information, see *References 1* and *2*.

TABLE II—RESULTS OF DISSOLUTION STUDIES OF COMMERCIAL LOTS OF CHLORAMPHENICOL CAPSULES[a]

Time, min.	% Total Drug Dissolved/Capsule						
	A	B Trial 1	B Trial 2	C	D Trial 1	D Trial 2	D Trial 3
10	91.8	9.9	8.3	48.7	7.2	9.8	9.3
20	97.5	16.9	17.5	88.3	13.4	21.7	16.8
30	98.6	21.3	28.2	94.3	19.1	35.9	20.4

[a] USP disintegration apparatus and artificial gastric fluid T.S. at 37 ± 0.5°.

ing techniques. However, qualitatively it is evident from Fig. 7 that the particle-size distributions of chloramphenicol in Capsules A, B, and D are not significantly different. The distribution of the drug particles in Capsule C is slightly different, showing a larger amount of fines which could be due to the presence of smaller chloramphenicol particles or alternatively due to the lubrication of the drug particles engendered during the sieve analysis by the additives in the capsule.

If the particle-size data presented in Fig. 7 are indeed representative of the distribution of chloramphenicol in the capsules, one would expect that the mean plasma level obtained with Capsule C would be higher than that obtained with the other capsules.

From the evidence presented, it appears that the deaggregation or dispersion rate is of importance in determining the availability of chloramphenicol (from the capsules) for dissolution and absorption.

Permeation Studies—The permeation studies using the everted sac technique were carried out to determine whether the additives in the chloramphenicol capsules interfered with the absorption of the drug by binding, *etc.*

The total quantities of drug permeating through the everted sac at various time intervals from the four lots of chloramphenicol capsules are given in Table III.

The profiles demonstrating the relative rates of permeation are shown in Fig. 8.

It is evident that the rates of permeation of Capsules A and C are similar, followed closely by Capsule B. The rate of permeation of Capsule D is approximately one-half of Capsule A, as is shown by the slope of the line.

It was noted that Capsule D contained a large quantity of an insoluble compound which coated the gut tenaciously during the permeation study. To determine whether the coating interfered with permeation of the drug, a second run was made with the capsule contents filtered before placing in the apparatus. Removal of the insoluble material produced a marked increase in both the rate and level of the drug. All four commercial chloramphenicol capsules were then treated similarly and resubmitted to permeation testing.

The quantities of drug permeating through the gut over the various time intervals for the filtered preparations are given in Table IV.

The profiles showing the relative rates of permeation after filtration are plotted in Fig. 9.

The increased permeation rates shown by the filtered solutions of the Capsules A, B, and C may be due to removal of the gelatin shell from the solution. The shaking time of 15 min. for the buffer solution containing the opened capsule was sufficient to saturate the solution with chloramphenicol, but was not sufficient to dissolve all of the gelatin capsule shell. The remainder of the gelatin shell dissolved during the 2 hr. of the experiment. Filtration of the buffer-capsule mixture before placing in the apparatus removed the undissolved gelatin material. Filtering the mixture from Capsule D removed the white insoluble material, thus increasing the permeability of the gut.

Assays of the ethanol extract of the gut, dried after use, showed less than 1% (of the dry weight) of chloramphenicol bound to the gut membrane.

If the permeation of the drug through the everted sac is related to the absorption process through the human intestine, one could postulate from the data that the permeation rate of chloramphenicol is not the rate-determining step in the absorption process.

It is difficult to assess the significance of the coating of the gut membrane observed with Capsule D. As indicated earlier, the coating reduced significantly the absorption through the everted sac of chloram-

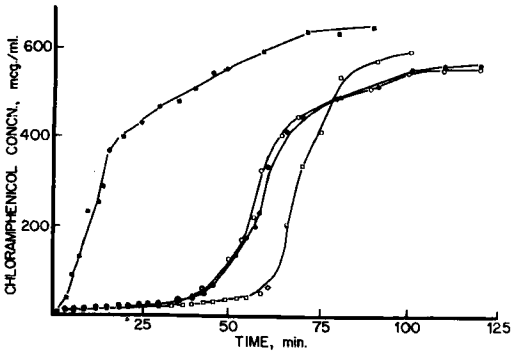

Fig. 6—Dissolution rates of chloramphenicol capsules in simulated gastric fluid T.S. Key: ■, Capsule A; □, Capsule B; ○, Capsule C; ●, Capsule D.

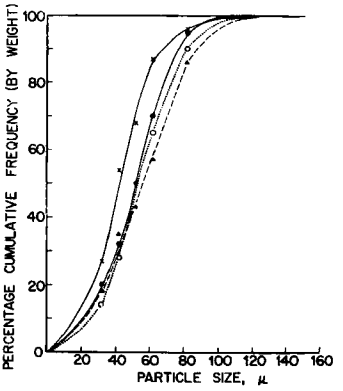

Fig. 7—Plot showing the particle-size distribution of chloramphenicol in Capsule A, ●; Capsule B, △; Capsule C, ×; Capsule D, ○.

TABLE III—COMPARATIVE PERMEATION OF CHLORAMPHENICOL FROM THE CAPSULES THROUGH THE EVERTED SAC (CUMULATIVE AMOUNTS IN mcg.)

Time, min.	Capsule A	B	C	D
5	82	38	50	81
15	183	122	152	177
25	412	308	323	294
35	573	523	515	414
45	862	667	707	557
60	1,052	896	1,030	709
75	1,464	1,189	1,422	889
90	1,752	1,560	1,750	1,057
105	1,976	1,873	2,046	1,211
120	2,340	2,414	2,376	1,414

TABLE IV—COMPARATIVE PERMEATION OF CHLORAMPHENICOL FROM THE CAPSULES THROUGH THE EVERTED SAC[a]

Time, min.	Capsule A	B	C	D
5	49	54	50	106
15	193	165	157	274
25	408	297	358	494
35	656	468	552	752
45	978	676	789	1,013
60	1,333	949	1,112	1,237
75	1,788	1,191	1,452	1,507
90	2,284	1,445	1,764	1,952
105	2,781	1,722	2,082	2,292
120	3,375	1,983		2,791
125			2,694	

[a] Solution of capsule contents filtered. (Cumulative amounts in mcg.)

phenicol from Capsule D. Since the total area present for absorption in the human intestine is very much larger, the quantity of the additives in the capsule may be too small to significantly affect the absorption in man.

GENERAL DISCUSSION

When a drug is administered in a solid particulate state, it is not unreasonable to assume that the absorption of the drug from the gastrointestinal media follows the sequence:

$$\underset{\text{drug}}{\text{solid particulate}} \rightarrow \underset{\text{drug}}{\text{dissolved}} \rightarrow \underset{\text{drug}}{\text{absorbed}}$$

If the intrinsic solubility of the drug is high, the permeation rate through the gastrointestinal barrier is assumed to be the rate-determining step in the absorption sequence. On the other hand, when a drug has a relatively low solubility, the build-up of an effective concentration at the absorption site will probably govern the rate of absorption.

Although the scheme outlined above has been shown to be true in many cases, it appears to be inadequate to describe the absorption of drugs from dosage forms, particularly from tablets and capsules.

It is proposed that a modified version such as:

$$\underset{\text{(tablet, capsule)}}{\text{drug in dosage form}} \xrightarrow{\text{deaggregation}} \underset{\text{solid state}}{\text{drug in particulate}} \xrightarrow{\text{dissolution}} \text{drug in solution} \xrightarrow{\text{absorption}} \underset{\text{drug}}{\text{absorbed}}$$

is a more realistic way of describing the absorption sequence.

Evidence gathered in the study emphasizes the importance of pharmaceutical factors in controlling the availability of chloramphenicol from the capsules for gastric absorption. As the solubility of chloramphenicol is approximately 5 mg./ml. at 37°, it would appear that the drug would saturate the gastrointestinal media relatively fast if it were released rapidly from the capsule. The higher and earlier chloramphenicol plasma level seen in humans receiving Capsule A correlates well with its faster rates of deaggregation and dissolution. The results of the study show that different chloramphenicol products containing analytically the same quantity of chloramphenicol are not equivalent in terms of drug release or drug availability.

The study also suggests *in vitro* methods of defining and establishing factors which control the absorption of a drug from dosage forms, particularly where a rapid plasma level is desirable. By determining the deaggregation and dissolution rates and using the everted sac technique to gauge any binding of the drug, one is able to define more clearly and obtain a better correlation of drug release and availability.

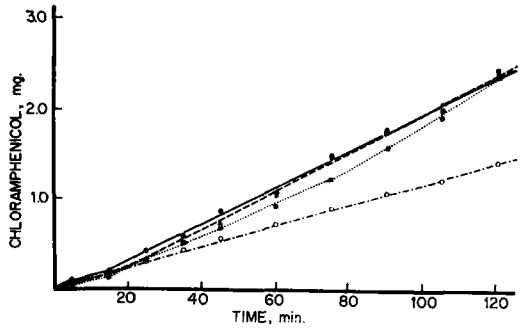

Fig. 8—Permeation rates of chloramphenicol from capsules through the everted sac. Solutions not filtered. Key: ●, Capsule A; ■, Capsule B; △, Capsule C; ○, Capsule D.

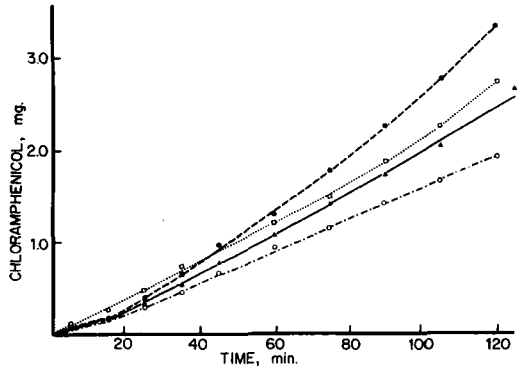

Fig. 9—Permeation rates of chloramphenicol through the everted sac, of filtered solutions from capsules. Key: ●, Capsule A; ○, Capsule B; ▲, Capsule C; □, Capsule D.

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Keyphrases

Chloramphenicol capsules
Release, availability—chloramphenicol capsules
Deaggregation rates, capsules—turbidity measurements
Dissolution, capsules—*in vitro*
Intestinal sac, everted—drug permeation

Significance of Salicylic Acid Sublimation in Stability Testing of Aspirin-Containing Solids

By A. Y. GORE*, K. B. NAIK, D. O. KILDSIG, G. E. PECK, V. F. SMOLEN, and G. S. BANKER

The salicylic acid content, formed from the decomposition of aspirin, was found to be an unreliable basis for judging the stability of aspirin tablets. Under conditions of accelerated stability testing, the loss of salicylic acid from the system by sublimation can incur appreciable errors in the direction of overestimating aspirin stability. Since aspirin was not detected to sublime under these same conditions, its residual content is an improved indication of its stability. A method for its simultaneous determination with salicylic acid is presented.

SALICYLIC ACID was observed to be lost from aspirin tablets undergoing accelerated stability testing in this laboratory. This is illustrated in Fig. 1 where deposits, analytically identified as salicylic acid, are shown on the surface of aspirin tablets coated with a cellulosic film.

Considering that salicylic acid is a hydrolytic decomposition product of aspirin and sublimation is a commercial method for its purification (1), its volatilization under the elevated temperature and humidity conditions employed in accelerated stability testing could be anticipated. However, this phenomenon apparently has not been previously studied. An earlier investigation (2) either overlooked it or treated it as being unappreciable.

A more than negligible loss of the salicylic acid formed from the decomposition of aspirin would preclude the common practice of analytically determining changes in salicylic acid content in solid dosage forms of aspirin as a measure of degrading aspirin. The salicylic acid method could obviously underestimate the extent of decomposition of aspirin and therefore provide

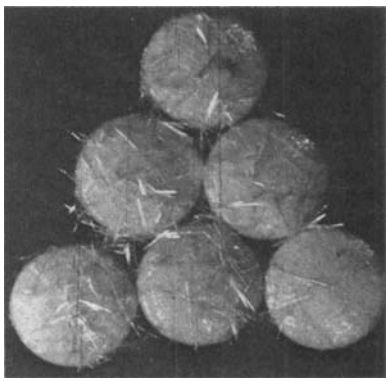

Fig. 1—Aspirin tablets coated with a cellulosic film and stored at 81.2% relative humidity and 50° for 98 days. The crystalline deposits on the surface were identified as salicylic acid formed from the decomposition of aspirin.

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