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COMPARISON OF THREE DISSOLUTION DEVICES FOR EVALUATING DRUG RELEASE

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ABSTRACT

The dissolution studies are usually conducted on "official" USP dissolution devices or "non-official" dissolution devices like the Rotating Bottle Apparatus. The recent introduction of the Bio-Dis® Tester exacerbates a difficult situation : no comparative dissolution studies have been done regarding the results for a drug and/or dosage form using these three different instruments. The purpose of this investigation was to evaluate and compare three dissolution devices - USP XXI Dissolution Apparatus II, Rotating Bottle Apparatus, and Bio-Dis® Tester - taking into account pertinent factors that can affect dissolution. Dissolution profiles were obtained for two drugs - theophylline and phenylpropanolamine HCl. Three dosage forms of each drug were evaluated at different agitation intensities using two different dissolution media (simulated gastric fluid and simulated intestinal fluid) on all three dissolution devices. Various advantages/limitations for each device were observed depending on the drug, dosage form, agitation speed and dissolution medium.

INTRODUCTION

The in vitro dissolution of drug from dosage forms is employed either as a primary aid in the characterization of formulations or as a quality control procedure for monitoring the uniformity and reproducibility of production batches, or both[1]. The in vitro dissolution profiles have also been used in an attempt to characterize the in vivo behavior of drugs, with little success[2-7].

The USP now recognizes seven devices as being "official" for dissolution testing[8]. Three of these devices are specifically designed for transdermal patches (Apparatus V, VI, VII). The other four (Apparatus I, II, III, IV) are intended to evaluate all dosage forms, no matter what the drug or the type of dosage form to be tested. With the wide variety of dosage forms being produced, most notable being the multiplicity of controlled release dosage forms on the market, the USP Dissolution Apparatus (I or II) is inadequate for all desired dissolution studies. In addition to the USP Dissolution Apparatus I and II, the Rotating Bottle Apparatus, which is nonofficial, has been used for many years, having been designed specifically for controlled release formulations. The recent introduction of the Bio-Dis Tester® (suggested as Apparatus III for solid dosage forms and also with appropriate disk attachment conforms to Apparatus VII criteria for patches) exacerbates a difficult situation, that is, no comparative dissolution studies (except one by Esbelin et al [9]) have been done regarding the results for a drug and/or dosage form using these three different instruments nor has research been conducted to demonstrate the need for different dissolution devices for different dosage forms.

It has been previously determined[10,11] that the factors that affect the dissolution profiles of dosage forms are due to the apparatus (such as structural design of the apparatus, type of agitation, speed of agitation), dissolution medium (including volume, sink or nonsink conditions, composition, pH, temperature), and other miscellaneous factors (including the sampling time and technique; shape, size, and type of dosage form, physicochemical properties of the drug, and the analysis procedure).

This study is aimed at evaluating and comparing all three dissolution devices, taking into account pertinent factors that can affect dissolution.

Dissolution profiles of two model drugs, one slightly soluble in water (theophylline) and one freely soluble in water (phenylpropanolamine HCl) from three different commercially available dosage forms of each were evaluated, one immediate release product and two different controlled-release products.

MATERIALS AND METHODS

Drug and Dosage forms :

Commercially available dosage forms were obtained for evaluation. As this is not intended to be a commercial evaluation of these dosage forms, the brand names and manufacturers will not be listed, only a description of the type of dosage forms and intended pattern of drug release.

I. Phenylpropanolamine HCl (Solubility in water : 1g/1.1 mL, pK_a : 9.04)

a. Immediate Release Capsules - 37.5 mg per capsule (Beads)
b. Timed Release Capsules - 75 mg per capsule (Coated Beads)
c. Precision Release Tablets - 75 mg per tablet (Osmotic pump type)

II. Theophylline (Solubility in water : 1g/120 mL, pK_a : 8.77)

a. Immediate release tablets - 100 mg per tablet (Compressed tablet)
b. Sustained Action Tablets - 100 mg per tablet (Matrix type)
c. Timed Release Capsules - 100 mg per capsule (Beads)

Instrumentation :

a. USP Six Spindle Dissolution Tester (Paddle-type) (Vanderkamp® 600 - VanKel Industries, Chatham , N.J.)
b. Vanderkamp® Sustained Release Apparatus (Rotating Bottle - VanKel Industries, Chatham , N.J.)
c. Bio-Dis Tester (Version 1, VanKel Industries, Chatham , N.J.)
d. IBM UV-Visible Spectrophotometer 9430.

Dissolution Studies :

The dissolution profiles (each data point is the mean of 3 values) of the various dosage forms containing theophylline and phenylpropanolamine HCl

were studied using the USP Dissolution Apparatus II (paddle method), Rotating Bottle Apparatus, and the Bio-Dis Sustained Release Apparatus, each fitted with a constant temperature bath set at 37°± 0.5° C.

Two different dissolution media, Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF), were used for dissolution studies. The composition of SGF (pH 1.2) per liter is as follows : Sodium Chloride (2.0 g), Concentrated Hydrochloric Acid (7.0 mL) and Tween 80 (0.2 mL). The composition of SIF (pH 7.4) per liter is as follows : Potassium Phosphate Monobasic (6.80 g), Sodium Hydroxide (1.52 g) and Tween 80 (0.2 mL).

The volume of dissolution medium in USP Apparatus II was 1 liter per flask. At each sample interval, an exact volume of a sample was withdrawn from each flask and replaced immediately with an identical volume of fresh medium. A correction factor was included in the calculations to account for the drug lost in the samples. The volume of dissolution medium was 100 mL in each bottle in the Rotating Bottle Apparatus. At sampling intervals, the entire volume of the dissolution medium in the bottle was emptied and replaced by fresh dissolution medium. The emptied contents were then analyzed for drug content. The volume of dissolution medium in each glass vessel (or outer tube) of the Bio-Dis Tester was 175 mL. At each sample interval, the set of glass reciprocating cylinders (or inner tubes) containing the dosage form traversed to a new set of outer tubes containing fresh medium. The previous set of outer tubes were analyzed for drug content. The dissolution fluids were maintained at 37°± 0.5° C throughout the studies. The agitation intensities and sampling times for each device are given in Table I.

Analytical Procedure :

The absorbance values of the samples were measured on an IBM UV-visible spectrophotometer 9430. The wavelength of maximum absorbance was found to be 273 nm for theophylline and 257 nm for phenylpropanolamine HCL. The samples were filtered and diluted as required, to suit the needs of the analysis.

Table I. Agitation Intensities and Sampling Times of Dissolution Devices

Apparatus	Agitation Intensity	Sample Times (hours) for all Controlled Release products and Phenylpropanolamine HCl Immediate Release Capsules	Sample Times (minutes) for Theophylline Immediate Release products
USP Apparatus II	50 & 100 rpm[a]	0.33, 0.66, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12	1, 2, 3, 4, 5, 15, 25, 35, 45
Rotating Bottle	50 & 100 rpm[a]	0.33, 0.66, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12	1, 2, 3, 4, 5, 15, 25, 35, 45
Bio-Dis Tester	20 & 25 spm[b]	0.33, 0.66, 1, 1.33, 1.66, 2, 3, 4, 5, 6, 7, 8, 10, 12	1, 2, 3, 4, 5, 15, 25, 35, 45

[a]rpm = revolutions per minute
[b]spm = strokes per minute

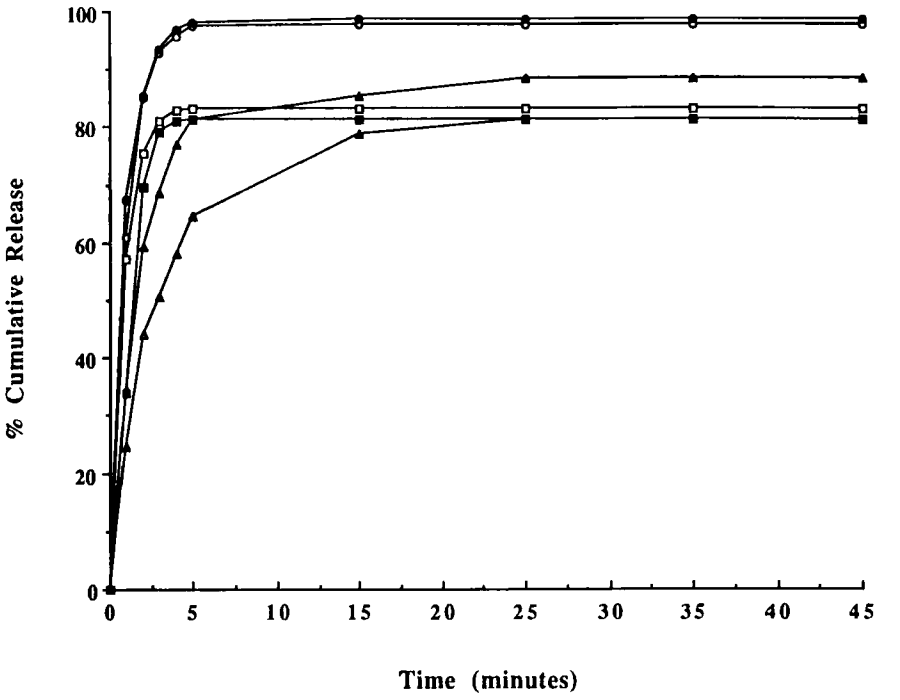

FIGURE 1
Dissolution of Theophylline Immediate Release Tablets in SGF

RESULTS AND DISCUSSION

Immediate Release Theophylline and Phenylpropanolamine HCl :

Figures 1 and 2 show theophylline released in SGF and SIF respectively from immediate release tablets. All the three dissolution devices were operated at two different agitation intensities. Most of the drug was released within 5 minutes when evaluated on the Bio-Dis Tester, irrespective of the dissolution medium, as compared to 15-25 minutes when evaluated on the USP Apparatus II or the Rotating Bottle Apparatus.

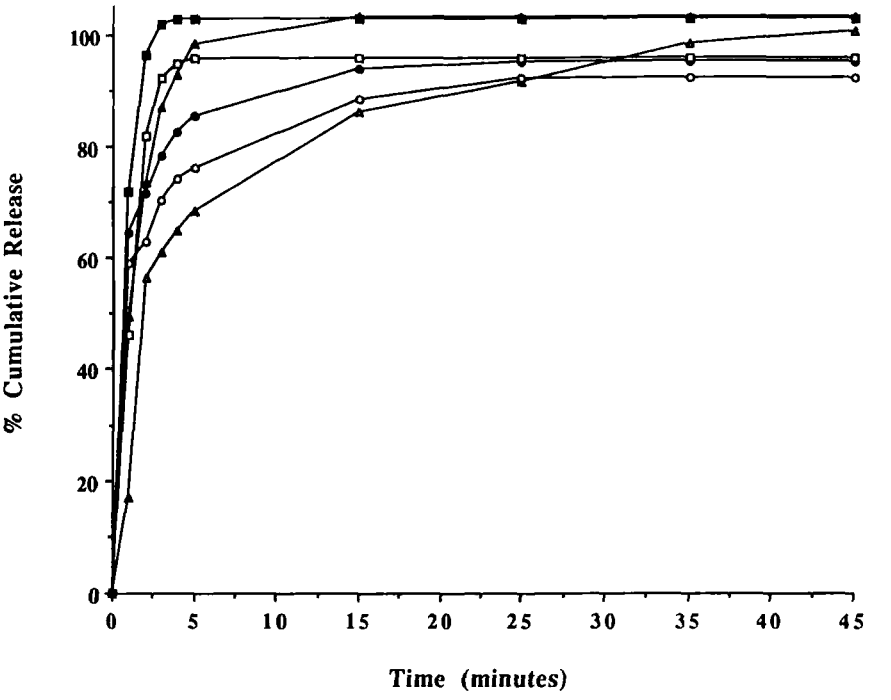

FIGURE 2
Dissolution of Theophylline Immediate Release Tablets in SIF

USP-50rpm — Rotating Bottle-50rpm — BioDis-20spm
USP-100rpm — Rotating Bottle-100rpm — BioDis-25spm

Faster drug release was observed in the Rotating Bottle Apparatus and Bio-Dis Tester at both the agitation intensities since the tablets fragmented faster in these devices as compared to the USP Apparatus II. The effect of agitation intensity on drug dissolution, however, was more pronounced for the USP Apparatus II than the other two devices, and faster drug release was observed from the tablets at 100 rpm.

For phenylpropanolamine HCl immediate release capsules (Figures 3 and 4), the drug release time ranged from 1-8 hours depending on the dissolution device. Most of the drug was released within 1-2 hours with the Bio-Dis Tester

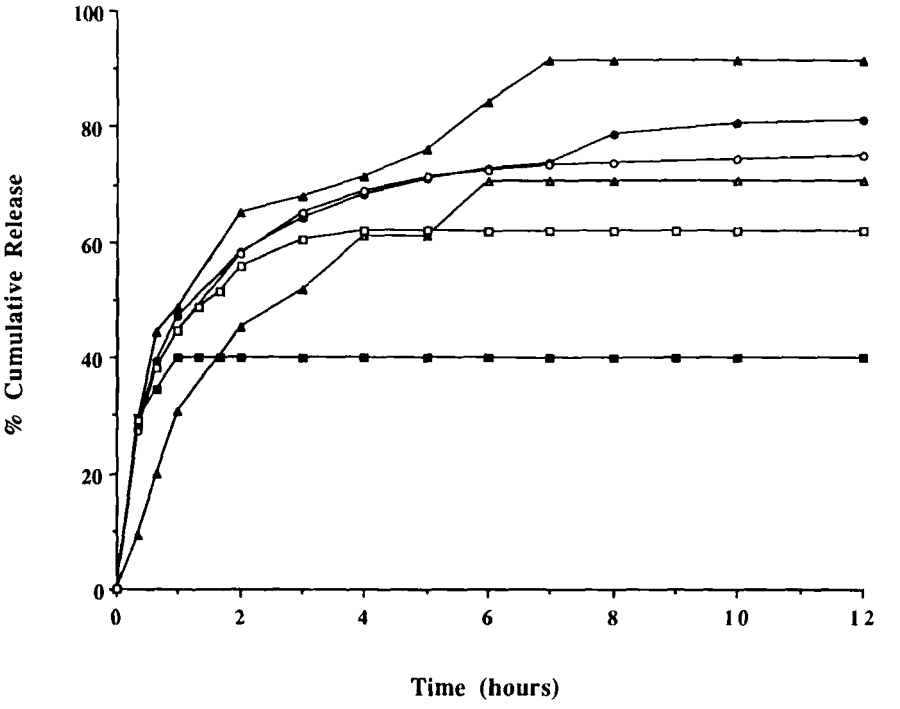

FIGURE 3
Dissolution of Phenylpropanolamine HCl Immediate Release Capsules in SGF

USP-50rpm — Rotating Bottle-50rpm — BioDis-20spm
USP-100rpm — Rotating Bottle-100rpm — BioDis-25spm

and 6-8 hours using the USP Apparatus II or the Rotating Bottle Apparatus. The dissolution profiles for phenylpropanolamine HCl differs depending on the speed and intensity of the agitation and is erratic, specifically with the USP Apparatus II. The uneven mixing in the USP Apparatus II can result in inconsistencies as has been reported by others[12,13]. The release rate was faster at 100 rpm than at 50 rpm in USP Apparatus II. The release rate was fastest with Bio-Dis Tester because of the high intensity of agitation provided by this instrument. Compared to the Bio-Dis, the release was more prolonged in the USP Apparatus II because the beads of the capsules accumulated at the bottom of the flask and hence the agitation was not as intense as the Bio-Dis Tester.

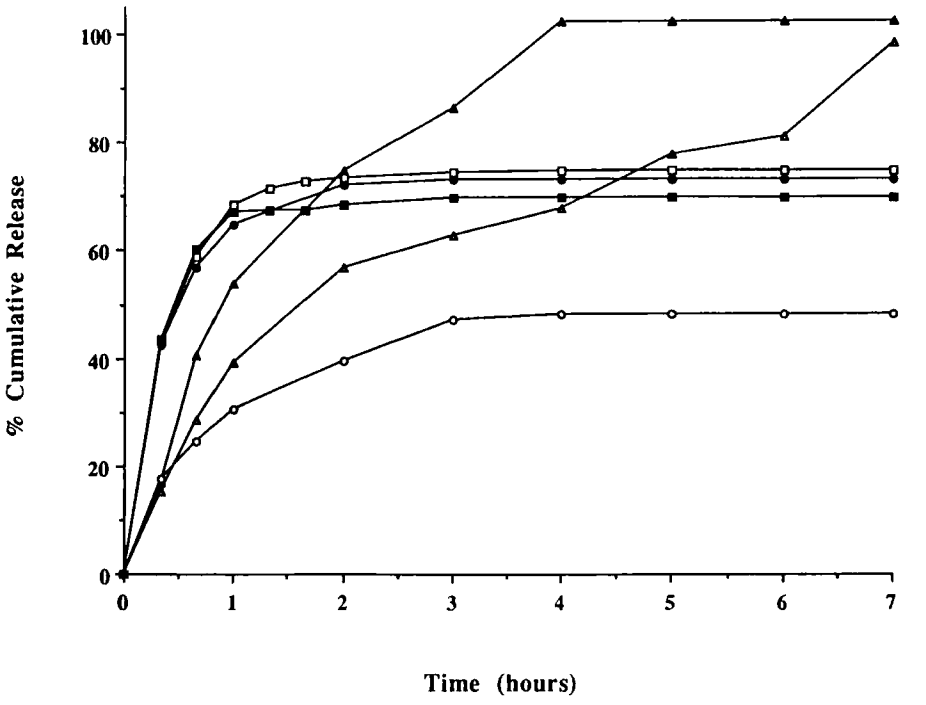

FIGURE 4
Dissolution of Phenylpropanolamine HCl Immediate Release Capsules in SIF

USP-50rpm — Rotating Bottle-50rpm — BioDis-20spm
USP-100rpm — Rotating Bottle-100rpm — BioDis-25spm

The release of phenylpropanolamine HCl was found to be much less than theophylline, in terms of cumulative percent release.

The problem of less than 100% cumulative release can be anticipated due to the extensive loss of dosage form fragments during the change of dissolution medium at each sample interval in the Rotating Bottle Apparatus and due to loss of dosage form fragments during the downward motion of the Bio-Dis Tester spindles when the dosage form fragments were displaced out of the airholes at the top of the inner tube basket into the outer tube. Higher drug release was observed at 20 spm than at 25 spm in Bio-Dis Tester because more of the dosage form was lost from the inner tube basket at higher agitation

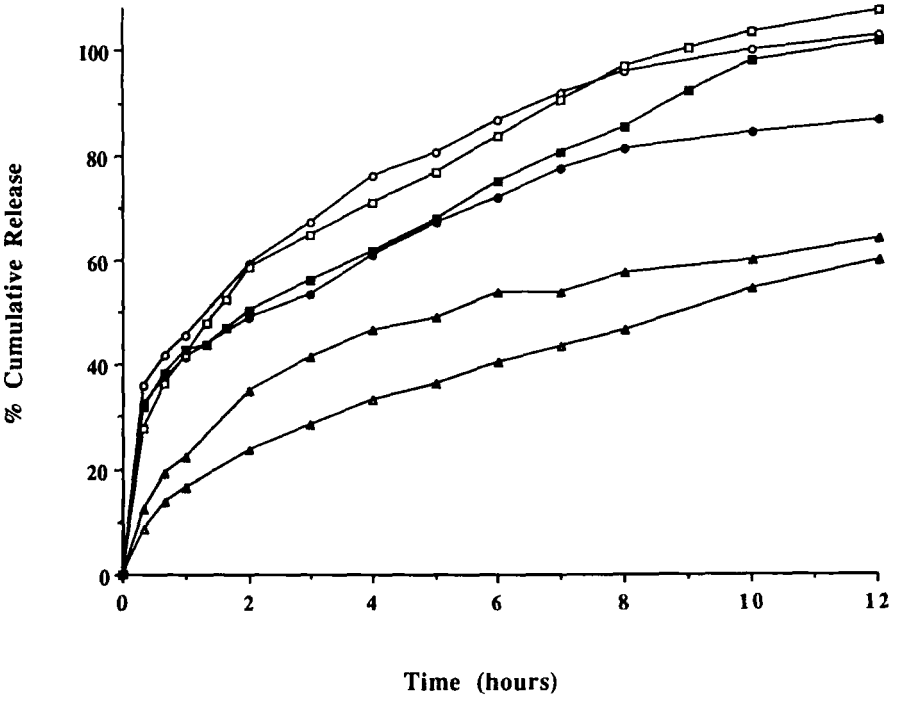

FIGURE 5
Dissolution of Theophylline Sustained Action Tablets in SGF

USP-50rpm — Rotating Bottle-50rpm — BioDis-20spm
USP-100rpm — Rotating Bottle-100rpm — BioDis-25spm

intensity. The loss of part of the dosage form in Rotating Bottle Apparatus and Bio-Dis Tester, along with the ease of sampling in USP Apparatus II makes the latter more appropriate for dissolution studies of immediate release formulations compared to the former dissolution devices.

Sustained and Timed Release Formulations of Theophylline :

For the theophylline formulations (Figures 5 - 8), the dissolution profiles differ not only with the dissolution devices but also with the agitation intensities. It is apparent from Figures 5 and 6 that drug release from theophylline sustained action tablets was the slowest in USP Apparatus II compared to the other two dissolution devices operated at both the agitation

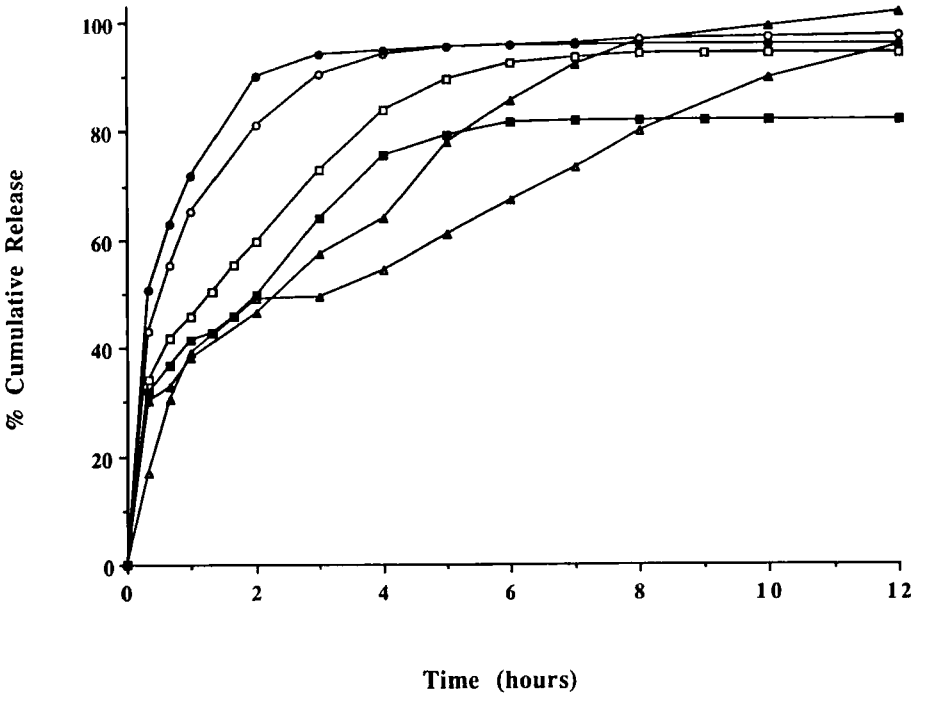

FIGURE 6
Dissolution of Theophylline Sustained Action Tablets in SIF

intensities. The release is fastest with the Rotating Bottle Apparatus and slowest with the USP Apparatus II because the tablet fragments or capsule beads tend to settle down to the bottom of the flask in USP Apparatus II, hence the release is slower compared to the Bio-Dis Tester or Rotating Bottle Apparatus where settling does not occur due to the continuous up and down motion of the spindles in the former or the constant rotation of the bottle in the latter.

An increase in the agitation intensity of the USP Apparatus II from 50 rpm to 100 rpm increased the drug release rate from both the sustained action theophylline tablets (Figures 5 and 6) and theophylline timed release capsules

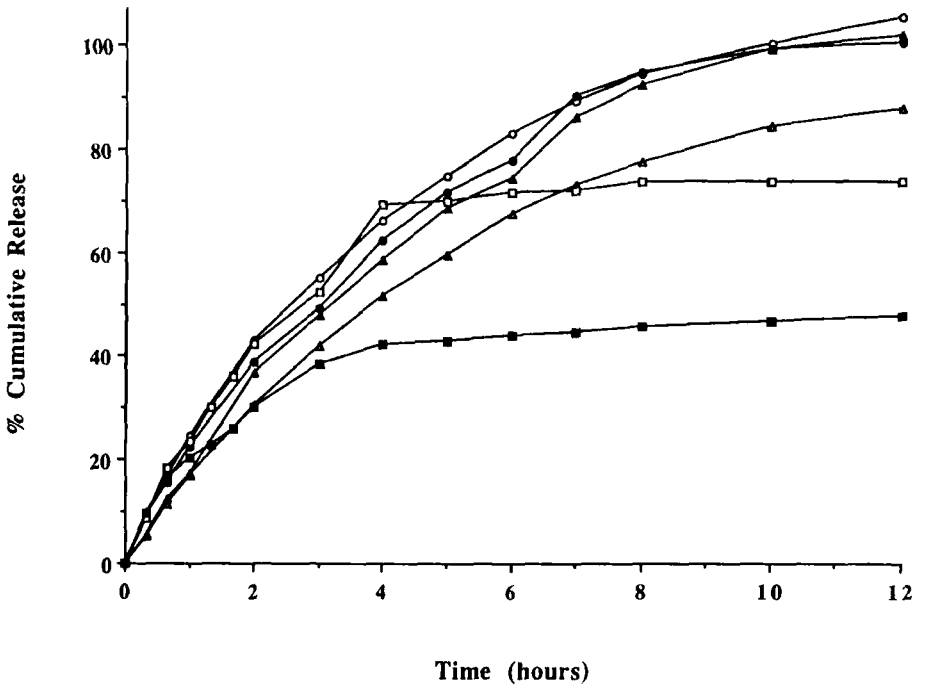

FIGURE 7
Dissolution of Theophylline Timed Release Capsules in SGF

USP-50rpm — Rotating Bottle-50rpm — BioDis-20spm
USP-100rpm — Rotating Bottle-100rpm — BioDis-25spm

(Figures 7 and 8) in both the dissolution media. However, increasing the agitation intensity of the Bio-Dis Tester from 20 spm to 25 spm decreased the drug release. This phenomenon can be explained as follows : at higher agitation intensity, the dosage form disintegrated quickly and during the downward motion of the inner tube where the entering dissolution fluid pushed the fragmented particles to the top and out of the airholes of the inner tube basket resulting in a substantial loss of dosage form and thus an overall decrease in the amount of dosage form being transferred to the next set of outer tubes. Hence, the release is higher at lower speed of agitation. Moreover, as a result, the

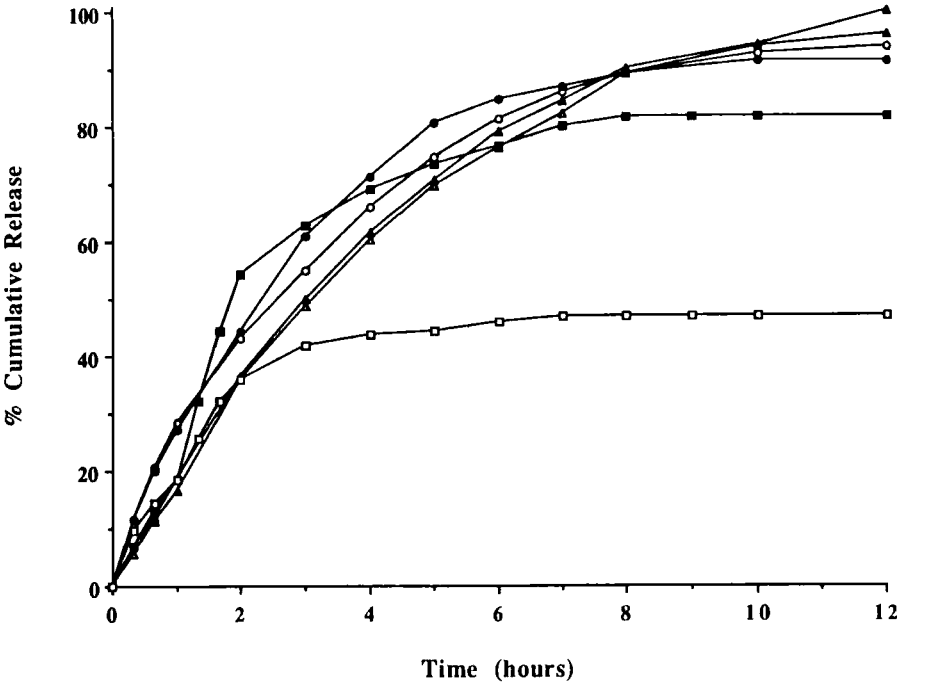

FIGURE 8
Dissolution of Theophylline Timed Release Capsules in SIF

cumulative percentage never reached 100% in case of theophylline timed release capsules.

Varying the agitation intensity of the Rotating Bottle Apparatus from 50 to 100 rpm had no significant effect on the drug release from both the theophylline formulations when tested in both dissolution media. It is also evident from the figures that drug release from theophylline formulations were independent of the pH of the dissolution media, since similar drug release was observed in both the dissolution media.

Precision and Timed Release Formulations of Phenylpropanolamine HCl :

The dissolution profiles of phenylpropanolamine HCl precision release tablets in both SGF and SIF using all three dissolution devices at two different

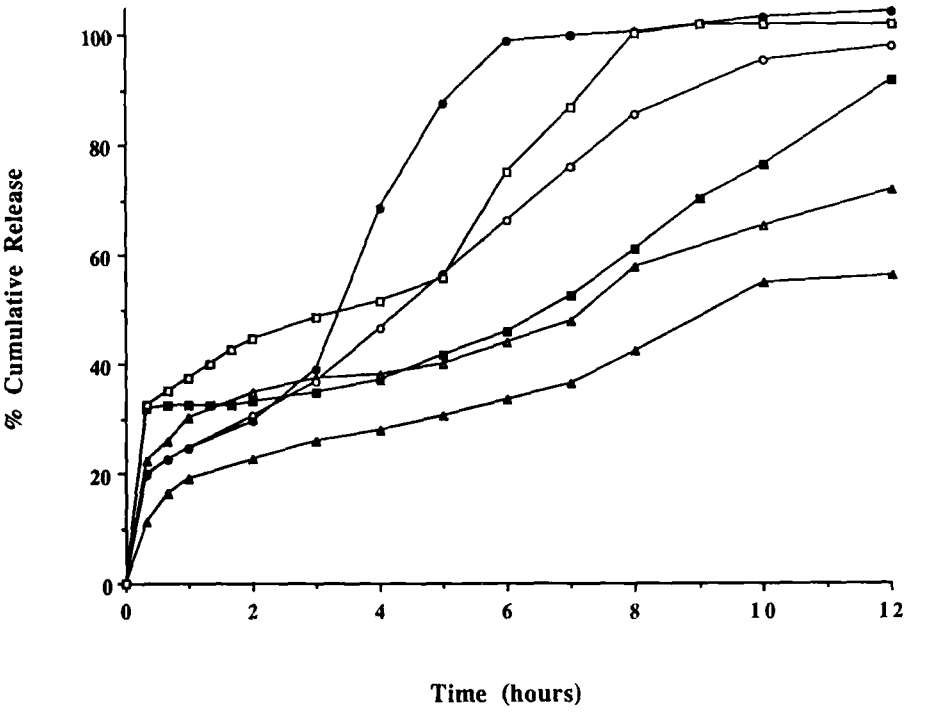

FIGURE 9
Dissolution of Phenylpropanolamine HCl Precision Release Tablets in SGF

agitation intensities are shown in Figures 9 and 10. It is evident from the figures that faster release occured at lower agitation intensity (20 spm) of the Bio-Dis Tester compared to the higher agitation intensity (25 spm). Slowest drug release occured in the USP Apparatus II in SGF followed by the Bio-Dis Tester and the Rotating Bottle Apparatus. A greater variation in the release profiles was observed in SGF than in SIF when the dissolution was performed in the Rotating Bottle Apparatus. In the Rotating Bottle Apparatus using SGF, there was a sudden, uncharacteristic burst effect between the 3-5 hour sampling interval probably due to the damaging effect of the physical collisions of the dosage form with the bottle and the acidic nature of SGF (pH 1.2) on the

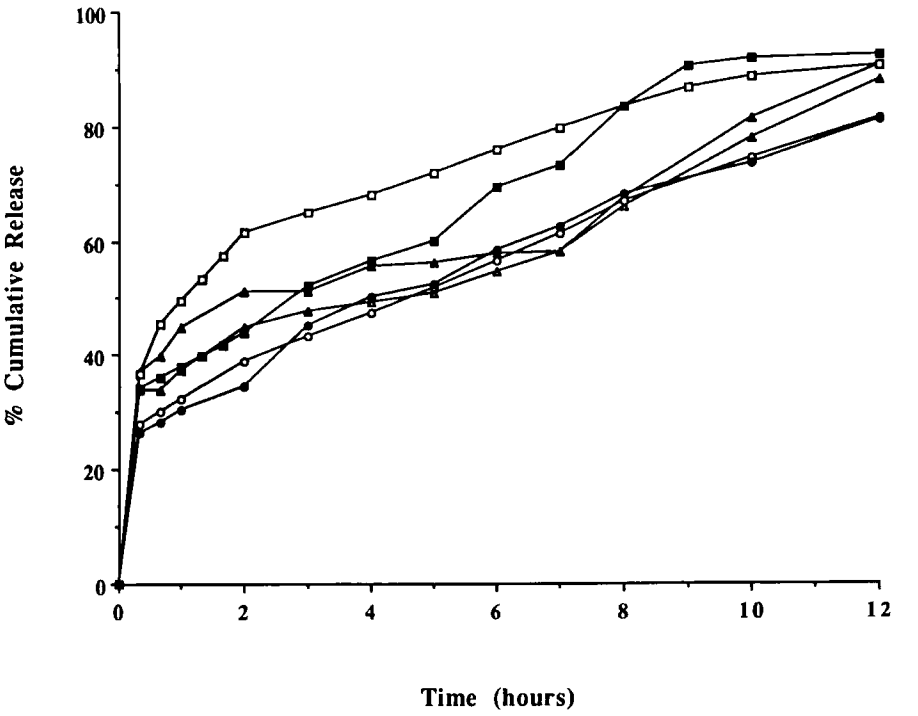

FIGURE 10
Dissolution of Phenylpropanolamine HCl Precision Release Tablets in SIF

USP-50rpm — Rotating Bottle-50rpm — BioDis-20spm
USP-100rpm — Rotating Bottle-100rpm — BioDis-25spm

semipermeable membrane of the tablet visually observed by the authors as flaking of the precision release tablet membrane. Like theophylline, the release of phenylpropanolamine HCl from the precision release tablet was slowest with the USP Apparatus II.

The effect of agitation intensity of the Bio-Dis Tester on drug release in SGF and SIF from phenylpropanolamine HCl timed release capsules (Figures 11 and 12) was similar to the results observed with other dosage forms. Greater variability in drug release was observed in SIF when USP Apparatus II was used at two different agitation intensities. Moreover, changing the pH of the dissolution medium from 1.2 (SGF) to 7.4 (SIF) significantly varied the drug

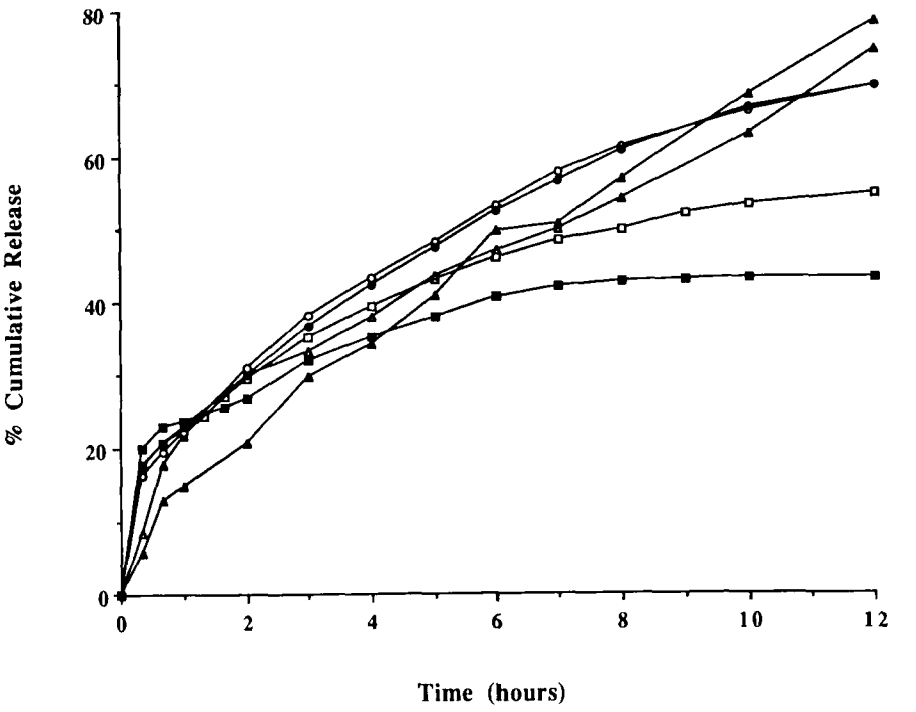

FIGURE 11
Dissolution of Phenylpropanolamine HCl Timed Release Capsules in SGF

release profiles with all the three dissolution devices operated at both agitation intensities.

CONCLUSION

Each device is best suited for particular types of dosage forms. The advantages/limitations of each device are listed in Table II. The USP Apparatus II is best suited for immediate release formulations. Its ease of use in terms of setup and sampling, ease of modifications for different dosage forms and little mechanical disturbance of the dosage form compared to other dissolution

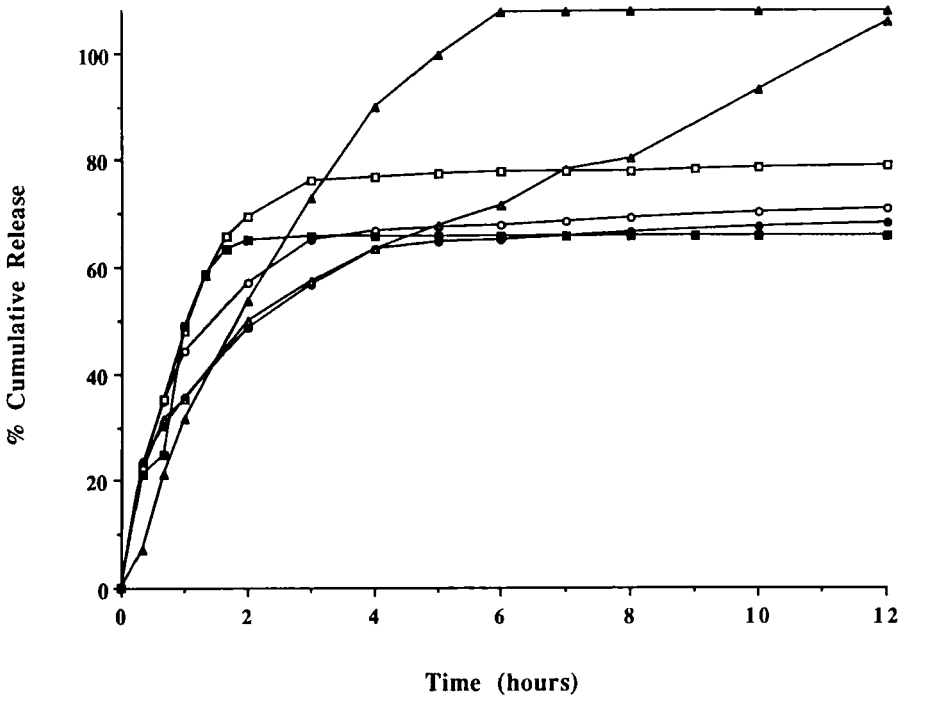

FIGURE 12
Dissolution of Phenylpropanolamine HCl Timed Release Capsules in SIF

USP-50rpm — Rotating Bottle-50rpm — BioDis-20spm
USP-100rpm — Rotating Bottle-100rpm — BioDis-25spm

devices lends to its popularity. However, nonuniform mixing of drug at low agitation intensities has been reported[12,13] and limitation of dissolution medium volume leading to saturation conditions for drugs with low solubility may pose serious problems. On the other hand, immediate release formulations cannot be adequately evaluated using the Rotating Bottle Apparatus or the Bio-Dis Tester as they were not designed for these types of dosage forms, especially in the Rotating Bottle Apparatus where sampling can be very tedious and the change of dissolution media leads to potential loss of the dosage form. The effect of agitation intensity was well illustrated by the study. The relationship between dissolution profiles for different speeds changed at pH 1.2 (SGF) when

Table II. Advantages and Limitations of the Dissolution Device

Device	Advantages	Limitations
USP Dissolution Device	• Ease of use (setup, samples, etc.) • Little mechanical disturbance of the dosage form.	• Sink conditions limited for low solubility drug. • Nonuniform distribution of drug at low speeds. • Sampling requires replacement of medium, which requires a correction factor for concentration determinations.
Rotating Bottle Apparatus	• Total sample removal provides for sink conditions and no correction factor needed for sample replacement.	• Change of dissolution medium for every sample is time consuming and may lead to potential loss of a fraction of dosage form. • Physical rotation imparts damage to dosage forms.
Bio-Dis Tester	• Automated features do not require constant attention to obtain samples for most programs. • Contamination between samples is minimal. • Physical movement provides minimal physical damage to dosage forms.	• Programming of agitation intensity and sample times limited for immediate release products. [Was not designed for these.] • Portions of dosage form could be lost through the top of the inner tube due to agitation.
All Devices	• Temperature was easily controlled. • Each device was very reliable [no breakdowns].	• Filtration may lead to loss of drug in the filter. • Change in agitation intensity altered the dissolution profile.

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PREPARATION OF ESSENTIAL OILS LOADED GRANULE BY MELT GRANULATION

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ABSTRACT

A comparative study on three granulation methods; melt granulation, fluidized bed granulation and wet granulation was performed to fabricate an essential oils loaded granule. The granule properties such as particle size distribution and the loading efficiency of anethole from fennel and cinnamaldehyde from cinnamon showed that the melt granulation in a high shear mixer was the most feasible method among the three methods.

In melt granulation, the granule particle size was well controlled by polyethylene glycol 6000 (PEG) content of which the optimum value was found to be 20%. Impeller speed and massing time in high shear mixer had small contribution to the particle growth when PEG content was optimized, while PEG particle size had some effect. Finer PEG powder improved the uniformity of granule size. Moreover, the cooling method of the hot mass affected the final granule properties significantly. The cooling with a fluid bed dryer was the best method.

Both of the retention rates of anethole and cinnamaldehyde in the final granule were more than 95% of initial doses irrespective of cooling method. Further, the adoption of a fluid bed dryer enabled very rapid cooling of hot granule with negligible loss of essential oils.

INTRODUCTION

Few studies have examined the granulation techniques for volatile materials. The use of porous materials such as cyclodextrins or microsponges[1] are applicable

6. Banakar, U. V. and Block, L. H., Beyond Bioavailability Testing. *Pharm. Technol.* **7** : 107-117 (1983).
7. Aiache, J., Pierre, N., Beyssac, E., Prasad, V. K. and Skelly, J. P., New Results on an In Vitro Model for the Study of the Influence of Fatty Meals on the Bioavailability of Theophylline Controlled-Release Formulations. *J. Pharm. Sci.* **78** : 261-263 (1989).
8. General Tests and Assays.*The United States Pharmacopoeia XXII. The National Formulary XVII.* Supplement 5. The United States Pharmacopeial Convention, Inc., Rockville, Maryland, Mack Publishing Company, Easton, Pennsylvania, 1991, pp. 2711-2715.
9. Esbelin, B., Beyssac, E., Aiache, J-M., Shiu, G. K. and Skelly, J. P., A New Method of Dissolution In Vitro, the "Bio-Dis" Apparatus:Comparison with the Rotating Bottle Method and In Vitro:In Vivo Correlations. *J. Pharm. Sci.* **80** : 991-994 (1990).
10. Abdou, H. M., *Dissolution, Bioavailability and Bioequivalence*, Mack Publishing Company, Easton, Pennsylvania, 1989, pp. 145-171.
11. Pernarowski, M., Dissolution Methodology. In L. J. Leeson and J. T. Carstensen (eds.), *Dissolution Technology,* Academy of Pharmaceutical Science, Washington, DC, 1974, pp. 58-105.
12. Iyer, R. M., Bocanegra, L., Jurewicz, J. T. and Mauger, J. W., Flow Visualization of the USP Dissolution Apparatus (Paddle Method) using Laser and Dye-Injection Techniques. Paper presented at *GRASP Seventh Annual Meeting,* Morgantown, West Virginia, 1987, pp. 14.
13. Bocanegra, L., Morris, G., Jurewicz, J. and Mauger, J., Fluid Velocity Measurements inside the USP Dissolution Vessel for the Paddle Dissolution Test Method. *Pharm. Res.* **5** (10) : S-114 (1988, October Supplement).