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Variations in dissolution rates of sugar-coated chlorpromazine tablets

Sawsan Abd El-Fattah and Saleh A.H. Khalil

Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Alexandria (Egypt)

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Summary

The dissolution rates of 14 batches of sugar-coated chlorpromazine tablets (10, 25 and 100 mg) were examined by the U.S.P. method. Although all the batches passed the U.S.P. disintegration test in 0.1 N HCl, none passed the U.S.P. dissolution limit (not less than 80% dissolution after 30 min). Poor dissolution rates were ascribed to delayed break-up of the sugar-coat. The dissolution and dialysis rates of tablets of one batch were dependent on the medium composition suggesting possible drug–excipient interaction.

Introduction

Variations in the dissolution rates of drugs from coated tablets can be ascribed to formulation factors of the cores and/or the coat. Chlorpromazine tablets are either film-coated or sugar-coated tablets containing chlorpromazine hydrochloride in strengths of 10–100 mg per tablet. In view of the water-solubility of the drug, it may appear that drug release from the tablets poses no problem once the coat breaks-up. In the recent years a number of reports point to the problem of physical instability of sugar-coated tablets and consequent poor drug release. In most cases, decreased drug release was ascribed to poor break-up of the sub-coat (Barrett and Fell, 1975; Chapman et al., 1980). One report suggested that the insolubility of the sub-coat was due to an incompatibility between gelatin and calcium carbonate commonly used in

Correspondence: S.A.H. Khalil, Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt.

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the sub-coating step (Ray-Johnson and Jackson, 1976). In addition to the influence of the sugar-coat on drug release, drug–excipient interactions can affect drug availability from tablet cores. Measurements of the dialysis and permeation rates through membranes were used to assess this type of interactions (Nakano, 1971; Northern et al., 1973).

Limited studies have been carried out of the bioequivalency of chlorpromazine tablets and the use of dissolution rate testing as a screening tool for detecting bioavailability differences. Desta and Pernarowski (1973), following the observations of Bankier and Mathewson (1972), examined the dissolution rate characteristics of two clinically-different brands of chlorpromazine-HCl tablets. The two brands showed significant differences in the dissolution rates under various conditions of the test. Curry et al. (1974) evaluated the bioavailability of 4 samples of chlorpromazine tablets by in vitro dissolution tests and by measurements of the level of the unmetabolized drug in the plasma of psychiatric patients. The author concluded that dissolution testing was sufficient to detect differences in bioavailability of chlorpromazine tablets. In the study of Smolen et al. (1975), comparative bioavailability was assessed of oral chlorpromazine dosage forms. Differences in the bioavailability were found between liquid concentrate, syrup and tablets in the descending order.

Whilst the B.P. monograph of chlorpromazine tablets contains no dissolution test, the U.S.P. specifies that not less than 80% dissolution should occur after 30 min in 0.1 N HCl.

The objective of the present work has been to examine the dissolution rate profiles of some commercial batches of chlorpromazine tablets of differing strengths. An attempt was made to correlate the dissolution characteristics of the batches with their dates of manufacture, disintegration times and uniformity of drug contents. The data of dissolution and dialysis rates in various media have been compared for two batches.

Materials and Methods

Samples of 14 batches of 3 commercial brands of chlorpromazine tablets were purchased from local pharmacies. The dates of manufacture were obtained from the companies. All the tablets were sugar-coated and each batch was subjected to the following tests.

(1) Disintegration time

The U.S.P. procedure was used, the medium being 0.1 N HCl and a guided plastic disc was used. Single tablets were examined and the average time of 6 tablets was calculated. Disintegration times were also determined in water as the medium.

(2) Content uniformity

This was carried out using single tablets (10 determinations). Each tablet was ground and extracted with 0.1 N HCl and drug content was determined spectropho-

tometrically at 256 nm. For tablets of batches A100 and B100, the effect of water, 0.001 N and 0.01 N HCl as the extraction media, was studied.

(3) Dissolution testing

The U.S.P. procedure was used, but instead of 'the single point' determination at 30 min, samples were analyzed periodically over 60 min. For some batches, the dissolution period was extended to 4 h. The conditions of the test were: rotating basket at 50 ± 1 rpm and 900 ml of 0.1 N HCl maintained at 37 ± 0.2°C. Tablets of batches A100 and B100 were also examined in water, 0.01 N HCl and 0.1 M NaCl.

A 6-station dissolution tester with a sampling device was used (Dissoette, Model QC 72R24-6M, Hanson Research, CA, U.S.A.). Twelve runs were carried out to enable the assessment of tablet-to-tablet dissolution variability within the same batch.

(4) Dialysis rates

These were measured using tablet grinds of batches A100 and B100. Chlorpromazine hydrochloride powder (B.P.) was used as a reference (100 mg in 5 ml of the medium). In the test, one tablet (containing 100 mg drug) was ground into a fine powder and suspended in 5 ml of either water (pH 5.8), 0.01 N HCl (pH 2.2), 0.1 N HCl (pH 1.2) or 0.1 M NaCl in water (pH 6.6). The suspension was transferred into a dialysis bag (10 cm in length) made from spectrapor membrane tubing (dry cylinder diameter 16 mm, dry thickness 0.0008 inch, Fisher Scientific, PA, U.S.A.). The dialysis bag was attached to the shaft of the U.S.P. dissolution apparatus rotating at 50 rpm. The contents were dialyzed against 900 ml of a medium of the same composition to that inside the bag. Dialysis rates were determined at 37 ± 0.2°C and at specified time intervals samples from the outside solutions were analyzed for drug contents at 256 nm. At least 3 replicate runs were carried out and the results averaged.

Results and Discussion

Figs. 1 and 2 show the dissolution rate plots of the 14 batches examined. Significant variations in both the rates and extents of drug dissolution were observed between the batches but none passed the U.S.P. dissolution limit (not less than 80% dissolution after 30 min).

Table 1 shows the dates of manufacture, contents uniformity and percentages dissolution after 30 min. Whilst all the batches complied with the U.S.P. tests for disintegration time and content uniformity, percentages dissolution after 30 min (the U.S.P. sampling time) differed significantly; the values obtained ranged from 1.6 to 77.8. Only tablets of batches A100 and B100 gave almost complete drug release after 1 h (Fig. 1). Some batches failed to release their drug contents over a period of 4 h in 0.1 N HCl; tablets of batch B_1 (Fig. 2_1) released only 69%. Inter-tablet dissolution variability within the same batch was assessed through percentages dissolution after 30 min of the 12 replicates. Representative data are shown in Fig. 3 for batches

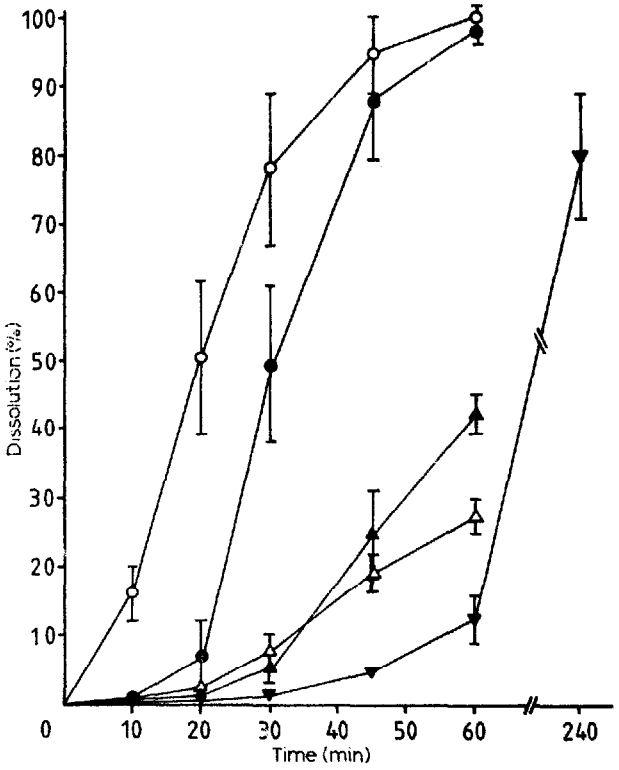

Fig. 1. Dissolution rates of chlorpromazine-HCl (100 mg) tablets. Batches: ○, A100; ●, B100; ▲, C_2; △, C_3; and ▼, C_1; in 0.1 N HCl at 37±0.2°C.

A100 and B100. Calculation of the coefficients of variation revealed significant tablet-to-tablet dissolution variability of most of the batches examined (last column of Table 1). However, no correlation was found between the extent of dissolution of a batch and the value of coefficient of variation.

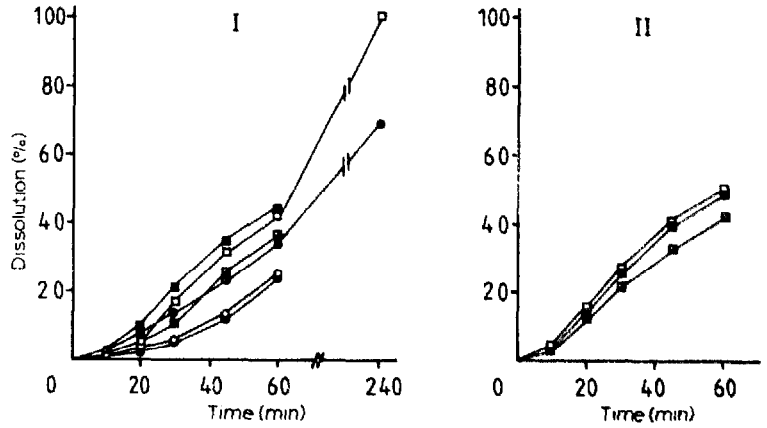

Fig. 2. Dissolution rates of chlorpromazine-HCl tablets in 0.1 N HCl at 37±0.2°C. (I) 25 mg tablets, batches: ■, C_2; □, C_1; ◪, C_3; ◑, B_1; ○, B_3; and ●, B_2. (II) 10 mg tablets, batches: □, C_1; ■, C_2; and ◪, C_3.

TABLE 1

DATES OF MANUFACTURE, CONTENTS UNIFORMITY AND PERCENTAGES DISSOLUTION AFTER 30 min OF SOME BATCHES OF SUGAR-COATED CHLORPROMAZINE HYDROCHLORIDE TABLETS, BRANDS A, B AND C *

Batch [a]	Date of manufacture	Content uniformity (Range %) [b]	Percent dissolution after 30 min (±S.E) [c]	Coefficient of variation ×100
A100	Not available	93.0–100	77.8 (6.3)	28.1
B100	May 1982	89.0– 97.0	49.4 (6.6)	46.0
C_1100	March 80	93.5–103.0	1.6 (0.3)	52.4
C_2100	Nov. 80	89.0– 96.0	5.5 (1.3)	81.6
C_3100	May 82	85.0– 92.0	8.3 (1.2)	50.3
$B_1 25$	July 1980	88.6– 95.0	13.4 (3.4)	87.6
$B_2 25$	Oct. 79	92.4–104.0	5.6 (1.7)	108.3
$B_3 25$	Feb. 82	94.4–106.5	6.2 (1.4)	79.0
$C_1 25$	Sep. 79	89.7–104.0	16.9 (1.0)	20.8
$C_2 25$	Jan. 81	88.6– 95.7	21.1 (0.7)	11.2
$C_3 25$	March 82	85.0– 92.0	11.0 (1.9)	60.5
$C_1 10$	Nov. 1981	85.6– 98.5	27.3 (3.0)	38.2
$C_2 10$	March 82	87.0–107.0	25.8 (4.1)	55.4
$C_3 10$	Oct. 82	87.0–97.0	21.8 (0.6)	8.7

[a] A, B and C are the brands; 100, 25 and 10 represent the strengths of the tablets in (mg), sub-scripts 1, 2 and 3 are the batch numbers.

[b] In 0.1 N HCl (10 determinations).

[c] Mean of 12 runs ± standard error of the mean.

* Brand A: Largactil tablets by May & Baker Ltd., Dagenham, U.K.
Brand B: Neurazine tablets by Misr Co. for Pharmaceutical Industries, Cairo, Egypt.
Brand C: Promacid tablets by Chemical Industries and Development, Giza, Egypt.

Eleven of the 14 batches examined were manufactured between March 1980 and October 1982 and this study was completed in March 1983. Therefore some of the batches were 5–36 months old; nevertheless poor dissolution characteristics were observed in most of the batches irrespective of their ages.

In most cases, dissolution failure was associated with non-disintegration of the tablets during the dissolution test, some remained intact at the end of the run. It must be emphasized that all the batches passed the U.S.P. disintegration test in 0.1 N HCl (the same medium of the dissolution test); disintegration was complete within 30 min. It follows, therefore, that no correlation existed between disintegration times and dissolution rates for the batches of chlorpromazine tablets studied. The up and down movement and the use of the guided disc in the disintegration test enhanced the break-up of the tablets.

Fig. 4 shows the effect of medium composition on the dissolution rates of the relatively fast-dissolving batches A100 and B100. Tablets of batch A100 showed similar dissolution rates in the 3 media: water, 0.1 N HCl and 0.1 M NaCl. The dissolution rates of batch B100, however, were dependent on the medium used (Fig. 4B). Whilst almost no drug was released within 1 h in water, 0.01 N HCl and 0.1 M NaCl, about 97% dissolution occurred in 0.1 N HCl. This was due to the failure of

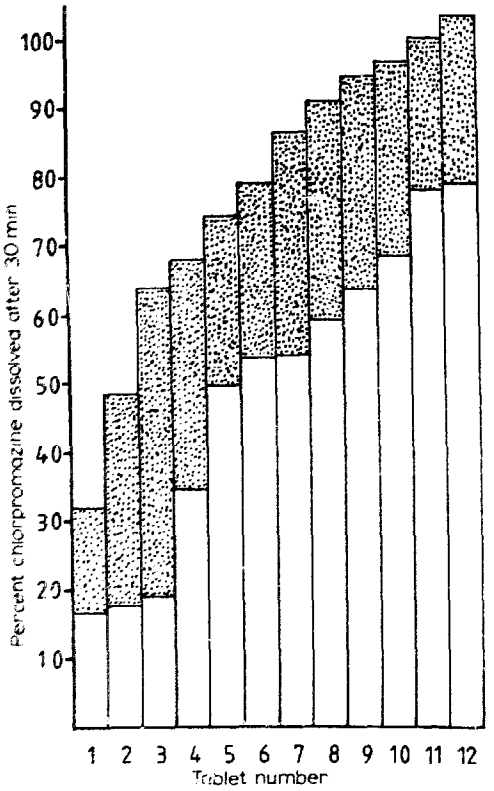

Fig. 3. Inter-tablet dissolution variability after 30 min in 0.1 N HCl; ▨, batch A100; □, batch B100.

the tablets of this batch to break-up in both water and 0.1 M NaCl during dissolution testing. In 0.1 N HCl, the tablets readily disintegrated.

The effect of medium composition similarly affected tablets of batch B100 during content uniformity testing (Table 2). Only partial extraction of the water-soluble drug occurred when tablet grinds of this batch were extracted with water or 0.001 N

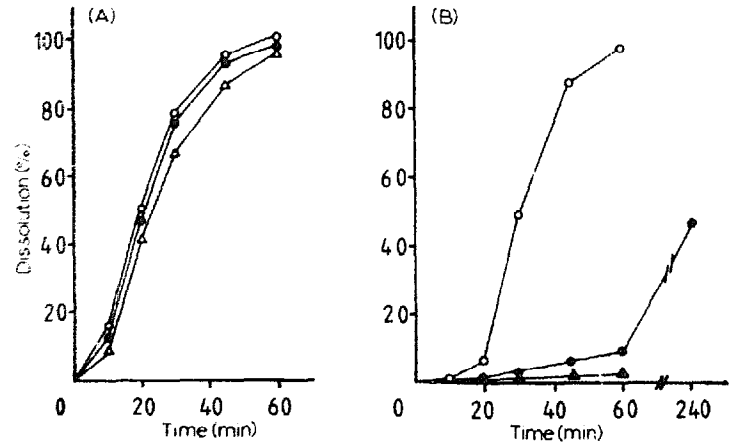

Fig. 4. Effect of medium on dissolution rates of batches A100 (A) and B100 (B) in ○, 0.1 N HCl; ●, 0.1 M NaCl; △, water: and ◑, 0.01 N HCl.

TABLE 2

EFFECT OF MEDIUM COMPOSITION ON PERCENT CHLORPROMAZINE HYDROCHLORIDE EXTRACTED DURING CONTENT UNIFORMITY TESTING OF TABLETS OF BATCHES A100 AND B100 (10 DETERMINATIONS)

Medium	Range of chlorpromazine-HCl extracted (%)	
	Batch A100	Batch B100
Water	88.6– 97.8	37.0–49.0
0.001 N HCl	99.5–102.0	57.6–64.0
0.01 N HCl	98.0–100.0	85.0–98.0
0.1 N HCl	93.0–100.0	89.0–97.0

HCl. The pH values of the extracts were 6.6 and 6.2, respectively. The elevation of the pH value (when 0.001 N HCl was used) from 3.2 to 6.2 indicates possible presence of excipient(s) that neutralized the acidity. In 0.01 and 0.1 N HCl, higher percentages recovery were obtained. Tablets of batch A100 gave almost complete drug extraction irrespective of medium composition (Table 2). When 0.001 N HCl was used, the extract had the same initial pH value (3.2).

The failure of tablets of batch B100 to disintegrate and to release the drug in water pointed to possible drug–excipient interaction; the level of which appeared to be dependent on the medium composition. To test this point, dialysis rates were measured of tablet grinds of batches A100 and B100 in water, 0.1 M NaCl, 0.01 N HCl and 0.1 N HCl. A solution of chlorpromazine hydrochloride (100 mg in 5 ml of the medium) was used as a reference. The results obtained are shown as first-order plots of log-percent drug to be dialyzed versus time (Fig. 5). The slopes and dialysis rate constants (K_d, h^{-1}) are shown in Table 3. The effect of medium composition was the same for batch A100 and the standard drug solution but not for batch B100. Figure 5_I and 5_{III} clearly indicates the resemblance of the effect of medium on

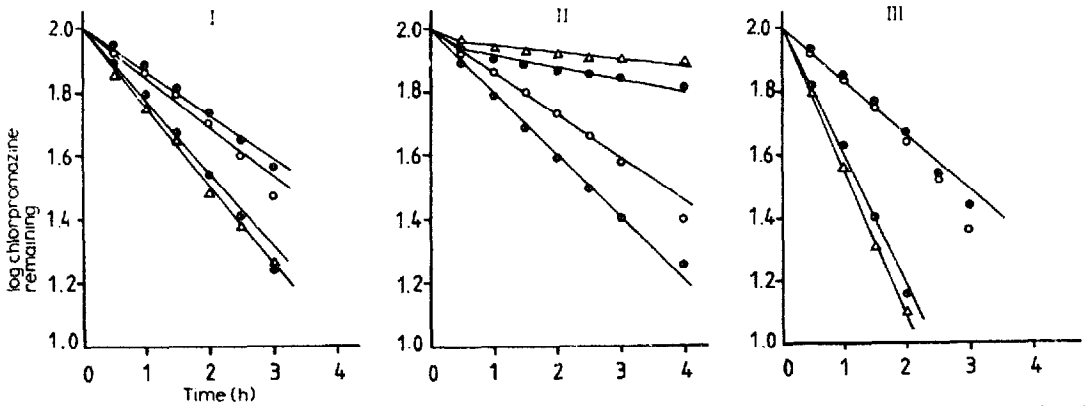

Fig. 5. First-order plots for dialysis rates of chlorpromazine-HCl at 37±0.2°C from tablet grinds of batches A100 (I) and B100 (II). B.P. powder (III) in the media: ●, 0.1 M NaCl; ○, 0.1 N HCl; ◑, 0.01 N HCl; and △, water.

TABLE 3

THE SLOPES AND DIALYSIS RATE CONSTANTS (K_d, h^{-1}) DETERMINED FROM THE FIRST-ORDER PLOTS FOR DIALYSIS OF CHLORPROMAZINE HYDROCHLORIDE FROM B.P. POWDER AND TABLET GRINDS OF BATCHES A AND B (100 mg STRENGTH) IN VARIOUS MEDIA AT 37 ± 0.2°C

Medium	B.P. Powder		Batch A100		Batch B100	
	Slope	K_d	Slope	K_d	Slope	K_d
Water	−0.387	0.890 (0.0035) [a]	−0.239	0.550 (0.034)	−0.021	0.048 (0.016)
0.01 N HCl	−0.523	1.204 (0.0185)	−0.258	0.594 (0.0075)	−0.197	0.454 (0.032)
0.1 N HCl	−0.220	0.507 (0.021)	−0.179	0.412 (0.028)	−0.142	0.327 (0.032)
0.1 M NaCl	−0.201	0.463 (0.024)	−0.152	0.350 (0.029)	−0.034	0.078 (0.014)

[a] Figures in parentheses are ± standard errors of the mean (n = 3).

dialysis rates; water and 0.01 N HCl gave almost identical dialysis rates in case of batch A100 and the standard drug solution. Also identical dialysis rates were obtained in 0.1 N HCl and 0.1 M NaCl, and in these two media the rates were much lower than in water or 0.01 N HCl. This can be explained on the basis of the effect of chloride ions on the micellar aggregation of chlorpromazine hydrochloride (Thoma and Arning, 1976). A previous study (Nambu et al., 1971) showed that the permeation rates, through cellulose membranes, of phenothiazines (including chlorpromazine) depended on their molecular weights; decreased permeability occurred with an increase in molecular weight. The 'aggregating' effect of chloride ions would, therefore, slow down the dialysis rates. Equimolar chloride ions concentration would have the same effect. This was found to be the case for 0.1 N HCl and 0.1 M NaCl (Fig. 5_{I} and 5_{III}). The pH of 0.1 M NaCl was 6.6, i.e. below the critical pH values for possible precipitation of chlorpromazine (D'Arcy and Thompson, 1973). Also, the salting-out effect is ruled out at this sodium chloride concentration (0.585%) in view of the high water-solubility of chlorpromazine hydrochloride (Miyazaki et al., 1981). Dialysis rates of tablet grinds of batch B100 depended on medium composition but not in the same way as was observed for batch A100 or the standard drug solution. Water in which the dialysis rates were fastest for batch A100, yielded the slowest dialysis rates for tablet grinds of batch B100. In 0.1 M NaCl, the rates were also slow. The effect of chloride ions is clearly shown when data in 0.01 N and 0.1 N HCl are compared (Fig. 5_{II}). The slow dialysis rates in water is due to a possible drug–excipient interaction in the tablet grinds which was favoured at relatively high pH values.

No relationship was found between dissolution and dialysis data. This is evidenced from a comparison of Figs. 4A and 5_{I} for batch A100. Needless to say that the 'aggregating effect' of chloride ions on chlorpromazine hydrochloride cannot be detected by the U.S.P. dissolution apparatus, but was clearly shown in the dialysis rates.

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