DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 10(10), 1639-1661 (1984)

COMPARATIVE RELEASE OF PHENYLPROPANOLAMINE HCl FROM LONG-ACTING APPETITE SUPPRESSANT PRODUCTS: ACUTRIM VS. DEXATRIM

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ABSTRACT

The release of phenylpropanolamine HCl from two commercially available long-acting appetite suppressant products, Acutrim and Dexatrim, was evaluated by using a dissolution apparatus modified from the well-calibrated Ghannam-Chien diffusion cells. The solubility profile of phenylpropanolamine showed extreme dependency on pH. The release of phenylpropanolamine from Acutrim tablets was observed to be fairly independent of pH and fluid dynamics, but is affected by the osmotic pressure in the dissolution medium. The release profiles of phenylpropanolamine

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 0363-9045/85/1010-1639$3.50/0

from both Dexatrim and Acutrim were observed to consist of two stages: an initial, fast-release phase and a sustained-release phase at steady state. While both products achieve 100% release of the loading dose, the sustained-release portion of the phenylpropanolamine dose was observed to release from Acutrim tablets at zero-order kinetics over a 8-hr period, but showed a gradual dissolution from Dexatrim granules for over a 4-hr duration. Therefore, a prolonged release of phenylpropanolamine over the target 16-hr period was achieved by Acutrim tablets, but not by Dexatrim capsules.

INTRODUCTION

Obesity is the pathological accumulation of fat, which exceeds the needs for optimum body functioning (1). Most obesity cases involve overeating, particularly of carbohydrates or fats. The calories ingested beyond those necessary for normal energy requirements are usually deposited and stored as fat. The question of why individuals ingest more calories than they need is complex. The answer may be related to physiological, genetic, environmental, or psychological factors. Studies have shown a significant association between mortality and obesity.

Two satisfactory means of long-term weight control are calorie reduction and physical activity (2). Persistent dietary restraint has been proven essential, but difficult to achieve. Various sympathomimetic and related drugs that depress appetite have been used to make a low-calorie diet more tolerable.

Phenylpropanolamine is one of the sympathomimetic agents most commonly used and has been formulated in several sustained-release dosage forms for appetite suppressant (3). It acts as an indirect sympathomimetic agent, exerting more prominent peripheral adrenergic effects with weak central stimulant actions (4). The drug, phenylpropanolamine, has been a very popular target for the consumers, due to its increasing therapeutic importance and possible adverse reactions. A study conducted by R. Noble of Cathedral Hill Obesity Clinic concluded that there is no "clinically significant hypertensive risk" to generally healthy individuals who use phenylpropanolamine for appetite suppression (5). However a drug delivery system with a predictable and controllable drug release profile is considered to be more desired, since the toxicity of the drug and any possible adverse reactions could be minimized.

A new long-acting appetite suppressant oral product, named Acutrim[1], was recently developed from the controlled-release osmotic pump technology (6-8) to deliver the phenylpropanolamine HCl at controlled rate for 16 hours. On the other hand, a long-acting Dexatrim[2] capsule, which has already established a very successful position in the appetite suppressant oral product market, was formulated from the sustained-release Spansule® technology (9) to administer the same drug at sustained release manner for 18 hours.

The purpose of this study is to compare the in-vitro release kinetics of phenylpropanolamine HCl from Acutrim and Dexatrim,

using a well-calibrated Ghannam-Chien diffusion system as the dissolution apparatus.

EXPERIMENTAL

Material:

The reagents used in this investigation were either USP or NF grades and were used as obtained. Acutrim[1] and Dexatrim[2] were evaluated as purchased.

Dissolution Apparatus:

The dissolution apparatus (Figure 1) was modified from the well-calibrated Ghannam-Chien diffusion system[3], which consists of three pairs of membrane permeation cells and one 6-station synchronous magnetic stirrer. An impermeable Teflon membrane was sandwiched between each pair of half cells to make two dissolution cells in mirror image for duplicate experiment. The six-station synchronous magnetic stirrers assure a uniform mixing condition among the six dissolution cells. Each of the cells was stirred by a Teflon-coated spin bar rotating at a constant speed of 425 rpm in a specially designed stirring platform. The cells were held at constant temperature of 37°C by circulating a thermostated water through the water jacketed compartment.

Dissolution Media:

A simulated gastric fluid without pepsin was prepared and used as the dissolution medium for the first two hours of dissolution studies. At the end of gastric dissolution the pH

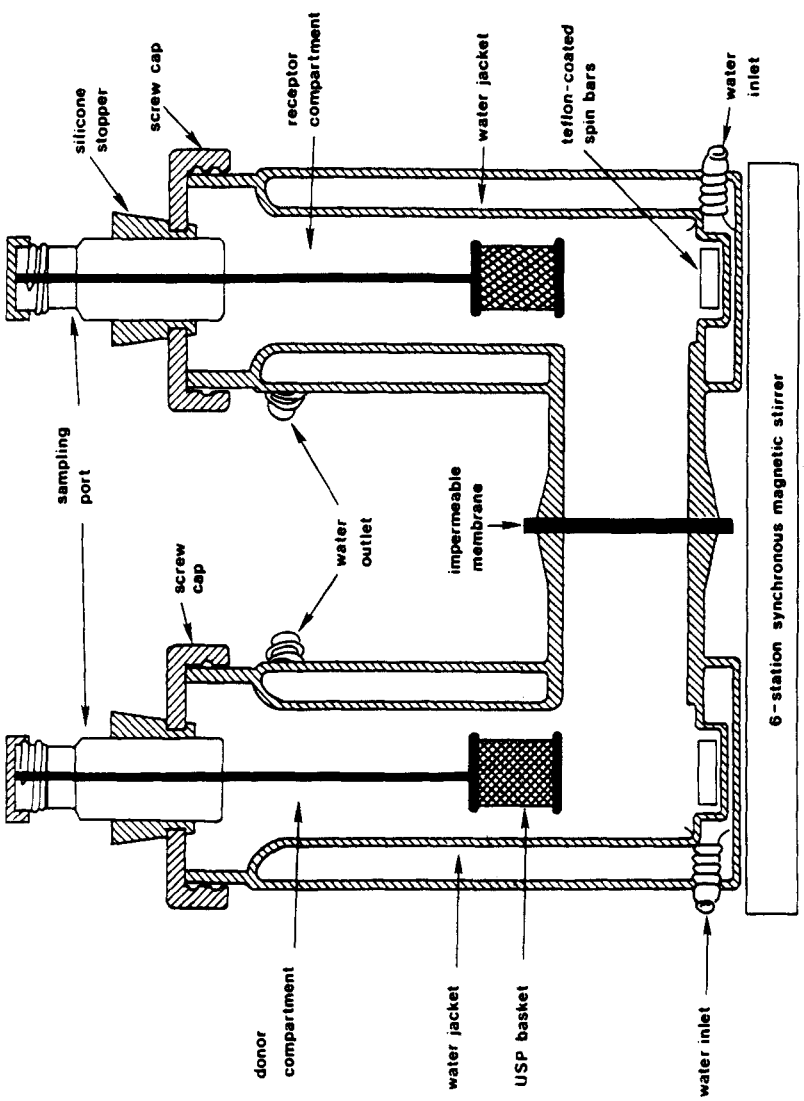

Figure 1: Diagrammatic illustration of the dissolution apparatus modified from the Ghannam-Chien diffusion system for dissolution studies of long-acting oral dosage forms.

was immediately adjusted to 7.5 ± 0.1 to simulate the intestinal condition by addition of 22.5 grams of trisodium phosphate ($Na_3PO_4.12H_2O$) to every liter of dissolution media (10).

Determination of Dissolution Rate:

One hundred and seventy (170) milliliters of simulated gastric or intestinal fluids was added to each of the six dissolution cells. In the case of Dexatrim[2] sustained-release capsules, one hard gelatin capsule was opened up and the granules were either dispersed in each of the dissolution media or loaded in each of the USP baskets suspending in the dissolution cells. In the case of Acutrim tablets, one tablet was loaded in each USP basket. The concentration of phenylpropanolamine in the dissolution media was determined spectrophotometrically[4] as a function of time at the specific wavelength of 207 nm.

Effect of Osmotic Pressure on Dissolution Rate

To study the effect of osmotic pressure on the release profile of phenylpropanolamine HCl, 3.532, 8.241, and 19.90 gm of NaCl were added into 170 ml of simulated intestinal fluid to increase the osmotic pressure from 12.16 atm to 30.16, 54.16 and 114.0 atm, respectively. The dissolution study of Acutrim tablets was carried out in these media in the same manner as outlined above.

Determination of Solubility

The solubility of phenylpropanolamine in citrate-phosphate buffer and simulated gastrointestinal fluid was determined by

stirring an excess amount of drug in each medium at 37°C in the dissolution cells for 24 hours to reach equilibrium. The solution pH was measured before and after each solubility experiment. At predetermined intervals aliquots of the solution were withdrawn from each cell using a pre-heated syringe with a 0.45 μm membrane filter. The content of phenylpropanolamine in the filtrate was determined, after proper dilution, by UV spectrophotometry[4].

RESULTS AND DISCUSSIONS

In-vitro dissolution test is now widely used as a standard method for studying the release of drugs from conventional oral dosage forms to provide the information on bioavailability and product uniformity. For conventional oral drug products the in-vitro dissolution criteria are usually expressed in terms of the fastest possible dissolution rate, whereas the requirement is quite different for long-acting drug products. In the latter case, optimum dissolution rate is not the fastest one that can be obtained, but rather some intermediate values, which hopefully will reflect the prolonged release of the drug in the GI tract, are desired. However, there are currently no official guidelines on the in-vitro dissolution tests of oral controlled dosage forms.

In this study, the dissolution was conducted in the recently developed Ghannam-Chien diffusion cells. The hydrodynamic properties of these cells have been well calibrated (11). The simulated gastric fluid used in the dissolution studies was found to be capable of maintaining the gastrointestinal pH's and a

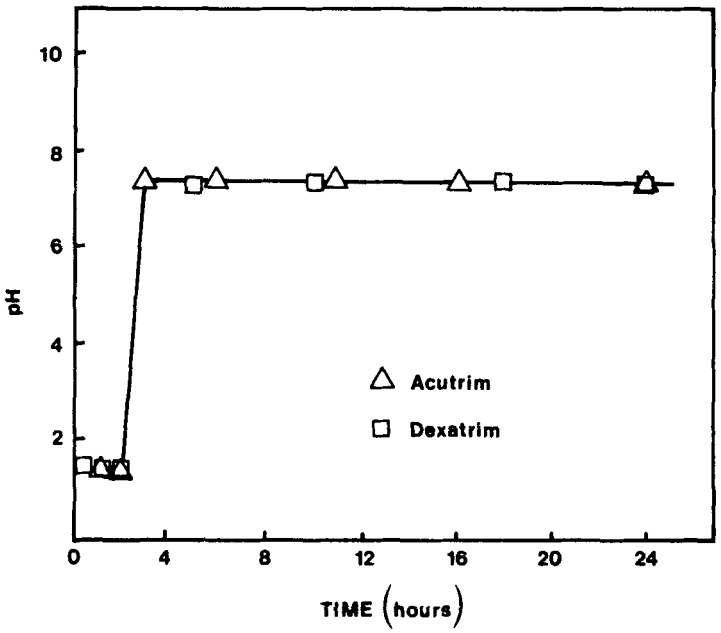

Figure 2: pH-time profile for the dissolution of Acutrim(△) and Dexatrim(□).

sufficiently high buffer capacity to tolerate the pH change due to the release of phenylpropanolamine HCl from the dosage forms. The immediate dissolution of trisodium phosphate, which was added at the end of second hour, was observed to shift the pH of the media rather quickly to simulate the intestinal condition. The pH profiles of Acutrim tablet and Dexatrim capsule under the dissolution conditions outlined above were comparably the same throughout the dissolution experiments (Figure 2).

Solubility-pH Profile of Phenylpropanolamine

The solubility of pharmaceutical amines and their hydrochloride salt may vary greatly in the gastrointestinal pHs

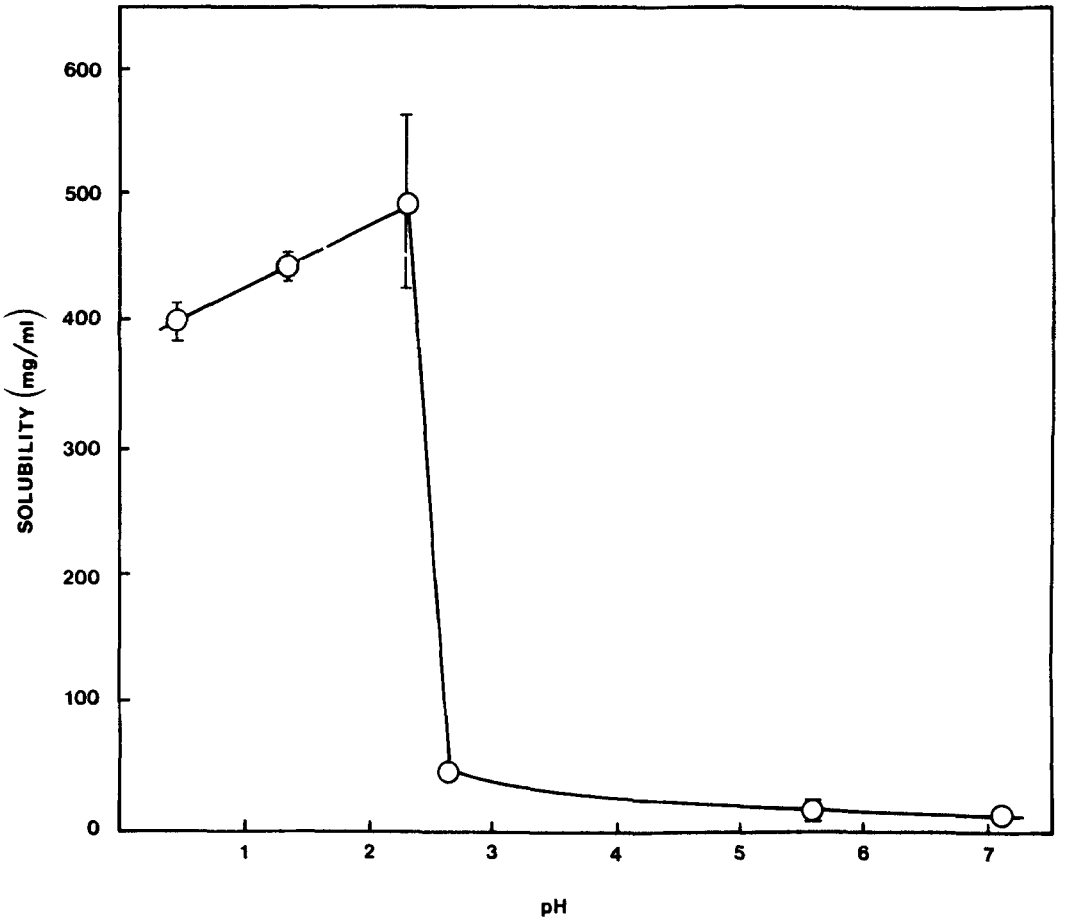

Figure 3: Solubility-pH profile of phenylpropanolamine HCl.

depending upon their pKa value. This pH-sensitive solubility behavior influences substantially the dissolution rate of these compounds in GI tract. Kramer and Flynn (12) showed that the solubility curves of a salt and its base intersect at a sharp angle at the pH of maximum solubility (pH_{max}) of both forms. The solubility-pH study of phenylpropanolamine indicated that the pH of maximum solubility is at around 2.5 (Figure 3). The

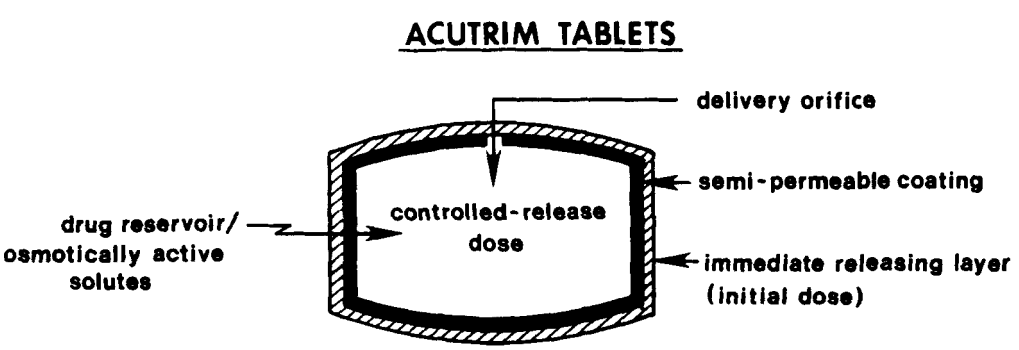

Figure 4: Diagrammatic illustration of Acutrim tablet composition.

aqueous solubility of phenylpropanolamine was determined to be ranging from 450 to 16 mg/ml in the pH range of 0.5 to 7.4. This solubility profile is much higher than the concentration of phenylpropanolamine (0.1 to 0.3 mg/ml) in the dissolution medium throughout the studies. In consequence, the sink condition was well maintained.

Release Profile of Acutrim

Acutrim is a recently marketed long-acting appetite suppressant product with the release of phenylpropanolamine HCl controlled by the osmotic pressure. Primarily, it consists of a reservoir of phenylpropanolamine HCl, as both a pharmacologically active ingredient and an osmotically active agent, in the core tablet (5.41 ± 0.004 mm in diameter) coated with a semipermeable polymeric membrane. It also contains a delivery orifice driven by the laser beam. The whole tablet is then surrounded by a coating film (0.47 ± 0.04 mm in thickness) to contain an

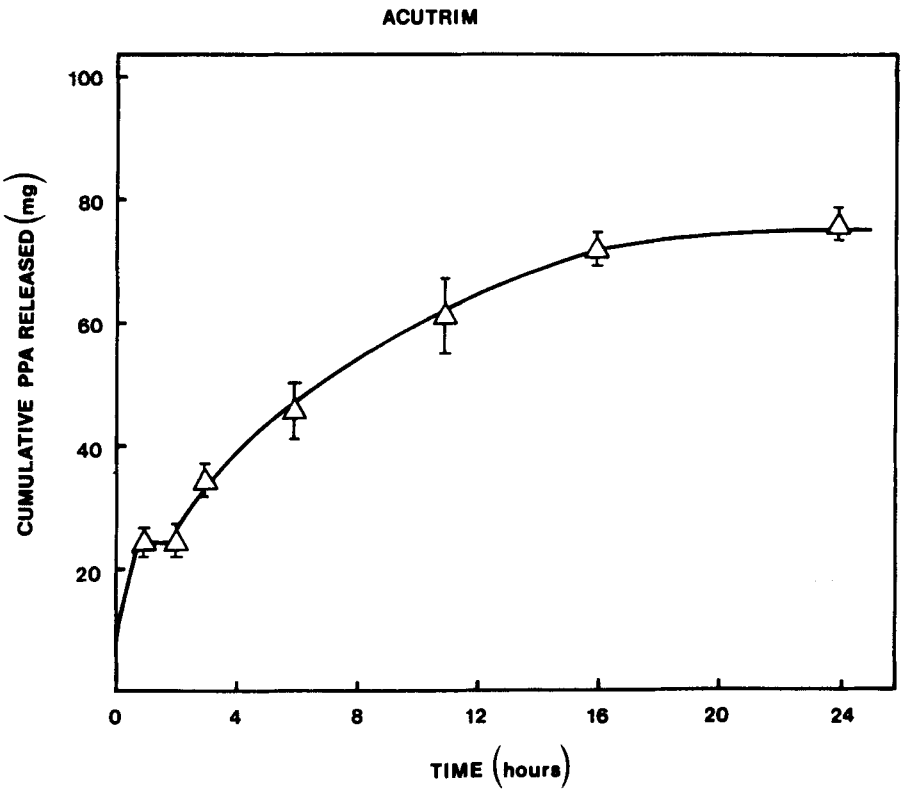

Figure 5: Release profile of phenylpropanolamine (PPA) from Acutrim tablets (N=6) in the simulated gastrointestinal fluid for the initial 2 hours and in the simulated intestinal fluid for the remaining 22 hours.

immediate-release dose of phenylpropanolamine (Figure 4). The release profile of phenylpropanolamine from Acutrim tablets in the dissolution medium was observed to encompass two stages (Figure 5): immediate release of the initial dose embedded in the coating film surrounding the semipermeable membrane, and the zero-order release of the maintenance dose in the tablet core.

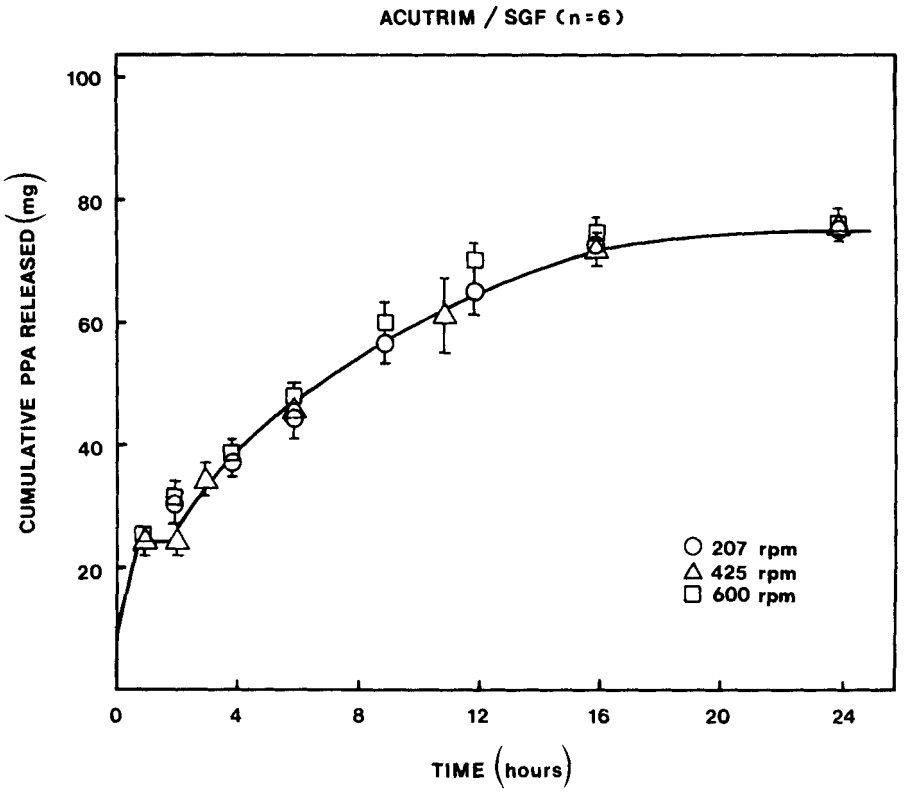

Figure 6: Effect of rotation speeds on the release profile of phenylpropanolamine from Acutrim tablets (N=6). Key: (○) 207 rpm, (△) 425 rpm, and (□) 600 rpm.

During the dissolution process, about 24 mg of the drug, which stands for 32% of the loading dose (75 mg), were released from the coating film on the outside of the Acutrim tablet in the first hour. This immediate release is designed for a rapid attainment of steady-state drug concentration in the body. The cumulative release of the drug from the Acutrim was then becoming proportional with time since the third hour of dissolution, i.e. zero-order delivery. After sixteen hours of release, the drug

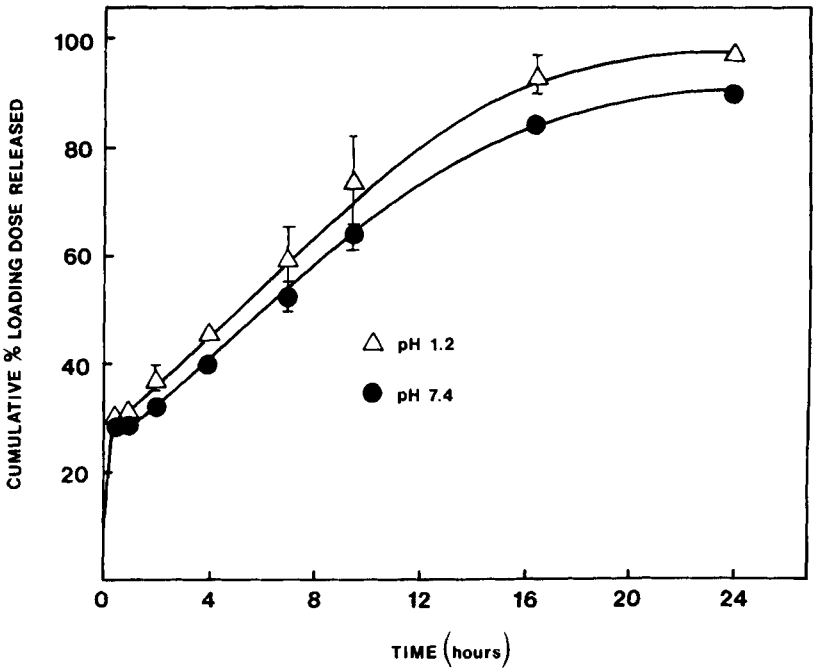

Figure 7: Effect of solution pH on the release profile of phenylpropanolamine from Acutrim tablets (N=6). Key: (△) pH 1.2 and (●) pH 7.4.

concentration in the Acutrim was no longer saturated and a non-zero-order release profile was then obtained. The total amount of phenylpropanolamine released in sixteen hours is 71.80 ± 3.98 mg per tablet, which is 95.74 (±5.31)% of the claimed dose (75 mg) in the tablet.

The release profiles of Acutrim at various rotation speeds were also studied. It was observed (Figure 6) that the rotation speeds have no influences on the release kinetics of Acutrim in the range of 200 to 600 rpm.

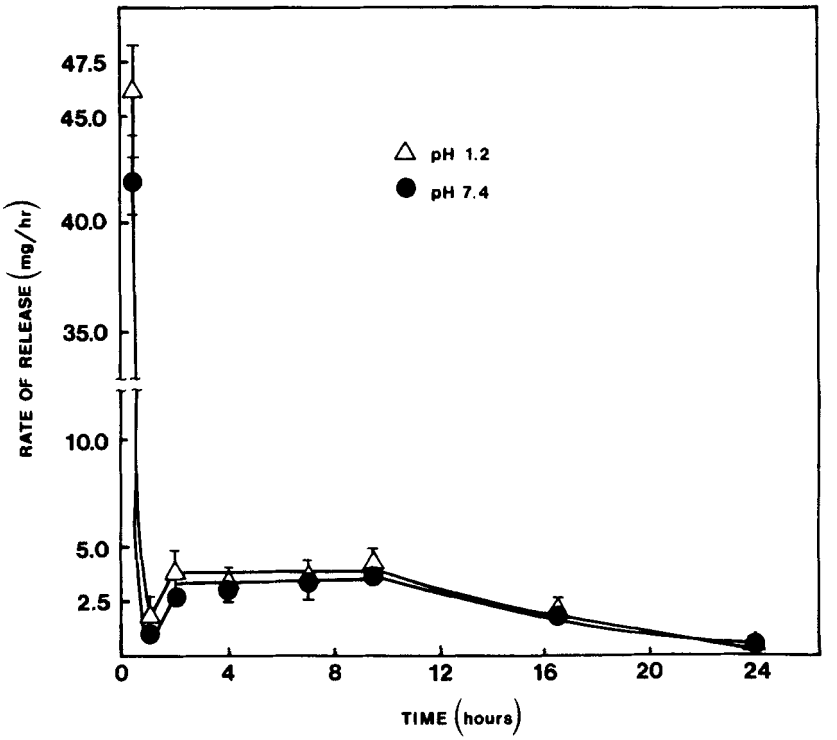

Figure 8: The time course for the release rate profile of phenylpropanolamine from Acutrim tablets at pH 1.2 (△) and pH 7.4 (●).

The effect of pH on the release profile of phenylpropanolamine from Acutrim tablet is shown in Figure 7. Theoretically, the release of drug from Acutrim should be independent of pH, however, the result obtained shows a faster rate and greater extent of release in the gastric than in the intestinal condition. This could be attributed to the effect of pH on the dissolution of the initial dose from the immediate releasing layer, and the increased osmotic pressure in the dissolution medium after the addition of trisodium phosphate at 2-hr point. The release of

phenylpropanolamine from the outer coat layer is dissolution controlled and thus would be affected by the solubility of the drug in the medium (Figure 3). As can be seen in Figure 8, the rate of release in the initial stage is much higher in gastric than in the intestinal condition.

Effect of Osmotic Pressure on Dissolution Profiles

The delivery rate of the maintenance dose from osmotic pump is defined by the following relationship:

$$\left(\frac{Q}{t}\right) = \frac{P_w A_m}{h_m} (\pi_s - \pi_e) S_D \qquad \text{(Eq. 1)}$$

where P_w, A_m, and h_m are, respectively, the water permeability, the surface area, and the thickness of the semipermeable coating membrane (Figure 4). These parameters should maintain constant if the device is under good quality control. S_D, the aqueous solubility of the drug inside the device, is also a constant value. However, the differential osmotic pressure, $(\pi_s - \pi_e)$, will be dependent upon the ionic solute concentration and osmotic pressure (π_e) in the environment, e.g. dissolution media in the present investigation the osmotic pressure in the dissolution media can be calculated by Van't Hoff's Relationship (13):

$$\pi_e = \frac{n}{v} RT \qquad \text{(Eq. 2)}$$

where n is the number of moles of the ionic solute in the dissolution media with a volume of v in liters; R is the gas constant equal to 0.082 liter atm/mole deg; and T is the absolute temperature.

Using Equation (2), the osmotic pressure of simulated gastric fluid was calculated to be 6.14 atm. Incorporation of phosphate salt into the gastric fluid to shift it to the simulated intestinal fluid resulted in the increase of osmotic pressure in the dissolution media by 6.02 atm to 12.16 atm. This increased osmotic pressure may explain the slightly slower release profile of phenylpropanolamine in the simulated intestinal fluid than in the simulated gastric fluid (Figures 7 & 8).

The effect of osmotic pressure in the dissolution media on the release profiles of phenylpropanolamine HCl from Acutrim tablets was further studied by addition of NaCl, an osmotically active salt, into the simulated intestinal fluid. Results indicated that the release of phenylpropanolamine HCl from the Acutrim tablet (controlled-release fraction) is dependent upon the osmotic pressure in the dissolution media (Figure 9). The greater the osmotic pressure in the media, the lower the release profile of phenylpropanolamine HCl.

No drug was released from the controlled-release dose as the osmotic pressure developed in the dissolution media was equal to or greater than the one in the core, i.e., $\pi_s \leq \pi_e$ or $\pi_s - \pi_e \leq 0$ (Equation 1). The effect of osmotic pressure on the rate of release from Acutrim tablet is shown in Figure 10. The results indicated that the rate of release of phenylpropanolamine HCl from Acutrim tablet's controlled-release fraction is linearly decreased as the osmotic pressure in the dissolution media increases.

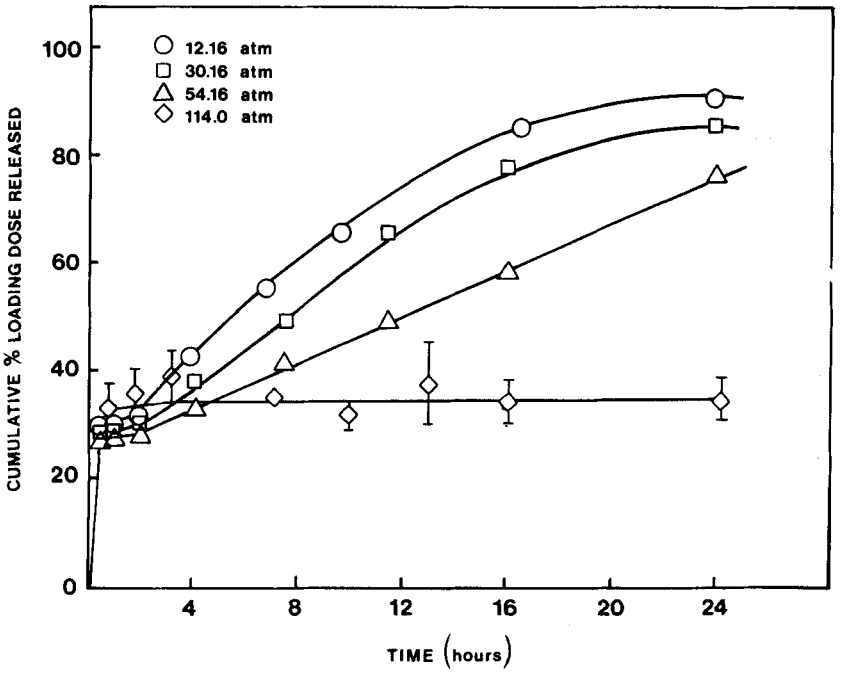

Figure 9: The effect of increased osmotic pressure in the dissolution medium on the release profile of phenylpropanolamine from Acutrim tablet at intestinal condition. Key: (◯) simulated intestinal fluid at 12.16 atm osmotic pressure, (□) with NaCl at 30.16 atm osmotic pressure, (△) with NaCl at 54.16 atm osmotic pressure, (◇) with NaCl at 114.0 atm.

Comparative Release of Acutrim and Dexatrim

The cumulative release of phenylpropanolamine from both products were compared under the same gastrointestinal condition. Dexatrim, the time-released capsule, is designed on the basis of dissolution-controlled mechanism. The capsule contains both immediate- and sustained-release granules. The drug was embedded

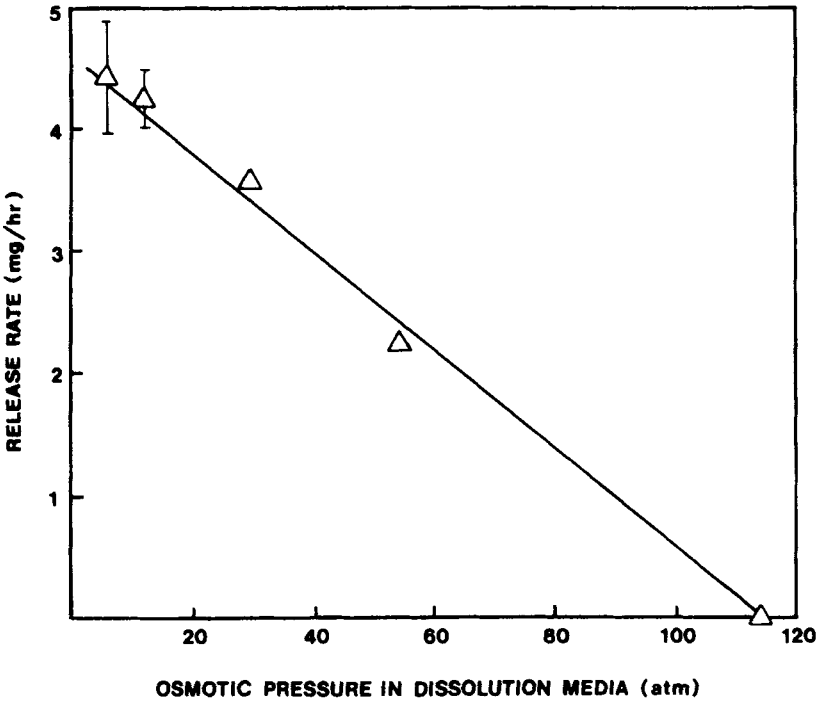

Figure 10: Effect of osmotic pressure in the dissolution media on the rate of release of phenylpropanolamine from Acutrim tablets.

in the coating layer surrounding the nonpareil seeds with the average diameter of 1.2 ± 0.1 mm. It is a common practice to employ one-third of the granules in non-sustained release form to provide the immediate availability of the drug, with the remaining two-thirds of the granules being coated to different thicknesses to provide a sustained effect over a desired period. The dissolution rate in the fluid medium can be described by Noyes-Whitney equation:

$$\frac{dm}{dt} = KS(C_s - C_t) \qquad \text{(Eq. 3)}$$

where dm/dt is the rate of dissolution of the drug in the medium. The dissolution rate is influenced by the dissolution constant (K), the effective surface area (S), the solubility in the dissolution medium (C_s), and the concentration in the dissolution medium (C_t) at time t. Since $C_t \simeq 0$ or $C_s \gg C_t$, so, Eq. 3 can be simplified to:

$$\frac{dm}{dt} = KSC_s \qquad \text{(Eq. 4)}$$

The results in Figure 11 indicated that Dexatrim also releases the active ingredient, phenylpropanolamine HCl, at two stages: a fast-release of the initial dose and a sustained-release of the maintenance dose. The initial release profile was found identical to that from Acutrim tablet. However, the release of drug from Dexatrim in the sustained-release phase (i.e., from 2 to 24 hrs) is much more rapid than the release from Acutrim. The results suggested that 100% of the total loading dose were released within 7 hrs from Dexatrim as compared to 16-18 hrs from Acutrim. Apparently, the release of phenylpropanolamine from Dexatrim in the sustained-release phase is not a zero-order release, while the release of drug from Acutrim is controlled by several constant system parameters, such as P_w, A_m, h_m and S_D, until the value of $(\pi_s - \pi_e)$ is no longer a constant as due to the fact that the drug concentration inside the Acutrim tablet

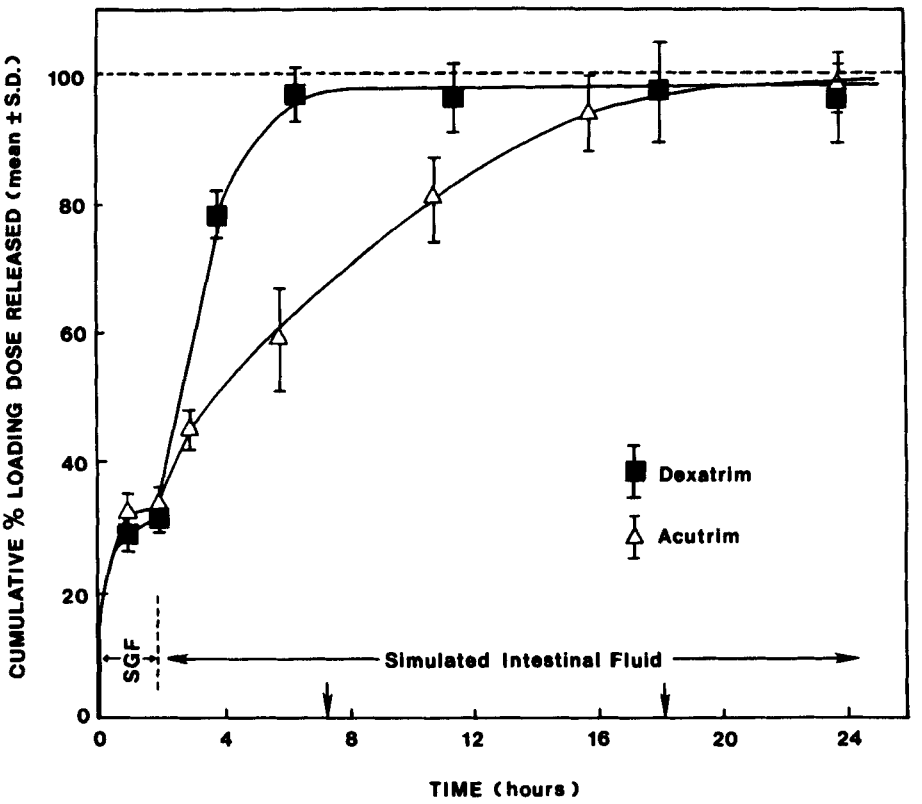

Figure 11: Comparative % loading dose released vs. time profiles for the release of phenylpropanolamine from Acutrim (△) and Dexatrim(■) in simulated gastric fluid (SGF) for 2 hours and then in simulated intestinal fluid for the remaining 22 hours.

falls below the saturation solubility and/or the condition of $\pi_s >> \pi_e$ can no longer exist.

CONCLUSION

The results lead us to conclude that the Acutrim tablet has provided a better control over the release of appetite

suppressant, phenylpropanolamine, from the maintenance dose portion than does the Dexatrim capsule. It is also recognized that more studies needed to be conducted to substantiate this in-vitro observation and also to establish the relationship between drug release and gastrointestional absorption.

ACKNOWLEDGMENT

The authors wish to express their appreciation to FMC Foundation for donation of an unrestricted grant in 1983 to support this research, Mr. Y. Sun for technical assistance and to Ms. M. Boslet for manuscript preparation.

FOOTNOTES

1. Ciba Consumer Pharmaceuticals, Edison, New Jersey 08837
2. Thompson Medical Co. Inc., New York, New York 10150
3. Bellco Glass Inc., Vineland, New Jersey 08360
4. Perkin-Elmer 559A UV/VIS Spectrophotometer, Perkin-Elmer Corp., Elmwood Park, New Jersey 07407

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