Development and Evaluation of a Novel Dissolution Apparatus for Medicated Chewing Gum Products

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A novel dissolution apparatus was developed for medicated chewing gum products. A prototype gum product containing phenylpropanolamine hydrochloride (PPA) was used to evaluate the apparatus. The apparatus consists of a conical Teflon base and a rotating, ribbed Teflon plunger suspended in a dissolution vessel. Parameters evaluated were rotation speed, plunger frequency, medium volume, medium type, medium sampling location, number of plunger ribs, and number of gum pieces. Samples were taken over a 20-min period and samples were analyzed by HPLC. Cumulative percentage released-versus-time profiles were obtained for each parameter evaluated. Statistical analysis of the gum product indicated that the only significant differences occurred at the lowest rotation speed and lowest plunger frequencies. A Level A correlation was found between the *in vitro* release profile for the 20-rpm and 30-cycles/min plunger frequency and the *in vivo* chew-out study.

KEY WORDS: dissolution; chewing gum; phenylpropanolamine hydrochloride; *in vitro–in vivo* correlation.

INTRODUCTION

Medicated chewing gum is a unique means of drug delivery in the pharmaceutical industry. Unlike the traditional dosage forms, a medicated gum product is intended to be chewed for 20 to 30 min; then the remaining mass is discarded (1). During the chewing process, most of the drug contained within the gum product is released from the mass into the saliva and is either absorbed through the buccal membrane or swallowed and absorbed via the gastrointestinal tract.

The present method for studying the release of drugs from medicated chewing gum products is the *in vivo* chew-out study. A chew-out study is performed by volunteers masticating a piece or pieces of gum for a certain period of time, expectorating the chewed mass into a vial, and analyzing the discarded mass for the drug remaining (2).

Two apparatuses have previously been developed for the study of the mastication of chewing gum products. Kleber *et al.* (3) constructed a device to study the ability of gum to polish teeth. Dissolution studies with this apparatus demonstrated that it was unsuitable for the *in vitro* investigation of drug release from medicated chewing gum products (4). The other apparatus was developed by Christup and Moeler (4). They found that there was a correlation between the *in vitro* dissolution results and the *in vivo* chew-out study results for a gum product containing ascorbic acid. However, an *in vitro–in vivo* correlation was not found when the apparatus was further tested with a gum product containing salicylamide (5).

The objectives of the present study were (i) to develop a novel dissolution apparatus for medicated chewing gum products, (ii) to test the apparatus with a prototype gum product containing phenylpropanolamine hydrochloride (PPA), and (iii) to correlate the dissolution results to chew-out study results for this gum product.

MATERIALS AND METHODS

Materials

The prototype gum products containing PPA and PPA powder were supplied by Schering-Plough Health Care Products, Inc. (Memphis, TN). Acetonitrile (HPLC grade) and sodium hydroxide were purchased from Fisher Scientific Co. (Fair Lawn, NJ). Dodecyl sodium sulfate (ACS grade), phosphoric acid (reagent grade), and tetramethylammonium hydroxide (ACS grade) were purchased from Aldrich Chemical Co (Milwaukee, WI). Carbon tetrachloride (reagent grade) was purchased from Taylor Chemical Co. (St. Louis, MO). Ephedrine sulfate, USP (ES), was purchased from J. T. Baker Chemical Co. (Phillipsburg, PA).

Dissolution Apparatus

The dissolution apparatus (Figs. 1 and 2) developed for the *in vitro* analysis of medicated chewing gum products consisted of a Teflon base (A), a Teflon plunger (B), a dissolution flask support system (C), a standard glass dissolution flask (D), a stainless-steel shaft (E), a pillow block (F), a motor (G), a Teflon plate (H), and a piston (I). The Teflon base used for this study had a 1.25-in. diameter. Two Teflon plungers were developed for this study. Each plunger had a 1.25-in. diameter; one had 8 plunger ribs and the other had 10 ribs. The plunger ribs were small indentions (approximately 1/16 in. deep) cut into the plunger. The ribs allowed for circulation of the dissolution medium within the base. The Teflon base was connected to the support system, which eliminated the transference of compaction forces to the glass dissolution flask. The support system also positioned the base in the middle of the dissolution flask. The Teflon plunger was connected to the stainless-steel shaft, which was attached to the motor. Shaft tilt and wobble were prevented by the pillow block. The motor and pillow block were mounted on the Teflon plate, whose vertical motion was controlled by the piston. One cycle of the piston consisted of one upward and one downward stroke of the piston. The stroke was 0.25 in., with the plunger (B) in contact with the inner bottom of the base (A) at the end of the downward

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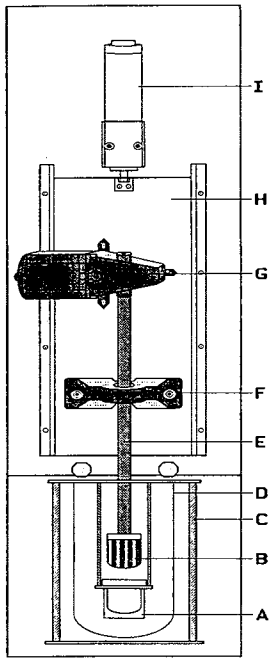

Fig. 1. The novel dissolution apparatus developed for the *in vitro* analysis of medicated chewing gum products.

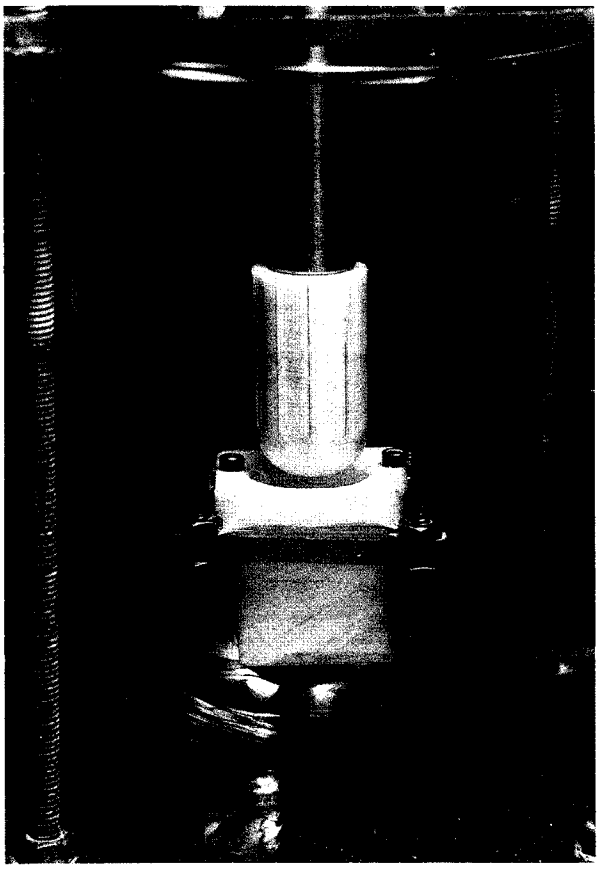

Fig. 2. The plunger/base assembly from dissolution apparatus. Plunger is positioned above base; in normal operation the two are pushed together with gum mass between them.

stroke when no gum was present. With gum present, the resistance of the gum would create a space between these two components. This gap would decrease during the dissolution run as the gum mass was hydrated, compressed, and sheered. Additional sheer was added to the gum mass by the constant rotation of the plunger (B). During the dissolution run the gum mass remained in the base, adhering to one or both of the surfaces of the base and plunger. The number of cycles per unit time taken by the piston was controlled by a digital timer located on the back of the apparatus. The speed of the motor was regulated by a rheostat, also located on the back of the apparatus.

Dissolution Procedure

Prior to the start of a dissolution test, the Teflon plate was raised. The Teflon base, support system, and dissolution flask were assembled. The dissolution medium was poured into the dissolution flask. The assembled support system was placed under the plunger in a water bath and the dissolution medium was allowed to equilibrate to 37°C.

At the start of a dissolution test, gum pieces were placed into the Teflon base, the Teflon plate was lowered, and the timer and rheostat were turned on. Most dissolution test runs lasted for 20 min. After each run, the rheostat and timer were turned off and the Teflon plate was raised. The gum mass remaining after a dissolution test run was physically removed from the base and plunger, and both were then cleaned with hexane.

HPLC Analysis

High-pressure liquid chromatography (HPLC) analysis was performed on all samples in this study. Four hundred microliters of dissolution medium and 100 μl of a ephedrine sulfate solution (0.15 mg/ml in purified water) were placed in a test tube, then vortexed, and 15 μl was injected into the HPLC. The HPLC column used was a 0.5-μm, C18, Beckman Ultrasphere, 4.6 mm × 15-cm column. HPLC parameters used are as follows: flow rate, 3.0 ml/min; wavelength, 210 nm; column pressure, 2400 psig; retention time for PPA, 4–5 min; and retention time for ES, 5–6 min. The mobile phase consisted of a mixture of 35.0% acetonitrile, 0.28% sodium hydroxide, 0.425% phosphoric acid, 0.01% tetramethylammonium hydroxide, and 0.288% dodecyl sodium sulfate in purified water. The pH of the mobile phase was adjusted to 3.5. Prior to use, the mobile phase was filtered and degassed using a 0.45-μm nylon filter.

Content Studies

Content studies were performed on all batches of medicated chewing gum product evaluated in this study. Three standard (approximately 200 mg of PPA powder) and three unknown samples were tested in each PPA content study. All samples were analyzed by HPLC. An internal standard solution was prepared by placing 0.75 g of ES into a 500-ml volumetric flask and diluting to volume with diluted phosphoric acid [a 1:200 dilution, by volume, of 85% (w/w) phosphoric acid]. A standard solution of PPA was prepared by placing 200 mg of PPA in a 100-ml volumetric flask and diluting to volume with diluted phosphoric acid. Standard samples were prepared by placing 25.0 ml of standard solution

Table I. PPA Content Studies

Study No.	Gum piece content: Mean (mg/gum)	σ_{n-1} (mg/gum)	RSD (%)
1 (Lot A)	8.204	0.073	0.89
2 (Lot A)	8.172	0.120	1.47
3 (Lot B)	8.244	0.183	2.22
4 (Lot B)	8.107	0.060	0.74

and 25.0 ml of internal standard solution in a 250-ml Erlenmeyer flask containing 100 ml of carbon tetrachloride and 50 ml of diluted phosphoric acid. Unknown samples were prepared by placing 5 gum pieces in a 250-ml Erlenmeyer flask and adding 100 ml of carbon tetrachloride, 25.0 ml of internal standard solution, and 75 ml of diluted phosphoric acid. Both standard and sample preparations were placed on magnetic stirrers and mixed vigorously for 3 hr. After this time, the aqueous and organic phases were allowed to separate. Five milliliters from the aqueous phase of each preparation was pipetted into a 25-ml volumetric flask and diluted with PPA mobile phase. The following formulae were used to analyze data produced by the HPLC:

$$\frac{\text{peak area PPA}}{\text{peak area ES}} = \text{ratio}$$

$$\frac{\text{(sample ratio) (standard weight) (0.25)}}{\text{(standard ratio) (no. gum pieces)}} = \text{mg PPA/gum}$$

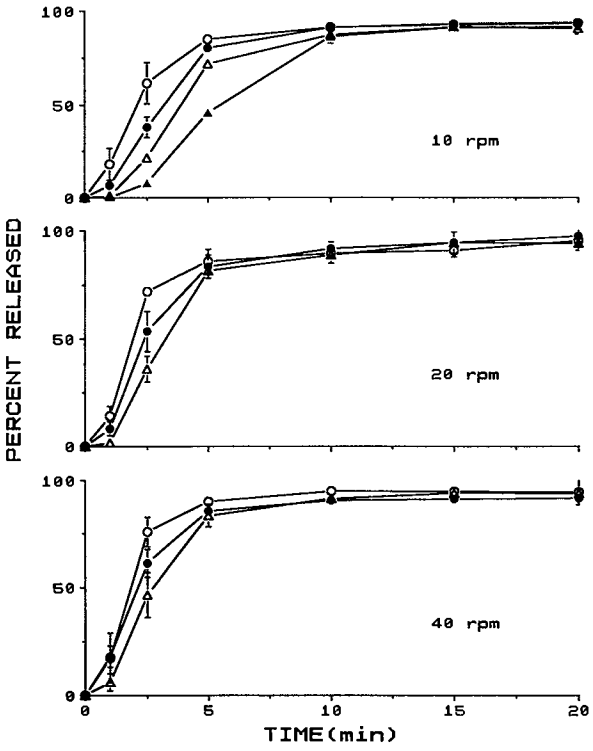

Fig. 3. Dissolution of a gum product containing PPA; constant rotation speed, variable plunger frequency. (○) 30 cycles/min; (●) 15 cycles/min; (△) 7.5 cycles/min; (▲) 3.75 cycles/min.

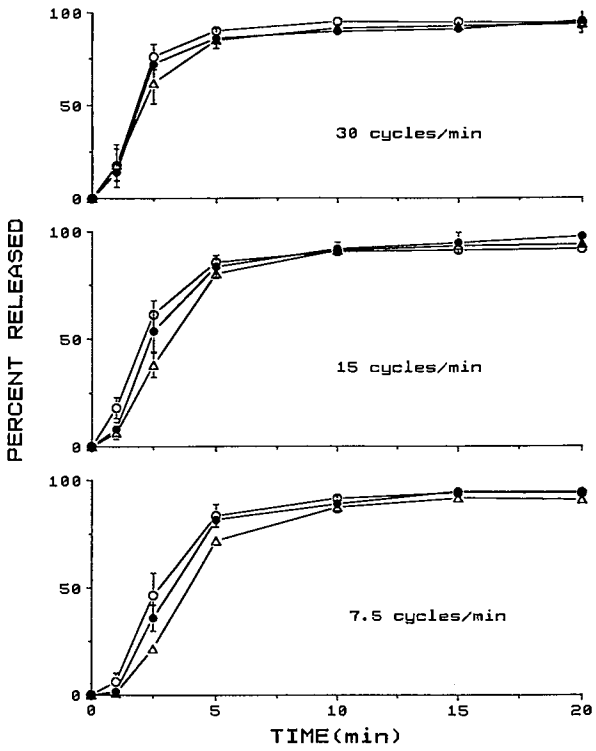

Fig. 4. Dissolution of a gum product containing PPA; constant plunger frequency, variable rotation speed. (○) 40 rpm; (●) 20 rpm; (△) 10 rpm.

Means, standard deviations, and relative standard deviations were determined for each content study.

Dissolution Tests

Three or more dissolution tests were performed on all medicated gum products evaluated in this study. During each test, 3-ml samples of dissolution medium were withdrawn through a probe placed into the dissolution medium. Samples were withdrawn at time intervals of 1, 2.5, 5, 10, 15, and 20 min. One milliliter of dissolution medium was washed through a 0.45-μm cellulose acetate filter, and the remaining 2 ml of dissolution medium was filtered and stored for HPLC analysis. Five hundred milliliters of purified water was used as the dissolution medium. The batches of gum product uti-

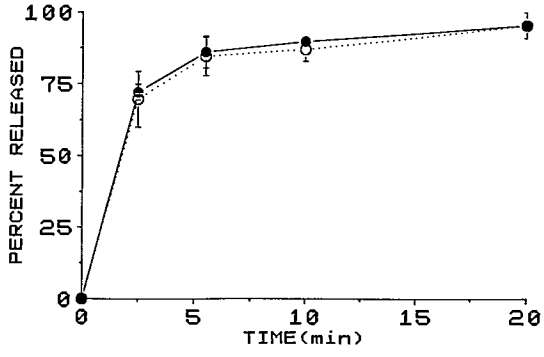

Fig. 5. Dissolution of a gum product containing PPA; chew-out versus dissolution at 20 rpm and 30 cycles/min. (○) Chew-out; (●) dissolution.

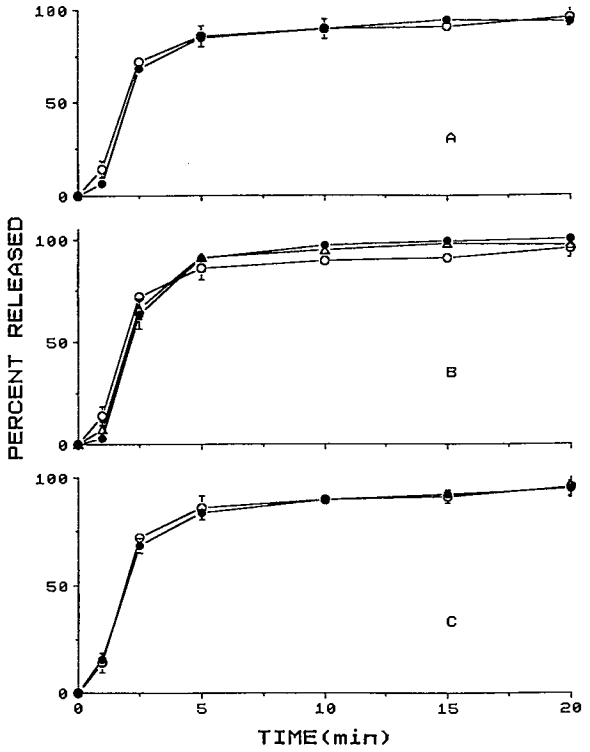

Fig. 6. Dissolution of a gum product containing PPA. (A) Variable dissolution volume: (○) 500 ml; (●) 900 ml. (B) Variable point of sampling: (○) middle; (●) bottom; (△) top. (C) Variable dissolution medium: (○) purified water; (●) artificial saliva.

lized in this portion of the project were randomly chosen from prototype batches of gum product. Parameters evaluated with the dissolution apparatus included the following: rotation speed (10, 20, and 40 rpm), plunger frequency (3.75, 7.5, 15, and 30 cycles/min), dissolution medium volume (500 and 900 ml), dissolution medium type (purified water and artificial saliva), sampling location (top, middle, and bottom of the dissolution medium), number of gum pieces (2 and 3 pieces), and number of ribs on the Teflon plunger (8 and 10).

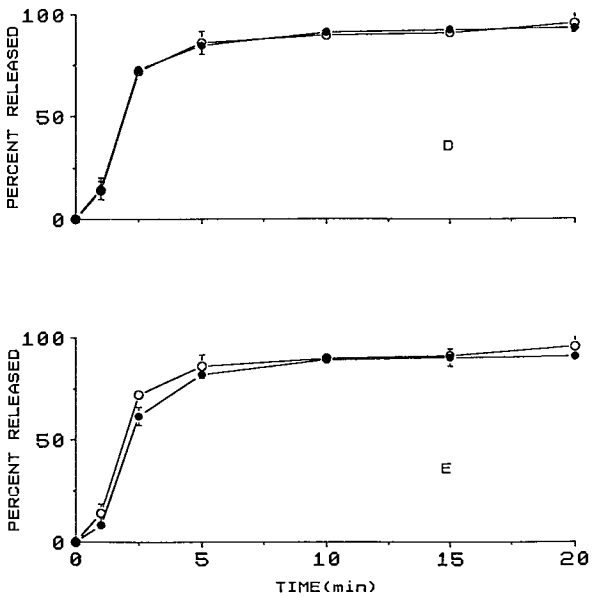

Fig. 7. Dissolution of a gum product containing PPA. (D) Variable number of gum pieces: (○) 3 gum pieces; (●) 2 gum pieces. (E) Variable number of ribs on the plunger: (○) 10 rib plunger; (●) 8 rib plunger.

Chew-Out Studies

A chew-out study was performed on the prototype gum product containing PPA. One gum piece was given to six volunteers for each time period. The volunteers chewed the gum pieces for 2.5, 5, 10, and 20 min. After each time period, the chewed mass was expectorated into a screw-capped jar and stored until HPLC analysis. The chewed masses were assayed for remaining PPA using the same procedure cited previously for content studies.

Statistical Analysis

Statistical analyses were performed on all dissolution tests. A three by three Latin square design was employed when evaluating the rotation speed and plunger frequency for the gum product used in the dissolution tests. A one-way analysis of variance (ANOVA) with Scheffe and Duncan post hoc tests or a *t* test was used to compare the data produced in dissolution tests and chew-out studies. A 95% confidence limit was placed on all statistical analyses.

RESULTS AND DISCUSSION

Content Studies

The results of the content studies performed in this project are listed in Table I. There were no statistical differences between the PPA gum samples.

Dissolution Tests

Figures 3–7 contain the results where the parameters were varied during a dissolution test and when a dissolution test was compared to the chew-out results. All dissolution profiles showed a 90% or greater release of PPA in 20 min. High release of drug from this gum product is attributed to the high aqueous solubility (1 g in 2 ml) of the compound (6).

Figure 3 shows the results when the rotation speeds were held constant and the plunger frequencies were varied. Figure 4 shows the results when plunger frequencies were held constant and rotation speeds were varied. For this gum product, increasing the plunger frequency and rotation speed produced enhanced initial release of PPA. Figure 5 shows the results of the comparison of the chew-out study profile and a dissolution test run profile. The analysis of the three by three Latin square revealed that there was a Level A correlation between the dissolution profile with a rotation speed of 20 rpm and a plunger frequency of 30 cycles/min and the chew-out study profile for the gum product containing PPA (7). All subsequent dissolution test runs were performed at this rotation speed and plunger frequency. Figure 6 shows the results when dissolution medium volume was varied (plot A), point of sampling was varied (plot B), and dissolution medium type was varied (plot C). Figure 7 contains the

Table II. Statistical Analysis[a]

	Time (min)				
	1	2.5	5	10	15
			Constant rotation speed		
rpm			cycles/min		
10	3.75 & 30 7.5 & 30	3.75 & 30 7.5 & 30	3.75 & 30 7.5 & 30 3.75 & 15 3.75 & 7.5 7.5 & 15	—	—
20	7.5 & 30	7.5 & 30	—	—	—
40	—	7.5 & 30	—	—	—
			Constant plunger frequency		
cycles/min			rpm		
7.5	10 & 40	10 & 40	10 & 40 10 & 20	—	—
15	10 & 40	10 & 40	—	—	—
			Sample location		
	Middle and top	—	—	Middle and top	Middle and top
			Dissolution medium		
	500 & 900	—	—	—	—
			Plunger ribs		
	—	8 & 10	—	—	—

[a] Denotes statistical differences that occurred when parameter listed was held constant. There were no differences at 20 min.

results when the number of gum pieces was varied (plot D) and the number of ribs on the plunger head was varied (plot E).

Statistical analyses of the dissolution profiles for the gum product are shown in Table II. These analyses revealed few significant differences when any parameters investigated were varied. When a 10-rpm rotation speed was held constant, differences were seen between a plunger frequency of 3.75 cycles/min and a frequency of 30 cycles/min from 1 to 5 min. Differences at this rpm were also seen between a plunger frequency of 7.5 cycles/min and a frequency of 30 cycles/min from 1 to 5 min. When a 7.5 cycles/min plunger frequency was held constant, differences were observed between 10 and 40 rpm from 1 to 5 min. For all other parameters investigated, statistical differences appeared to be random in nature. Statistical differences observed at these times are due to increased initial release rates.

CONCLUSIONS

Evaluation of the novel dissolution apparatus for medicated chewing gum products indicated that the dissolution profiles for the gum product containing PPA were reproducible. Dissolution profiles obtained when the rotation speed and the plunger frequency were varied also showed that the apparatus was flexible to changes in these parameters. A Level A correlation was found between an *in vitro* dissolution profile and an *in vivo* chew-out study profile for the gum product.

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