DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 12(14), 2431-2442 (1986)

DISSOLUTION PROFILING OF SIX MODIFIED-RELEASE ORAL SOLID DOSAGE FORMS

R. Baweja
School of Pharmacy
University of Wyoming
Laramie, Wyoming 82071

ABSTRACT

Dissolution testing was conducted for six non-combination, single entity, modified-release oral solid dosage forms. Dissolution medium was water and 0.1 N hydrochloric acid. USP Apparatus 1 and Apparatus 2 were used and were rotated at either 50 or 100 rpm. A complete dissolution profile was obtained for all six dosage forms based on their stated dosing interval, D. The three strengths of Theo-dur tablets, Norpace CR 150 mg capsules, and the two strengths of Chlor-trimeton tablets passed the Compendial Case One requirements (USP XXI, 2S, 1906). Thorazine spansules and Quinidex tablets were unable to meet the specifications with water as the dissolution medium; the latter showed improved dissolution character in 0.1 N hydrochloric acid. Tenuate Dospan 75 mg tablets showed good release characteristics in water when the authentic dosing interval (D = 24

0363-9045/86/1214-2431$3.50/0

hours) was changed to a modified dosing interval of D* = 12 hours. All dissolution aliquots were assayed by UV absorbance measurements at the absorbance maximum for each drug and were also checked for excipient interference. Newer drugs appearing on the market will be more likely candidates for meeting compendial specifications; modified-release pharmaceuticals that appeared before the new specifications may have to be allocated specifically expanded window percentages.

INTRODUCTION

Tablets and capsules representing oral solid dosage forms make up about 85% of the Pharmaceutical products on the market (1). In the 1960s it became apparent that the dissolution of a drug was a better scientific measure of bioavailability (2). Modern pharmaceutical technology makes possible the design of dosage forms that modify bioavailability of a drug into the blood stream in addition to being vehicles for storage, portability, and administration. For drugs formulated into modified-release dosage forms it is also well known that 'in vitro' dissolution data by itself cannot be used as a predictor of 'in vivo' performance. Dissolution testing, however, is useful and valid as a primary quality control procedure; in product development studies; and in the demonstration of differences among products of various manufacturers. Therefore, with the growing interest and potential for modified-release formulations, the Compendia set some definitions in order and have now provided procedures for their dissolution.

The present study was undertaken for the six top-selling single entity oral solid dosage forms and the purpose was to ascertain the compendial conformity of these formulations.

MATERIALS AND METHODS

The reference standard chemicals were theophylline (Sigma Chemical, Lot No. 54F-0178), disopyramide phosphate (Lot No. 296), chlorpromazine hydrochloride (Lot No. 22-OTZ), quinidine sulfate (Lot No. 32219), diethylpropion hydrochloride (Lot No. 5205A) and chlorpheniramine maleate (Lot No. 4-CMG-162-A). Except for theophylline, all chemicals were complimentary. Theo-Dur 100 mg tablets (Key Pharmaceuticals, Lot No. 424891), Theo-Dur 200 mg tablets (Key, Lot No. 410391), Theo-Dur 300 mg tablets (Key, Lot No. 433921), Chlor-trimeton 8 mg Repetabs (Schering Corporation, Lot No. 3CC14) and Chlor-trimeton 12 mg Repetabs (Schering, Lot No. 3AAE7), were purchased on the open market. Norpace CR 150 mg Capsules (G.D. Searle, Lot No. 384039), Thorazine 150 mg Spansules (Smith, Kline and Beckman, Lot No. 1012T66), Thorazine 200 mg (SKB, Lot No. 2013T67RD), Quinidex 300 mg Extentabs (A.H. Robins, Lot No. 3315), and Tenuate Dospan 75 mg Tablets (Merrell Dow, Lot No. 1200 SF) were kindly provided by the respective pharmaceutical companies. Water was prepared by a commercial deionization process (Barnsted Corporation). Hydrochloric acid (J.T. Baker Co., Lot No. 112074) was reagent grade. All reference standard samples and reagents were used without further purification.

Preliminary testing was conducted using reference standards of each drug to obtain Beer's Law plots to ascertain that a linear

relationship exists between UV absorbance at the maximum and the assay concentration.

Dissolution testing was performed on a calibrated Hanson Dissolution Tester (Model 72-RL-115). Quinidex Extentabs, Tenuate Dospan tablets, and both strengths of Chlor-trimeton Repetabs were subjected to dissolution testing using paddle (Apparatus 2) at 50 rpm. All other formulations were subjected to dissolution testing with basket (Apparatus 1) at 100 rpm. In all runs, 1000 ml of medium (water or 0.1 N hydrochloric acid) was placed in each of the six flasks, and equilibrated to 37°C. Glass syringes were used to withdraw dissolution aliquots and the samples were filtered using Gelman GA-6 filters. Sampling intervals as per compendial criterion were 0.25 D, 0.50 D, and 1.0 D, where D is the dosing interval of the drug in hours. UV absorbance measurements at the maximum were obtained on the Beckman 25 spectrophotometer using 1-cm cells. Dissolution testing was performed in duplicate, in other words, the average percentage of a drug dissolved at a specified time was obtained from twelve aliquots. Absence of excipient interference to the analytical technique was checked for each drug.

RESULTS

The determination of Beer's Law plots using Reference Standards was to ascertain that a linear relationship exists between UV absorbance at the maximum and the assay concentration; correlation coefficient of 0.999 or better being the acceptable limit.

Table 1

Average Percentage of Drug Dissolved in 1000 ml of Water at 37°C

Drug	Dosing Interval, D (hours)	Average[a] Percent Dissolved ± S.D.% 0.25D	0.50D	1.00D
Theo-Dur 100mg Tablets	12	40 ± 5	54 ± 6	83 ± 7
Theo-Dur 200mg Tablets	12	28 ± 4	58 ± 8	92 ± 7
Theo-Dur 300mg Tablets	12	24 ± 2	42 ± 5	88 ± 4
Norpace CR 150mg Capsules	12	33 ± 2	57 ± 3	85 ± 4
Thorazine 150mg Spansules	24	59 ± 3	76 ± 4	86 ± 6
Thorazine 200mg Spansules	24	61 ± 3	76 ± 3	95 ± 3
Quinidex 300mg Extentabs	8	25 ± 3	29 ± 2	39 ± 1
Quinidex 300mg Extentabs[b]	8	39 ± 2	51 ± 2	71 ± 2
Tenuate Dospan 75mg Tablets	24	82 ± 3	112 ± 4	118 ± 2
Tenuate Dospan 75mg Tablets	12	53 ± 2	86 ± 4	114 ± 2
Chlor-trimeton 8mg Repetabs	12	49 ± 4	57 ± 9	84 ± 14
Chlor-trimeton 12mg Repetabs	12	49 ± 2	54 ± 6	96 ± 11

[a] n = 12 units
[b] Dissolution medium is 0.1 N hydrochloric acid.

Case One conditions for dissolution are met when water is the medium and the drug dissolution percentage falls into the following profile (3):

At a time equal to 0.25 D, between 20% and 50% of the labeled amount is dissolved, and

At a time equal to 0.50 D, between 45% and 75% of the labeled amount is dissolved, and

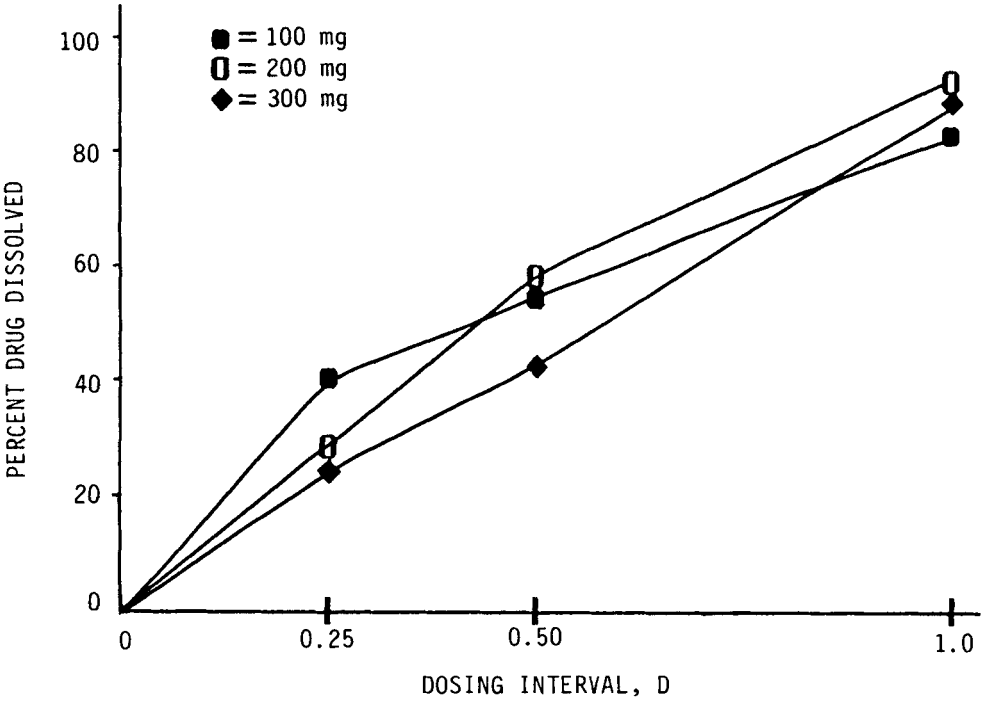

FIGURE 1

Average percentage of theophylline dissolved from Theo-dur® tablets in 1000 ml of water

Thereafter at any time up to 1.0 D, not less than 75% of the labeled amount is dissolved.

Case Two applies where the chemistry or physical characteristics of a drug or formulation do not allow the application of Case One. Examples of this case are (a) that the drug release characteristics are over a time period less than the dosing interval, D; (b) the medium be changed from water to any other medium, e.g., 0.1 N hydrochloric acid or 0.05 M phosphate buffer.

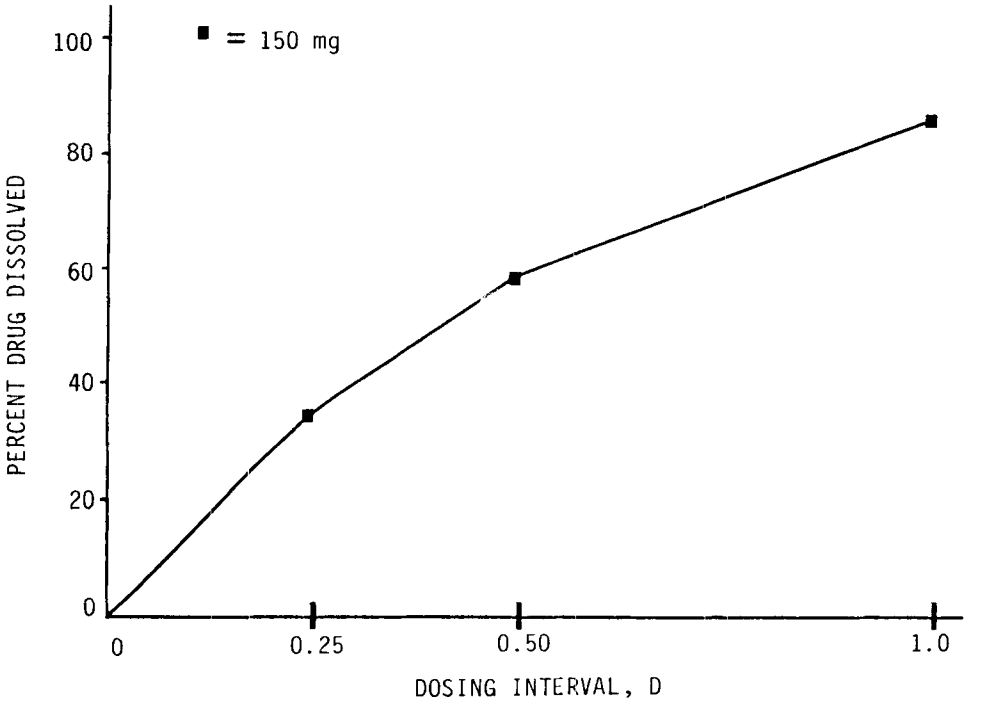

FIGURE 2

Average percentage of disopyramide phosphate dissolved from Norpace CR® 150 mg capsules in 1000 ml of water

Table 1 shows the average percent of a drug dissolved at three testing points, i.e., 0.25 D, 0.5 D, and 1.0 D. The three strengths of Theo-Dur tablets, Norpace CR 150 mg capsules, and the two strengths of Chlor-trimeton tablets passed the dissolution profiling based on Case One conditions, thereby satisfying compendial objectives (Figures 1-3). For Theo-Dur 100 mg and 200 mg strengths the unit-to-unit variation was slightly high whereas Norpace CR 150 mg capsules showed considerably lower unit-to-unit digression. Statistically Chlor-trimeton 8 mg and 12 mg tablets also met Case One criterion. For both strengths the unit-to-unit

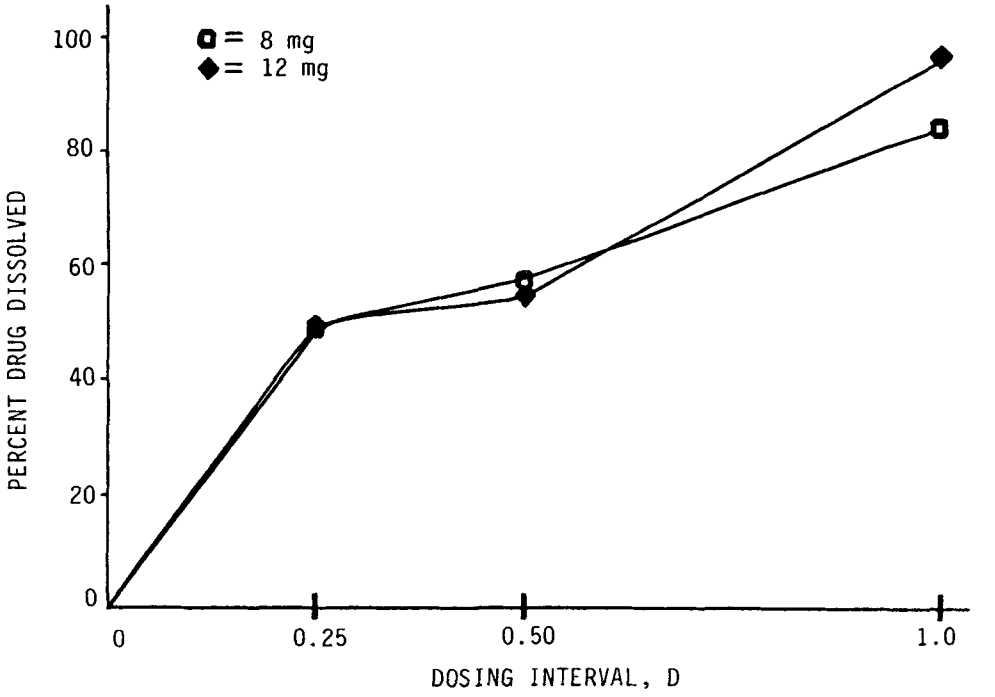

FIGURE 3

Average percentage of chlorpheniramine maleate dissolved from Chlor-trimeton Repetabs® in 1000 ml of water

variation was high at the final sampling point, i.e., 1.0 D. Thorazine 150 mg and 200 mg capsules were close to meeting Case One objectives; the first testing point (0.25 D) showed 59% and 61% of the drug dissolved respectively (Figure 4). In other words, thorazine spansules released more drug by 0.25 D than what the compendia stipulates, i.e., 20-50%. The later sampling points were statistically in adherence to the specifications. Quinidex 300 mg Extentabs were unable to show a progressive dissolution profile in water (Figure 5). Replacing water with 0.1 N

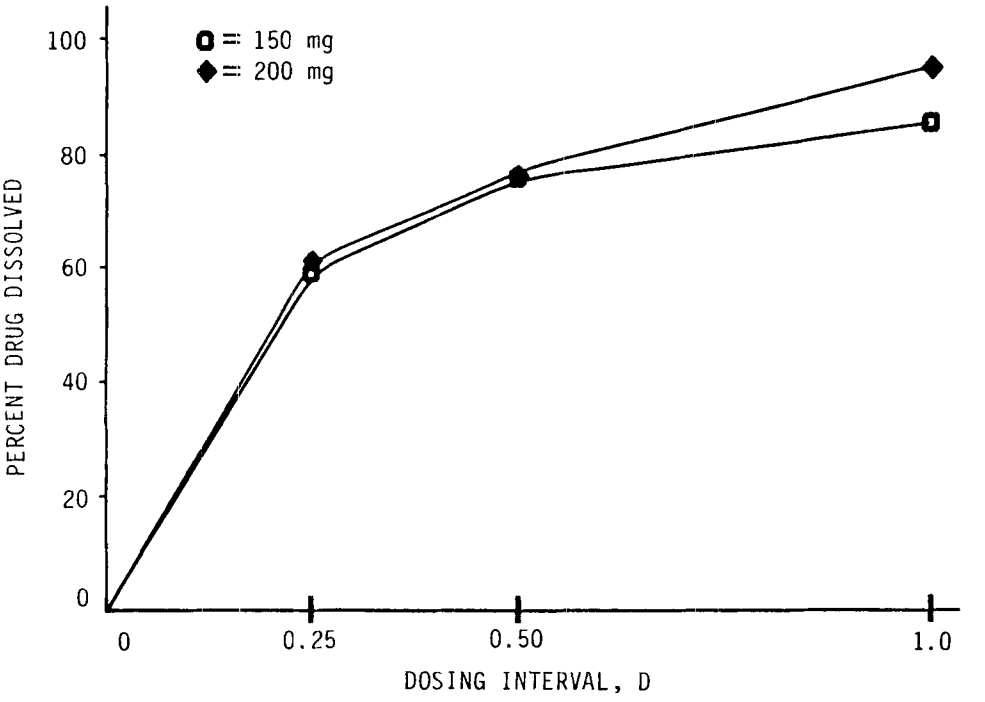

FIGURE 4

Average percentage of chlorpromazine hydrochloride dissolved from Thorazine spansules® in 1000 ml of water

hydrochloric acid helped the dissolution process to the extent where it could be inferred that quinidine sulfate tablets should be tested in the acidic medium where they appear to satisfy Case Two requirements. Tenuate Dospan 75 mg tablets showed a large amount (82%) of the label claim dissolved at 0.25 D (6 hours; based on D = 24 hours) (Figure 6). When the dosing interval was changed (for testing purposes) from D = 24 hours to a D^* = 12 hours, the inference that could now be drawn is that almost 100% of the drug dissolves in about 6-8 hours and then a plateauing effect for this percentage is observed for 24 hours.

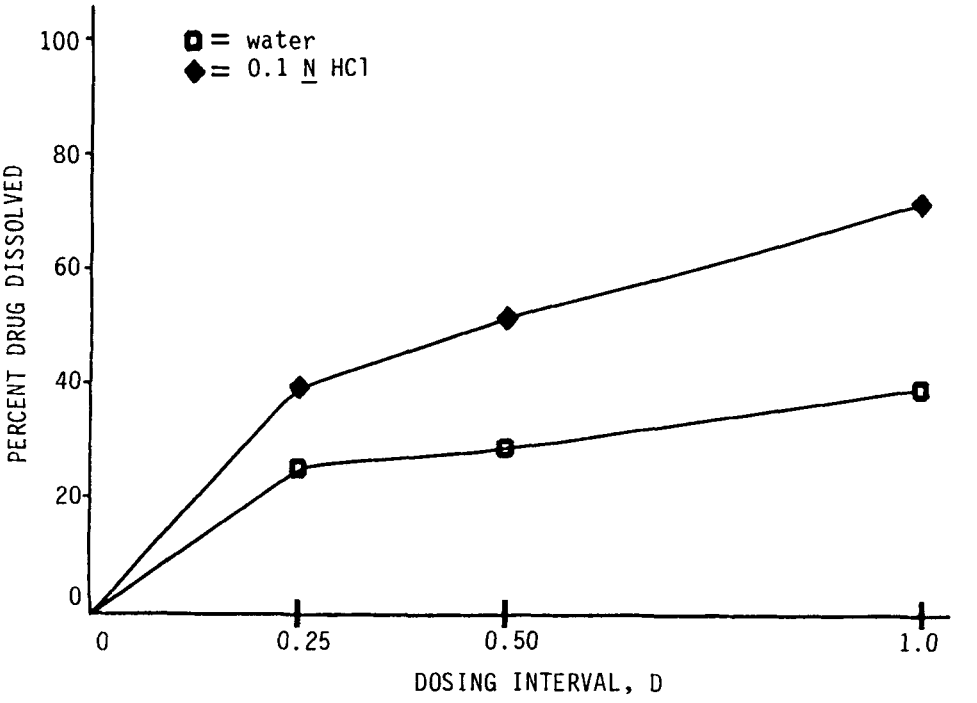

FIGURE 5

Average percentage of quinidine sulfate dissolved from Quinidex 300 mg Extentabs® in 1000 ml of medium

DISCUSSION

It is well documented and understood that before any bioequivalency and clinical studies are conducted, dissolution testing provides for an excellent screening procedure, as well as a mechanism for making changes in the formulation of modified-release oral solid dosage forms. The compendia believe that regardless of whether a Case One or a Case Two objective is met, all modified-release oral solid dosage forms must pass the window profiling of dissolution testing. The philosophy probably is two-fold: (a) let there be no dose-dumping at the first sampling

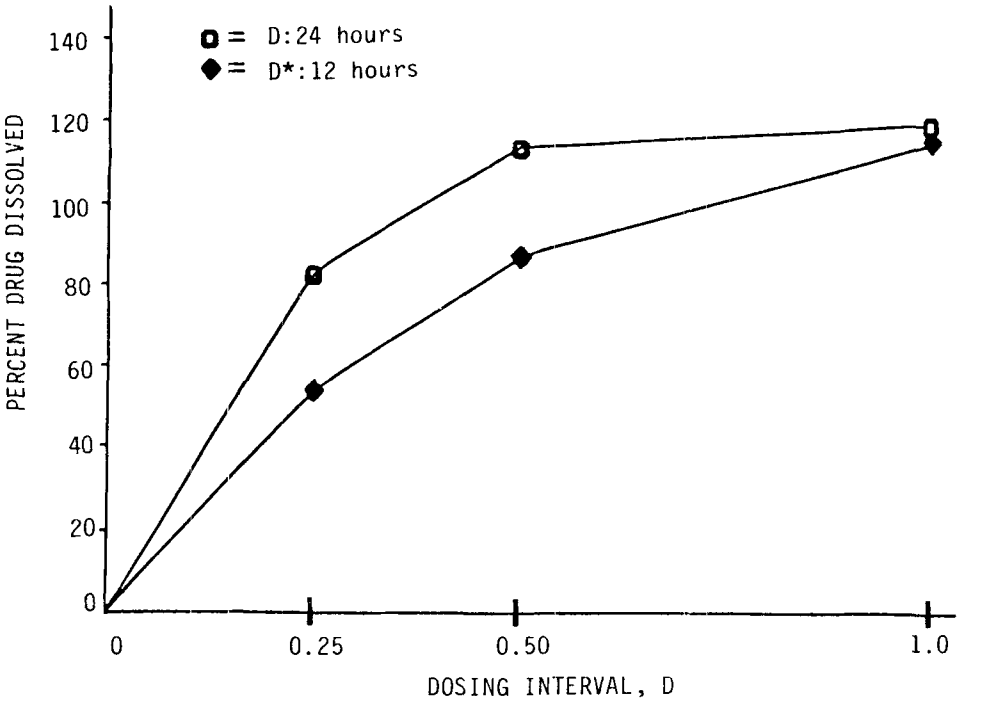

FIGURE 6

Average percentage of diethylpropion hydrochloride dissolved from Tenuate Dospan® 75 mg tablets in 1000 ml of water

point; and (b) that at the 1.0 D time point, at least 75% of the label claim is released and therefore available for physiological absorption. While this approach makes for setting uniform standards, it does not appear feasible from an industry -- manufacturer's viewpoint. The basic objective for modified-release dosage forms is to meet convenience and therapeutic objectives not offered by conventional dosage forms. For Thorazine spansules the basic objective may be to release a large amount of the drug initially (61% of the label claim at 0.25 D), thereafter release the drug gradually over the full time course. Similarly, Tenuate

Dospan tablets used as a diet suppresant may have 'formulation -- dissolution character' relevant to the initial hours after intake (D^*) rather than the full dosing interval of D = 24 hours. Quinidex 300 mg Extentabs satisfy the stipulation by exhibiting a strong and a complete profile in 0.1 N hydrochloric acid thereby meeting Case Two requirements. It should be pointed out that drugs that did pass the compendial windows profiling characteristics are new formulations that appeared on the market in the early 1980s. This may provide a basis for their formulation and dissolution character meeting official specifications. In other words, these products probably satisfy both compendial standards and dosage form design objectives. New modified-release drugs appearing on the market will be more likely candidates for meeting dissolution profiles; formulations before 1980 may have to be allocated specially expanded window percentages.

ACKNOWLEDGEMENTS

The author is grateful to Mr. Robert Burdett for the technical assistance.

REFERENCES

1. R.E. King, (Ed.): "Dispensing of Medication," Mack Publishing Company, Easton, PA, 1984.

2. A.R. Gennaro, (Ed.): "Remington's Pharmaceutical Sciences," Mack Publishing Company, Easton, PA, 1985.

3. The United States Pharmacopeia, XXI Revision, The United States Pharmacopeial Convention, Inc., Rockville, MD, 1985.

4. J.W. McGinity, C.G. Cameron and G.W. Cuff, Drug Devel. Indust. Pharm., 9, 57 (1983).

5. R. Groning, Drug Devel. Indust. Pharm., 6, 475 (1980).