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TECHNICAL ARTICLES

A Critical Analysis of a Capsule Dissolution Test

R. J. WITHEY and C. A. MAINVILLE

Abstract □ A suitably modified USP disintegration apparatus has been used to obtain dissolution rate data for chloramphenicol capsules. Differences between various commercial and laboratory formulations of this drug were reflected in their dissolution profiles. Several shortcomings of this apparatus are described.

Keyphrases □ Capsule dissolution testing—methodology □ Chloramphenicol capsules—dissolution □ Particle size effect—capsule dissolution rates □ Lactose effect—capsule dissolution rates □ Diagram—dissolution apparatus □ UV spectrophotometry—analysis

The desirability of an *in vitro* test which adequately reflects the physiological availability of solid dosage forms of drugs is now well recognized. The inadequacy of disintegration times in this context has been pointed out (1). The measurement of a parameter which is related to the rate of dissolution of a solid has been suggested as a more realistic variable and this has led to an abundance of papers [see for example (2–6)] describing different methods and equipment for following dissolution rates. One of the more widely used methods (7) adapts, with suitable modifications, the apparatus recommended by either the USP (8) or FDD (9) for the measurement of disintegration time of tablets.

Important requirements for an adequate dissolution test include:

(*a*) The design of the equipment and protocol should allow a rapid evaluation of some specified dissolution parameter by using equipment or components that are either commercially available or readily fabricated. The dimensions and geometry of the individual components of the apparatus should be rigidly specified, together with tolerances, so that inter- and intra-laboratory variations are kept to a minimum.

(*b*) Analysis of the dissolution medium, in order to establish the dissolution profile,[1] should be rapid, sensitive, and simple.

(*c*) The procedure used should rank different formulations of the same drug in the same order as their *in vivo* availability.

(*d*) A detailed description of the procedure used in the kinetic analysis and derivation of suitable dissolution parameters is essential.

(*e*) Enough specimens of each formulation should be examined to permit a significant statistical analysis. The resulting statistical parameters should reflect inter-vehicle formulation differences and permit differentiation of formulation and manufacturing variables.

In this paper one dissolution test, which involves the use of a modified version of the USP disintegration apparatus (8), was used to obtain dissolution profiles of a variety of encapsuled formulations of one drug (chloramphenicol).

EXPERIMENTAL

Equipment—The USP disintegration apparatus, without disks or plungers, was used. Since the specifications (8) for the dimensions and geometry of this apparatus allow some variation, the apparatus which was used is illustrated in Fig. 1.

Procedure—Eight hundred milliliters of simulated gastric juice solution was allowed to equilibrate with a thermostat whose temperature was controlled at 37 ± 0.5°. Two methods were used to follow the dissolution of a given formulation:

[1] In this paper, the term is used to mean the curve obtained when percent dissolved is plotted against sampling time.

Table I—Reproducibility of "Six Capsules Simultaneously" Dissolution Test for Brand B_1 Capsules

Time, min.	% Dissolution/Run No. 1	2	3	4	5	6	Mean	$\pm s$	100 s/Mean
10	71.7	76.1	73.6	71.0	73.6	73.6	73.2	1.8	2.4
20	79.5	83.1	79.0	77.5	80.2	78.3	79.6	2.0	2.5
30	82.0	88.6	82.4	81.3	83.5	82.6	83.4	2.6	3.1

(*a*) "Single capsule tests" in which one capsule was placed in one of the cylindrical baskets of the dissolution apparatus.

(*b*) "Six capsules simultaneously test" in which six capsules, one in each of the cylindrical baskets, were placed simultaneously in the apparatus.

Aliquots (1.00 ml.) were withdrawn after 10, 20, and 30 min. from the beginning of the test or, where the initial portion of the dissolution profile was required in more detail, samples at 2, 4, 6, and 8 min. were taken in addition. Samples were taken with a 1.00-ml. tuberculin syringe (B-D Yale), graduated from 0.00 to 1.00 in units of 0.01 ml., fitted with a medium porosity fritted-glass filter. The filter was fabricated from an immersion filter tube (No. 35-050, Canlab Ltd.) cut close to the fritted disk, and joined to a Luer-fitting female joint (No. K-66350-1F, Kontes Glass Co.).

After suitable dilution the absorption of the sample was then measured at 278 mμ in a 1-cm. path length cell on a spectrophotometer (Beckman DU 2). The concentration of drug in solution was calculated from a value of the absorptivity of chloramphenicol (USP standard) which had been determined from a Beer's law calibration curve. The percent of drug dissolved at the sampling time, t, was calculated from either the weight of drug placed in the capsule (for laboratory manufactured capsules) or from the label claim (250 mg.) of commercially manufactured capsules. Corrections were made for the loss of drug present in the volume of previously removed samples and for the progressive decrease in volume of the dissolution medium. These corrections were already included in a computer program, which has been devised for use with a desk computer (Olivetti Programma 101), although due to the small sample volumes they affected the values of percent dissolved at a time t by less than 0.1%.

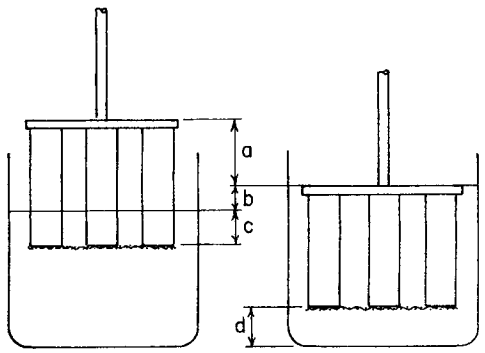

Figure 1—*USP disintegration apparatus as modified for following rates of dissolution of capsule dosage forms.*

Stroke: 5 cm. (USP states: not less than 5 and not more than 6 cm.).
Frequency: 30 c.p.m. (USP states: constant frequency rate between 28 and 32 c.p.m.).
Liquid temperature: 37 ± 0.5° (USP states: thermostatted between 35 and 39°).
Volume of liquid used: 800 ml. (USP gives no precise volume. Specifies volume of liquid must be such as to comply with distances, specified above, for depth of immersion of wire mesh on maximum and minimum displacement on upward and downward stroke).
Liquid: Simulated gastric juice. 2 g. NaCl + 7 ml.-concd. HCl + 3.2 g. pepsin/l. pH of solution 1.2.
Vessel: 1000-ml. beaker, Fisher Catalog No. 2-540

Key: a = *stroke 5 cm.;* b = *liquid levels, max. and min.;* c = *2.6 cm. (USP states: at the highest point of the upward stroke the wire mesh remains at least 2.5 cm below the surface of the water);* d = *3.75 cm. (USP states: the wire mesh descends to not less than 2.5 cm. from the bottom of the vessel on the downward stroke).*

Data Analysis—Dissolution profiles were drawn to allow comparison of data and the interpolation of t_{50} (the time at which 50% of the drug has dissolved). Where possible, six identical dissolution tests were carried out for each formulation and the six values of t_{50} were statistically analyzed to give the mean, $\bar{t}_{50}$, the standard deviation, s, and the coefficient of variation, 100 $s/\bar{t}_{50}$. In addition, the six values of percent dissolved obtained for each sampling time were similarly analyzed so that a "mean dissolution curve" together with $\pm s$ limits for each point could be constructed. These statistical data accompany the dissolution profile figures in the tables.

Studies with Commercially Manufactured Brands—Dissolution profiles were obtained for 250-mg. capsules of chloramphenicol which were purchased by Food and Drug Directorate personnel directly from the manufacturers. A total of 19 lot numbers from 12 manufacturers were examined both by the "single" and "six simultaneous" test. Different manufacturers' brands are identified by capital letters, a subscript number indicating different lot numbers of the same brand. The results are presented in Tables I, II, and III.

Studies with Pure Chloramphenicol—*Laboratory Manufactured Capsules*—Crystalline samples of pure chloramphenicol were obtained of 11 different lot numbers from six different companies. Since the quantity of drug, for a given lot number, varied from 300 mg. to 10 g. only one "single capsule test" was carried out for most of the samples.

Capsules were manufactured in the laboratory by weighing, to 0.1 mg., about 250 mg. of the pure drug which was loosely packed, by hand filling, into a size 0 gelatin capsule. The results of the dissolution studies for these are given in Tables IV, V, and VI.

Effect of Particle Size—Pure drug, Brand *R*, was sieved in a pocket interchanger sieve (Endecotts Ltd.) through standard size meshes which varied in aperture from 149 μ (A.S.T.M. No. 100) to 62 μ (A.S.T.M. No. 230). Fractions of the following particle size range were collected: (*a*) >149 μ, (*b*) 74–149 μ, (*c*) 62–74 μ, (*d*) <62 μ. The dissolution profiles for these capsules are illustrated in Fig. 2.

Table II—Percent Dissolution at 10, 20, and 30, min. for Commercially Manufactured Chloramphenicol Capsules[a]

Brand	% Dissolved, min. 10	20	30	t_{50} [b] min.
A	76.3	82.4	81.5	2.4
B_1	71.7	79.5	82.0	4.0
B_2	66.3	73.2	78.1	3.0
C	46.6	79.1	86.4	10.0
D	45.3	53.1	59.6	16.0
E	41.5	76.0	82.9	11.5
F	39.3	80.4	88.7	12.5
G	38.8	78.9	90.1	13.0
H_1	37.9	69.7	84.9	13.0
H_2	28.3	49.8	62.8	20.2
I_1	37.3	66.8	77.3	13.5
I_2	33.2	68.1	75.7	14.0
I_3	40.8	66.8	74.6	12.5
I_4	35.3	63.4	70.8	14.0
J_1	31.2	70.6	81.3	13.0
J_2	33.3	65.7	81.6	15.0
K	27.2	59.6	77.8	16.5
L_1	14.0	25.5	26.3	— [c]
L_2	15.6	23.0	25.0	—

[a] One "six capsules simultaneously" test was used. [b] Values were graphically interpolated. [c] No values were possible since dissolution was followed for less than 50%.

Table III—Dissolution Data for Commercially Manufactured Chloramphenicol Capsules Obtained by the "Single Capsule Test" Method

Brand	Time, min.	% Dissolved/Capsule No. 1	2	3	4	5	6	Mean % Dissolved	$SD \pm s$	$100s/\text{Mean}$	$\bar{t}_{50}$	$\pm s$	$\frac{100s}{\bar{t}_{50}}$
A	10	106.5	94.3	82.6	100.3	97.0	102.5	97.2	8.3	8.6	3.4	1.5	43.6
	20	113.0	99.1	97.8	106.5	108.9	103.5	104.8	5.8	5.6			
	30	113.0	103.2	100.3	106.5	110.0	106.9	106.7	4.6	4.3			
B_1	10	82.2	80.9	84.6	84.2	85.0	90.2	84.5	3.2	3.8	4.4	1.3	30.1
	20	86.6	93.5	96.9	97.8	96.4	96.9	94.7	4.2	4.5			
	30	97.2	97.5	101.3	100.0	101.1	98.9	99.3	1.8	1.8			
B_2	10	86.6	101.2	81.1	82.6	81.1	82.3	85.8	7.8	9.1	3.8	0.8	20.8
	20	97.0	104.6	95.8	92.6	90.9	91.1	95.3	5.2	5.4			
	30	100.2	104.6	97.3	96.6	102.0	103.5	100.7	3.3	3.3			
C	10	30.0	46.7	30.9	15.9	78.4	27.3	38.2	22.0	57.7	12.0	3.4	28.3
	20	75.3	90.5	81.3	77.2	94.1	92.9	85.2	8.3	9.7			
	30	95.1	93.7	92.9	86.0	96.5	97.4	93.6	4.1	4.4			
D	10	53.2	70.2	63.0	63.8	53.2	57.3	60.1	6.8	11.3	7.5	1.4	18.7
	20	72.9	84.0	83.3	81.2	73.7	70.0	77.4	6.2	7.9			
	30	84.3	89.0	92.7	92.1	85.9	79.4	87.2	5.1	5.8			
E	10	31.0	28.0	43.0	83.8	61.6	33.4	46.8	21.8	46.7	11.2	3.7	32.7
	20	86.0	78.2	92.9	100.6	88.4	74.6	86.8	9.5	11.0			
	30	92.2	89.1	101.3	101.5	95.1	83.8	93.8	6.9	7.4			
F	10	19.4	61.6	60.9	58.7	42.6	48.2	48.6	16.2	33.3	10.7	3.5	32.8
	20	60.6	102.0	97.1	97.9	93.1	88.8	89.9	15.0	16.7			
	30	89.2	103.2	100.7	102.8	97.9	102.7	99.4	5.4	5.4			
G	10	35.3	48.3	31.7	51.3	32.6	44.6	40.6	8.5	20.9	12.3	2.1	17.3
	20	74.4	90.2	78.0	92.2	70.1	76.4	80.2	8.9	11.2			
	30	104.3	92.8	96.2	97.6	87.8	90.4	94.9	5.9	6.2			
H_1	10	34.4	45.4	20.9	38.8	26.7	32.9	33.2	8.7	26.1	13.3	2.5	18.7
	20	80.0	87.8	60.0	92.1	82.4	93.5	82.6	12.3	14.9			
	30	87.4	94.6	84.8	97.6	92.4	98.2	92.5	5.4	5.9			
H_2	10	13.3	30.2	21.9	33.7	60.9	26.0	31.0	16.3	47.2	18.1	5.7	31.3
	20	41.2	60.4	44.8	54.1	85.0	48.6	55.7	15.9	28.6			
	30	63.9	76.2	65.9	68.1	88.5	68.3	71.8	9.2	12.8			
I_1	10	30.7	68.2	3.2	32.8	37.9	48.9	36.9	21.5	58.5	13.2	4.0	30.5
	20	62.8	87.4	60.0	64.3	77.1	78.7	71.7	10.9	15.2			
	30	83.6	88.0	72.9	85.5	88.9	86.1	84.2	5.8	6.9			
I_2	10	46.2	34.4	50.3	73.3	27.2	32.3	43.9	16.8	38.3	12.0	3.8	31.3
	20	67.5	81.6	93.1	87.5	63.0	61.9	75.8	13.4	17.7			
	30	83.8	90.8	97.8	89.1	79.9	78.4	86.6	7.3	8.4			
I_3	10	40.2	26.3	50.4	52.4	40.7	15.3	37.6	14.3	38.1	13.1	4.1	31.2
	20	73.5	71.0	80.5	76.9	80.2	48.5	71.8	12.0	16.7			
	30	80.8	79.9	87.6	87.4	86.8	67.6	81.7	7.7	9.4			
I_4	10	39.5	31.4	41.0	44.8	39.0	32.4	38.0	5.2	13.6	12.1	1.1	9.3
	20	74.7	81.8	80.7	94.2	77.7	72.5	80.2	7.7	9.6			
	30	83.7	90.9	86.3	96.8	86.4	77.5	87.0	6.5	7.5			
J_1	10	25.5	33.0	32.2	15.3	28.7	37.8	28.8	7.8	27.0	14.2	3.8	27.1
	20	77.8	85.8	71.1	46.0	87.5	90.3	76.4	16.5	21.5			
	30	89.6	91.5	89.8	59.5	98.9	96.3	87.6	14.3	16.3			
J_2	10	19.6	25.1	17.5	77.1	14.6	23.2	29.5	23.6	80.1	22.2	10.9	49.1
	20	44.5	63.6	31.8	87.6	27.5	51.2	51.0	22.2	43.5			
	30	57.7	80.2	48.1	88.2	39.6	69.2	63.8	18.8	24.4			
K	10	8.2	18.4	6.0	15.4	9.8	18.5	12.7	5.4	42.8	26.3	8.9	34.0
	20	28.3	45.9	23.2	49.2	43.8	46.8	39.6	10.9	27.6			
	30	49.3	73.2	38.0	80.7	75.6	62.4	63.2	16.7	26.4			
L_1	10	6.6	9.9	10.3	12.2	12.4	10.2	10.3	2.1	20.3	—	—	—[a]
	20	13.7	20.2	18.8	24.7	21.7	22.6	20.3	3.8	18.8			
	30	20.6	23.8	26.4	27.4	23.8	26.8	24.8	2.6	10.4			
L_2	10	7.2	8.8	10.9	12.0	12.4	11.4	10.4	2.0	19.4	—	—	—[a]
	20	17.3	21.0	20.0	17.9	19.8	19.1	19.2	1.4	7.2			
	30	23.3	23.2	23.2	21.9	20.9	21.2	22.3	1.1	5.0			

[a] No values obtained since dissolution followed for less than 50%.

Table IV—Dissolution Data for "Single Capsule Tests" of Laboratory Manufactured Capsules

Brand	% Dissolved, min. 2	4	6	8	10	20	30	t_{50}
N_1	37.2	85.7	91.3	95.3	97.9	100.1	100.1	2.5
N_2	0.5	60.5	83.9	90.2	95.0	99.8	99.5	3.6
N_3	7.0	22.2	58.8	70.7	76.6	89.4	95.3	5.2
N_4	3.1	19.7	33.9	44.8	55.4	71.1	88.1	8.8
O_1	64.8	98.0	99.0	99.0	99.0	99.0	99.0	1.8
O_2	30.2	80.4	89.4	92.9	95.0	96.6	98.0	2.4
P	34.3	84.0	89.9	93.2	95.3	98.8	98.6	2.4
Q	10.5	59.7	71.4	75.1	81.4	86.9	86.9	3.2
R	2.0	54.5	67.2	72.5	78.1	89.8	95.7	3.6
S_1	24.5	46.6	58.1	67.4	76.2	95.5	99.3	4.6
S_2	18.8	48.7	59.0	68.4	73.7	89.2	97.9	4.4

Effect of Added Lactose—Since most of the commercially manufactured capsules contained the pure drug mixed with lactose, the effect of added lactose on the rate of dissolution of chloramphenicol from laboratory manufactured capsules was examined.

Pure drug, Brand *R*, was mixed with lactose BP in proportions which contained 16.6, 43.4, and 79.8% by weight of lactose. A weighed sample of pure drug and lactose BP were mixed in a screw-cap bottle by rotating the bottle and its contents about its longitudinal axis in a horizontal position at 50 r.p.m. for 24 hr. Quantitative tests showed that a homogeneous mixture was obtained by this procedure. The mixture was then placed in a size 0 gelatin capsule, so that each capsule contained about 250 mg. of chloramphenicol. The results are illustrated in Fig. 3. Each point was derived from the mean of six values and the standard deviation is indicated by the limits.

Photographic Studies—Since significant differences in dissolution profiles for chloramphenicol capsules (both for commercially and laboratory manufactured) were observed, photomicrographs (×70) of capsule contents were taken with the following objectives:

(*a*) To compare relative crystal size distribution of pure drug. (*b*) To see if the extent of agglomeration of pure drug crystals was a significant variable with respect to observed dissolution profiles. (*c*) To compare, in some cases, the crystal size in the pure drug and commercially manufactured capsule contents which were known to have been derived from the same bulk drug lot number. (*d*) To illustrate the distribution of additives throughout the capsule content matrix. (*e*) To examine the structure of the "liquid" capsule contents of Brand *L*.

Photomicrographs of sixteen different pure drug samples and ten selected commercial capsule contents were taken. Where possible the largest and smallest crystals were included in the same frame and where some special qualities were apparent (*e.g.*, a wide variation in crystal size, a heterogeneous distribution of additives, agglomeration, *etc.*) more than one frame was taken. Altogether forty different samples were photographed, eight of which are illustrated in Fig. 4.

DISCUSSION

It is now well recognized that the rate at which a solid dissolves in a solvent is usually a very complex process (10). In addition many factors, including temperature, agitation (11), viscosity of the dissolving medium (12), and specific intermolecular interactions with additives (13, 14) can affect the kinetics of the dissolution process.

Meaningful kinetic coefficients, which describe the entire dissolution process, can be obtained only if both the apparatus and the drug vehicle under test satisfy the stringent requirements laid down by Hixson and Crowell (15). Any apparatus which is used for following the dissolution process must therefore be specified rigidly with regards to dimensions, geometry, and energy input as well as having as few variables as possible if reproducible results are to be obtained.

The modified USP disintegration apparatus, which was used in the work reported here, falls short of many of these requirements and commercially manufactured solid dosage forms do not satisfy the necessary assumptions which have to be made in order to derive meaningful kinetic coefficients. Nevertheless, despite the large number of variables in both the apparatus and dosage forms, important differences in formulation which significantly affected the dissolution rate of the chloramphenicol capsules used in this study, were distinguishable.

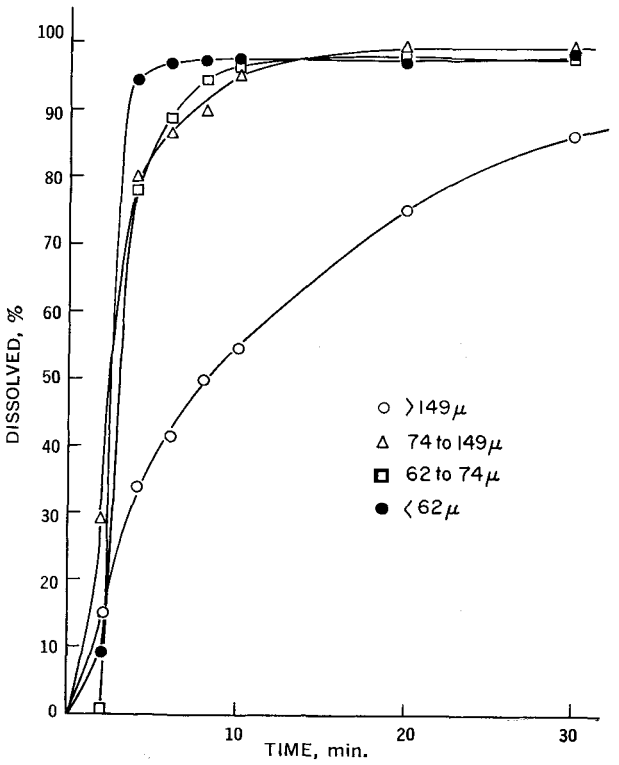

Figure 2—*Effect of particle size on dissolution rate* (*Brand* R).

Particle size or, more specifically, the surface area per unit mass, is one of the more important factors which affects the rate at which a sparingly soluble substance dissolves. Two examples of commercially manufactured chloramphenicol capsules, for which particle size is almost certainly the reason for the differences in the observed

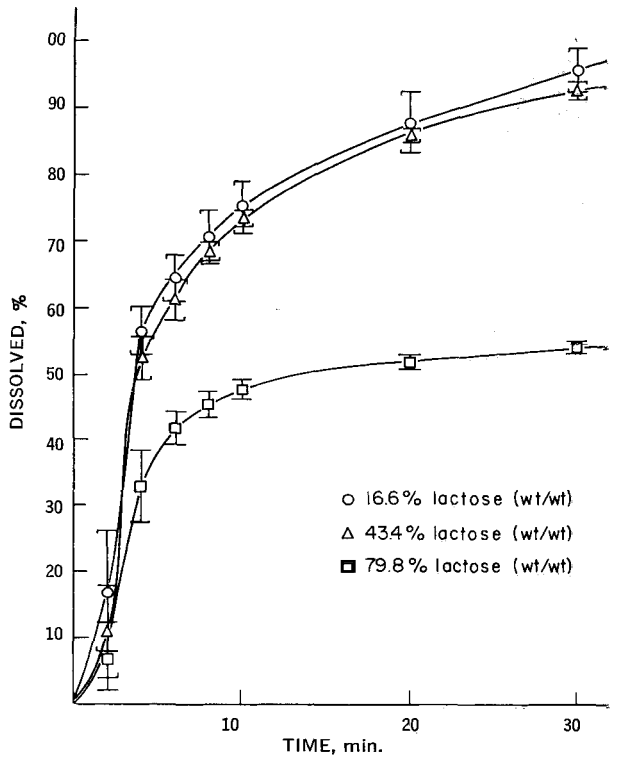

Figure 3—*Effect of lactose on dissolution rate* (*Brand* R).

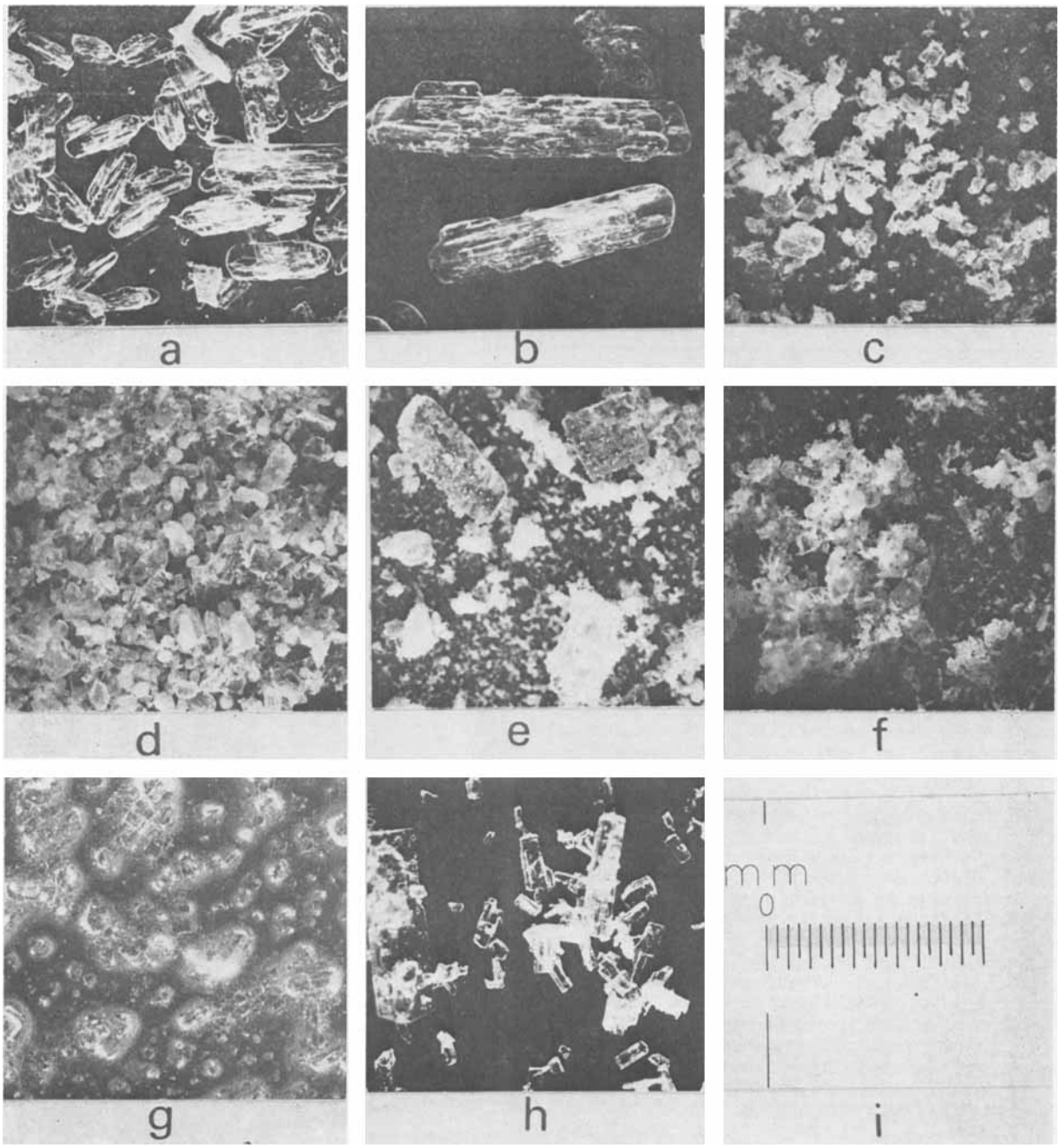

Figure 4—*Photomicrographs of chloramphenicol:* (a) *and* (b) *pure drug, Brand* S_2*;* (c) *capsule content, Brand* B_1*;* (d) *and* (e) *capsule content, Brands* H_2 *and* H_1*;* (f) *pure drug, Brand* N_4*;* (g) *capsule content, Brand* L_1*;* (h) *pure drug, Brand* R*;* (i) *1 mm. (1000 μ) scale which is subdivided into units of 10 μ.*

dissolution profiles, can be seen in the figures presented in Tables I and III. Two different lot numbers of the same brand, H_1 and H_2, differed appreciably in the extent of dissolution observed at the selected times both in the "single" and "six simultaneously" test. The photomicrographs presented in Fig. 4 (*d* and *e*) show clearly that the crystals of drug in capsules H_2, which dissolved more quickly, are smaller than those in H_1.

Several manufacturers kindly released formulation details for their chloramphenicol capsules, including the fact that Lots N_3, P, S_2, O_1, and O_1 of pure drug had been used to manufacture Lots J_1, J_2, B_1, K, and G, respectively, of finished capsules. It is of interest to note that the manufacturing process involved, in most cases, only the premixing of pure drug with lactose (or in some cases magnesium stearate was added) before encapsulation. The data in Tables IV and III allow a comparison of percent dissolved at similar times for laboratory manufactured capsules containing pure drug and the finished commercial product. Alternatively, the values of t_{50} and $\bar{t}_{50}$ may be compared. Where this comparison is possible, the dissolution rate for encapsulated pure drug alone is considerably faster than those for the commercial product with the exception of Lots S_2 and B_1.

Photomicrographs of pure Drug S_2 and the commercially manufactured capsule content which included S_2 are shown in Fig. 4 (*a*, *b*, and *c*). It is plainly evident that, before encapsulation, the pure Drug S_2 had been subjected to some process which reduced its crystal size. From measurements taken from enlarged photographs the longitudinal dimensions of pure drug crystals of S_2 appeared to be about 0.45 mm. [Fig. 4 (*a*)] although crystals as long as 1.45 mm. [Fig. 4 (*b*)] were observed. The longest crystal that could be discerned in the commercially manufactured capsule content [Fig. 4 (*c*)] was about 0.25 mm. but the majority were less than 0.05 mm. long. It could be concluded from these observations that crystal size has been recognized by the manufacturer as an important parameter which can affect dissolution rate for chloramphenicol

Table V—Dissolution of Six Laboratory Manufactured Capsules of Pure Drug, Brand S_2, in Single Capsule Tests

Time (min.)	% Dissolved/Capsule No. 1	2	3	4	5	6	Mean % Dissolved	$\pm SD$ (s)	$\frac{100s}{\text{Mean}}$
2	18.9	10.8	15.7	27.0	19.3	21.9	18.9	5.5	29.0
4	49.4	44.7	46.7	55.3	45.6	45.9	47.9	3.9	8.2
6	58.6	53.7	53.6	66.1	54.8	56.0	57.2	4.7	8.3
8	67.3	61.9	59.5	74.6	63.8	62.9	65.0	5.4	8.2
10	73.3	67.8	68.3	80.4	71.3	66.4	71.3	5.2	7.2
20	90.9	85.1	86.9	91.7	88.6	84.7	88.0	2.9	3.3
30	93.1	94.7	96.5	95.6	94.2	94.1	94.7	1.2	1.3

Table VI—Dissolution of Six Laboratory Manufactured Capsules of Pure Drug, Brand R, in Single Capsule Tests

Time (min.)	% Dissolved/Capsule No. 1	2	3	4	5	6	Mean % Dissolved	$\pm SD$ (s)	$\frac{100s}{\text{Mean}}$
2	47.7	34.2	11.0	18.5	30.6	13.5	25.9	14.1	54.6
4	64.1	60.7	58.1	55.2	60.7	61.1	60.0	3.0	5.0
6	68.0	66.0	65.7	70.4	67.3	68.8	67.7	1.8	2.6
8	74.2	71.1	70.3	74.7	74.0	74.6	73.2	1.9	2.7
10	76.2	74.6	74.5	79.9	74.0	79.2	76.4	2.6	3.4
20	88.6	85.4	87.1	88.1	89.5	92.3	88.5	2.3	2.6
30	92.9	91.4	91.4	93.5	102.2	95.4	94.5	4.1	4.3

crystals to the extent that pretreatment of the bulk drug material to reduce the particle size is a desirable manufacturing step. However, it is recognized that some manufacturers mill their pure drug material as a routine step after crystallization without necessarily being concerned over rates of dissolution.

Tables V and VI present more extensive data for the dissolution of laboratory manufactured capsules in which pure drug of Brands S_1 and R was used. Unfortunately, these were the only samples which were available in sufficient quantity to permit examination in depth but the data obtained indicate a higher reproducibility than those for commercially manufactured capsules. The rapid decrease in the coefficients of variation (100 s/mean) shows that the reproducibility increases as dissolution proceeds. The reason for this is probably that the gelatin capsule material influences the initial stages of dissolution in an unpredictable way. The "capsule effect" has been noticed before (17, 18), but no precise conclusions have been drawn.

The effect of particle size on dissolution rate was further examined. Fractions of the pure drug, Sample R, Fig. 4 (h), were sieved to give particle sizes ranging from >149 to <62 μ. Particles retained on a 149-μ screen differed appreciably in dissolution profile, see Fig. 2, from the other three ranges. The cross over of curves is again probably due to the "gelatin capsule effect" in that, for two of the capsules, dissolution did not commence until a minute or so after the beginning of the test. If the linear slopes for each of these curves, between 2 and 4 min., is measured then the initial rate of dissolution for these fractions can be expressed in percent dissolved per minute. These figures, presented in Table VII, show a progressive decrease in dissolution rate with increasing particle size although these data should be viewed semiquantitatively. A more precise analysis of the particle size effect on dissolution rates would require rigorous control of other variables (like the packing of the crystalline material within the capsule and the separation of crystal sizes into narrower ranges).

Of the pure drug samples which were examined, Brand S contained the largest crystals while Brands N_3 and N_4 were composed of crystals that were considerably smaller [see Fig. 4 (f)]. However, the extent of dissolution, particularly in the early stages, for N_3 and N_4 was less than that of either S_1 or S_2. No clear reason for this anomaly can be given at this stage but two factors were noticed which may contribute: (a) The photomicrographs of Crystals N_3 and N_4 [Fig. 4 (f)] show excessive "clumping" or agglomeration. (b) Brand S_1 or S_2 crystals appeared to be more easily wetted than N_3 or N_4.

Table VII—Effect of Particle Size on Initial Dissolution Rate for Encapsulated Pure Drug

Particle Size, μ	Initial Dissolution Rate, %/min.
>149	7.8
74 to 149	25.3
62 to 74	38.8
<62	43.0

In a recent paper by Aguiar *et al.* (18) a method for assessing the deaggregation rate of the contents of chloramphenicol capsules was described. They concluded that the rate of deaggregation limits the rate of dissolution of the contents of the commercially manufactured chloramphenicol capsules examined by them. The "clumping" or agglomeration of capsule contents, similar to that shown in Fig. 4 (f), probably affects in an adverse way the deaggregation rate and so effects a reduction in the observed dissolution rate. It has also been noted (20) that crystals which are good electrical insulators can build up a static charge during the milling process and, at some optimal size and charge, this can result in clumping. The effective surface area exposed to the dissolution media would thus be reduced compared to that of slightly larger particles with a smaller charge. The difference in agglomeration and wetting of the pure drug is possibly related to the method of crystallization or, perhaps, to a coating process,[2] which facilitates wetting, for Brand S.

When lactose was mixed with pure drug crystals and encapsulated, little effect on the dissolution rate was observed when up to 50% (wt./wt.) of lactose was present. A distinct decrease in dissolution rate was observed (see Fig. 3) when 80% (wt./wt.) of lactose was present and after 10 min. of the dissolution test an approximately linear rate of dissolution, equivalent to 0.14% per minute, was observed. Photomicrographs of commercially manufactured capsule contents [Fig. 4 (c, d, and e)] show that the particle size of the lactose is very much smaller (<10 μ) than any of the chloramphenicol crystals and that each of the latter have areas which are covered with lactose. It is not easy to account for the effect of lactose on dissolution rate but it is worth speculating that there may be intermolecular interaction between lactose and chloramphenicol or that the former contributes to the "gelatin capsule effect" referred to earlier. It is also possible that lactose, which would be expected to dissolve very rapidly in these tests (say in less than 2 min.) might effect the solvent properties of the dissolving medium sufficiently to effect the observed decreases in the dissolution rate of chloramphenicol.

The contents of Brand L capsules dissolved more slowly than any other brand examined (see Tables I and III). The pure drug sample

[2] The authors have no knowledge that Brand S crystals were coated. In a blind study Brands S_1 and S_2 were easily distinguished from all other brands, including N_3 and N_4, by dropping a small quantity of the crystals onto the surface of distilled water. Brands S_1 and S_2 spread rapidly over the surface of the water and then sank. Brands N_3 and N_4 and others remained as an aggregate lump on the surface.

obtained from this company, Brand *Q*, dissolved as fast as the majority of the other pure drug samples when placed in a gelatin capsule.

After 30 min. of the dissolution test, when the extent of dissolution was about 25% or less, the rate of dissolution of Brand *L* decreased until it was almost negligible (about 1%/hr.). This behavior was examined by following the dissolution profile for a period of 2 hr. Similar results were obtained for Brand *L* capsules when the dissolution was carried out in "single" or "six simultaneously" tests. The formulation of this brand of capsules was entirely different from any other examined. They were fabricated as soft elastic capsules containing a suspension of the crystalline drug in a viscous liquid [Fig. 4 (*g*)]. The liquid was shown to resemble paraffin oil when examined by IR spectroscopy. It is hardly to be expected that the heterogeneous phase, present in Brand *L* capsules, should behave in the same manner as that in the contents of the other formulations examined but visual observation of the dissolution process and the shape of the dissolution profile for these capsules allows some conclusions to be drawn concerning the involvement of the apparatus to the measured dissolution extent.

Visual inspection of capsules, other than Brand *L*, during dissolution tests revealed that the capsules floated for a brief period (2–5 min.) and that the gelatin container dissolved rapidly (in less than 5 min.) in most cases. During this period the solid contents were spilled into the dissolution medium then particles (or aggregates) of solid capsule content moved throughout the whole active volume. A few of the larger particles or aggregates fell to the bottom of the containing vessel but the piston-like action of the USP disintegration apparatus basket caused sufficient agitation to effect movement and dissolution of most of these during the 30 min. of the test. No effort was made to restrict the floating of capsules (*e.g.*, by the use of plungers) since it was felt that irregular impaction and adhesion of the gelatine would introduce irreproducible apparatus variables.

The soft gelatin container of Brand *L* capsules dissolved over a period of 20 min. of the test and the liquid contents were spilled slowly into the dissolving medium. The hydrophobic nature and specific gravity (>1) of the heterogeneous contents excluded intimate contact of all of the crystals of chloramphenicol with the solvent except during the period between release of the contents from the capsule and their deposition on the floor of the containing vessel. The limited agitation of the oily layer, containing crystalline chloramphenicol, at the bottom of the beaker, permitted only a very slow partition of chloramphenicol into the bulk of the dissolving medium.

In a separate and semiquantitative test, capsules of Brands B_2, *D*, and L_1 were placed in a 2-l. cylindrical glass jar which was completely filled with simulated gastric solution which had been warmed to 37°. The cylinder was rotated about a horizontal axis at right angles to its length at 50 r.p.m. so that a capsule prescribed an elliptical path through the solution and did not adhere to or come into contact with the walls of the vessel. The contents of Brand L_1 capsules, shortly after the gelatin had dissolved (about 3 min.) formed a homogeneous emulsion with the liquid contents of the cylinder. For Brands B_2 and *D*, the solid contents were released from the capsules within 5 min. and proceeded to follow elliptical paths of motion through the liquid. After 30 min. the rotation of the cylinder was stopped, a sample of solution was extracted and assayed, and the extent of dissolution was calculated. The percent dissolved for capsules of Brands B_2, *D*, and L_1 was found to be 82, 70, and 100%, respectively. Clearly, the much more rapid dissolution of the contents of Brand L_1 capsules in the "tumbling cylinder" apparatus was due to the more intimate exposure of the chloramphenicol crystals to the dissolving medium than was possible in the USP disintegration apparatus.

It can be seen, by inspection of Table III, that the inter-capsule variation in the percent dissolved at a given time may be quite large. For example in the case of Brand J_2 there is a standard deviation of as much as 23.6 in 29.5 after 10 min. Such variations would be masked by performing the "six simultaneously" dissolution test. In addition if only one "single" test was carried out then the results could be very misleading, compare for example Capsule No. 5 of H_2 with Capsule No. 3 of H_1 which reverses the order of the extent of dissolution. In cases where the standard deviation is small for "single" capsule data, the mean percent dissolved at a time, *t*, is always larger than for comparable data for "six simultaneously" tests. The reason for this is probably more complex but may result from the more rapid approach to saturation of the dissolution medium in the "six simultaneously" test. The aqueous solubility of chloramphenicol as determined by Weiss (19) was 2.5 mg./ml. at about 28°. The concentration of chloramphenicol in the dissolution medium reaches about 80% saturation after complete dissolution in the "six simultaneously" test and only about 13% saturation in the "single" capsule test. The medium also contains six times the concentration of gelatin and excipients (usually lactose), in the "six simultaneously" test, shortly after the test begins since these dissolve quickly.

A general conclusion, based on our experience with the USP disintegration apparatus, is that the dissolution of chloramphenicol from capsules occurs too quickly to allow hyperfine differentiation of the various formulations examined. Caution must be exercized in the use of parameters obtained from dissolution profiles. After 10 min. the influence of the gelatin capsule container is still significant, since there is a wide variation in the coefficients of variation for the percent dissolved in the "single capsule" tests presented in Table I. The wider variation in this parameter for pure drug capsules in the more detailed examination of the early stages of the dissolution process is given in Tables IV, V, and VI.

At 30 min. over 90% of the dissolution process was complete for more than half of the commercial brands which were examined. Inter-formulation differences in the percent dissolved at 30 min. are probably less desirable for quality control purposes owing to the small differences observed. Interpolated t_{50} or $\bar{t}_{50}$ values were included with other data since this is a common parameter used to define a rate process. Again, because the dissolution process is so fast, t_{50} values are too small and too imprecisely defined to be of practical value. More rigorous experimental control and a continuous recording of the dissolution process would be required if either of these parameters is to be considered in quality control standards. Probably the most reliable values are therefore those which represent the extent of dissolution which has occurred at 20 min.

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