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PREPARATION AND EVALUATION OF EUDRAGIT® ACRYLIC RESIN FOR CONTROLLED DRUG RELEASE OF PSEUDOEPHEDRINE HYDROCHLORIDE[1]

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ABSTRACT

The preparation of a sustained release dosage form for pseudoephedrine hydrochloride was evaluated. Beadlets (PS) containing pseudoephedrine hydrochloride were prepared by spraying a slurry of pseudoephedrine hydrochloride, Eudragit® S-100, dibutyl sebacate and alcohol onto non-pariel seeds via the Wurster column process. The oven-dried PS beadlets were coated with different levels of Eudragit® RS (poorly water permeable) and Eudragit® S-100 (enteric resin). In-vitro dissolution

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studies of these beadlets indicated the coating levels, types of resins and types of plasticizers in the film play a major role in determining the release rate profiles of the drug from the coated beadlets. Drug release from the coated beadlets appeared to follow first order kinetics. An overcoat of Eudragit® S-100 resin (2% coating level) can eliminate the formation of soft lumps which are commonly observed with Eudragit® RS coated beadlets. The Eudragit® S-100 overcoat also contributes to retard drug release from the coated beadlets in dissolution media ranging from pH 1.2 to 6.5.

INTRODUCTION

The potential of using Eudragit® resins as a polymer system to prepare sustained release formulations via the fluidized bed process has been demonstrated recently.[1-3] Indomethacin (very slightly soluble in water) sustained release beadlets were successfully prepared via a Wurster column process utilizing Eudragit® resins.[4] The effect of raw materials and processing conditions on the quality of the finished product for this layering process were also studied.[5] In the earlier study[4], it was found that the release rate profile of the indomethacin Eudragit® S-100 beadlets (IS) was affected by the pH of the dissolution media. For instance, 96% of the indomethacin was released at the 45 minute interval at pH 7.2 phosphate buffer,

whereas only 44% of total drug content was released at the end of 8 hours in pH 6.5 phosphate buffer. It was apparent that the release rate profile of IS beadlets was influenced by the chemical properties of Eudragit® S-100. Eudragit® S-100 is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester and is intended to be used for enteric coating.[6,7] Eudragit® S-100 film is insoluble in buffer solutions below pH 6.0, and also in gastric juices. It is slowly soluble in the region of the digestive tract where the juices are neutral to weakly alkaline, and in buffer solution above pH 7.0.[6] In pH 6.5 media, Eudragit® S-100 remained intact. Therefore, the release of indomethacin from the IS beadlets remained a diffusin controlled process. However, in pH 7.2 media, the Eudragit® S-100 started to dissolve. This destroys the indomethacin Eudragit® S-100 matrix structure and allows for more rapid release of the indomethacin. This study demonstrated that Eudragit® S-100 could be used effectively as an enteric polymer for this matrix system. Since indomethacin is practically water insoluble, it will be interesting to study whether Eudragit® S-100 can still be an effective enteric polymer in this matrix system with a water soluble drug. In the present study, pseudoephedrine hydrochloride (very water soluble) and Eudragit® resin systems are utilized in the Wurster column process to prepare sustained release beadlets. The effect of the nature of drug on the release rate profiles of the finished beadlets was examined. In addition, the types and amount of plasticizers used

with the Eudragit® resins on the release rates of the coated beadlets was also investigated.

MATERIALS AND METHODS

Materials.

Pseudoephedrine hydrochloride was NF grade (Granes Chemicals, New Jersey), talc (Charles B. Crystal Company, New York), 18-20 mesh nonpareil seeds (Ingredients Technology Corporation Pennsauken, NJ) and alcohol were USP grade. Dibutyl sebacate (Union Camp, Ohio), polyethylene glycol 8000 (Carbox®-8000 Fluke, Union Carbide Corporation), and diethyl phthalate (Eastman Chemical Products, Inc., Tennessee) were used as received. Eudragit® S-100 and RS were gifts from Rohm Pharma (Rohm Tech., Inc., Malden, MA). All reagents were analytical grade or better. Sudafed 12 hour capsules were used as received (Burroughs Wellcome Co, N.C.).

Preparation of Pseudoephedrine Hydrochloride, Eudragit® S-100, Dibutyl Sebacate, Alcohol Slurry.

To a two-liter stainless steel container holding 500 g of alcohol equipped with a lightning mixer, 6.8 g of dibutyl sebacate (DBS) was added and mixed. Sixty eight grams of Eudragit® S-100 were added gradually into the container and mixed until all the powders were dispersed. One hundred fifty grams of pseudoephedrine hydrochloride (as is) was introduced and mixed

until all powders were dissolved. Additionally, one hundred fifty grams of micronized pseudoephedrine hydrochloride was added and mixed until all powders were dispersed. The resultant slurry was then filled to 1080 g of total weight with additional alcohol. The solid content of the slurry was 34.6% (w/w).

Preparation of Pseudoephedrine HCl, Eudragit® S-100 Beadlets (PS Beadlets).

Beadlets containing pseudoephedrine hydrochloride were prepared by spraying the pseudoephedrine HCl, Eudragit® S-100, dibutyl sebacate, alcohol slurry onto 500 grams of the 18/20 mesh fractions of nonpareil seeds via the Wurster column (Aeromatic Strea-1 Coater, Aeromatic Ltd., Towaco, NJ). The coating parameters for this process are given in Table I. The resultant beadlets were dried at 50°C for 32 hours to remove the residual solvent from the beadlets.

Coating Operation of Pseudoephedrine HCl Sustained Release Beadlets.

Seven hundred grams of PS beadlets were coated in an Aeromatic strea-1 coater (Wurster insert) using either Eudragit® RS, or Eudragit® S-100 resins, or a combination of these two resins. The coating parameters are given in Table II.

Two different levels of diethyl phthalate (DEP) were incorporated into Eudragit® RS dispersions (10:1::RS:DEP and 10:2::RS:DEP). Polyethylene glycol 8000 was also utilized to

Table I

General Operating Parameters of the Aeromatic S-1 Coater and the Settings during the Manufacturing of Pseudoephedrine HCl Eudragit® S-100 Beadlets

Operating Parameters	Setting
Atomizing Air Pressure	2 Bars
Fluidizing Air Velocity	30 - 60 M^3/H
Partition Height	2 cm
Pump/Drive	Masterflex 16 Pump Head
Nozzle	1.2 mm Schnick Nozzle
Inlet Temperature	52 - 56°C
Outlet Temperature	34 - 36°C
Flow Rate of Coating Solution	10 - 20 g/min.

Table II

General Operating Parameters of the Aeromatic S-1 Coater and the Settings during the Coating of Pseudoephedrine HCl Sustained Release Beadlets

Operating Parameters	Setting
Atomizing Air Pressure	1.6 Bars
Fluidizing Air Velocity	50 - 60 M^3/H
Partition Height	2 cm
Pump/Drive	Masterflex 16 Pump Head
Nozzle	0.8 mm Schnick Nozzle
Inlet Temperature	46 - 50°C
Outlet Temperature	28 - 32°C
Flow Rate of Coating Solution	9 - 12 g/min.

Table III

Composition of Eudragit® RS and/or Eudragit® S-100 Dispersion (Polymer:Plasticizer::10:1)

	Weight (g)
Eudragit® RS or S-100	6.0
Talc, USP	1.8
PEG or DEP or DBS	0.6
Alcohol	86.6
Distilled Water	5.0

plasticize Eudragit® RS resin (10:1::RS:PEG). Eudragit® S-100 dispersions plasticized with dibutyl sebacate (10:1::S-100:DBS) were utilized for precoat and overcoat. The composition for these resin dispersions are presented in Table III and IV. The coating levels of each specific formula are given in Table V.

Dissolution.

In-vitro dissolution studies were carried out using the USP dissolution II apparatus (Paddle) at 37°C and 100 rpm. The dissolution media (900 ml) were various phosphate buffers (pH 1.2, 3.0, 5.0, 6.5, and 7.2). Samples were withdrawn from the

Table IV

Composition of Eudragit® RS/Diethyl Phthalate Dispersion
(Eudragit RS:DEP::10:2)

	Weight (g)
Eudragit® RS	6.0
Talc, USP	1.8
DEP	1.2
Alcohol, USP	86.0
Distilled Water	5.0

dissolution vessels at preselected time intervals. The collected samples were filtered through a 0.8 micron Millex filter unit and assayed spectrophotometrically at 257 nm for pseudoephedrine hydrochloride content. Each determination was carried out in triplicate. Absorbance followed Beer's Law over the range of concentrations encountered.

Assay.

Total drug content of PS beadlets was determined by dissolving accurately weighed portions of each batch in 100 ml phosphate buffer (pH 6.5, 0.07 M) and observing the spectrophotometric absorbance at 257 nm. Duplicate samples were assayed and the mean values were reported.

Table V

Composition of Coating Formula for Pseudoephedrine Hydrochloride Sustained Release Beadlets

Formulation No.	Coating Composition					
	Innercoat				Overcoat	
	Eudragit RS/DEP(10:1) (%) w/w	Eudragit RS/PEG(10:1) (%) w/w	Eudragit RS/DEP (5:1) (%) w/w	Eudragit S-100/DBS(10:1) (%) w/w	Eudragit RS/DEP(10:1) (%) w/w	Eudragit S-100/DBS(10:1) (%) w/w
I	2, 3, 4, 5, 6, 7, 8	-	-	-	-	-
II	8	-	-	-	-	1, 2
III	-	3, 5, 6, 7, 8	-	-	-	-
IV	-	8	-	-	-	1, 2
V	-	-	2, 3, 4, 6, 7	-	-	-
VI	-	-	-	1, 2	-	-
VII	-	-	-	2	1, 3, 5, 7, 8	-

DEP: Diethyl Phthalate DBS: Dibutyl Sebacate PEG: Polyethylene Glycol

RESULTS AND DISCUSSIONS

Physical Properties of Pseudoephedrine HCl, Eudragit® S-100 Beadlets (PS Beadlets).

Table VI shows that the Wurster column coating process is a reproducible means of preparing PS beadlets. The true density values, assay values of pseudoephedrine hydrochloride content in the finished beadlets, and the yield of beadlets for six batches of PS beadlets were similar. Furthermore, the particle size distribution for these six replicate batches of PS beadlets demonstrated that the layering process is reproducible. Ninty-nine percent of the finished beadlets were found on 14/18 mesh cut. The average arithmetric beadlet diameters ranged from 1266 to 1277 microns.

Table VII shows the cumulative percent of pseudoephedrine hydrochloride released from the six replicate batches of PS beadlets in pH 6.5 phosphate buffer. The standard deviations for the release rate data of these six batches of PS beadlets were very small indicating that the coating process was very reproducible. However, the release of drug from the beadlets was more rapid as compared to a similar system developed using Indomethacin.[4] Ninty-five percent of drug was released at the five minute interval. Eudragit® S-100 resins did not provide any retardation to the release of pseudoephedrine hydrochloride from the matrix beadlets. Its primary function was to bind drug onto the substrate (nonpareil seeds). A similar system developed

Table VI

Physical Properties and Physical Testing Data for Six Batches of PS Beadlets

Batch No.	Yield of The Process (%)	Efficiency of the Process (%) $\frac{\text{Actual Assay}}{\text{Theoretical Assay}} \times 100\%$	True Density (g/ml)	Particle Size Distribution			Mean Particle Diameter (microns)
				14/16 Mesh	16/18 Mesh	18/20 Mesh	
1	98.7	95.9	1.172	92.9	6.9	0.2	1276
2	99.2	95.7	1.188	93.2	6.5	0.3	1277
3	98.6	94.4	1.187	89.8	9.9	0.3	1269
4	98.6	94.4	1.186	93.0	6.9	0.1	1276
5	97.4	94.7	1.193	88.1	11.6	0.3	1266
6	97.9	95.4	1.196	91.6	8.1	0.3	1273
Average (S.D.)	98.4 (± 0.64)	95.1 (± 0.67)	1.187 (± 0.008)				1273 (±4.4)

Table VII

In-Vitro Dissolution Profiles of Six Batches of PS Beadlets

Batch Number	Dissolution (pH 6.5 Phosphate Buffer)		
	5 Minutes	10 Minutes	15 Minutes
1	96	97	100
2	94	100	100
3	94	100	100
4	99	101	100
5	94	99	100
6	92	99	100
Average (S.D.)	94.8 (± 2.4)	99.3 (± 1.4)	100

using indomethacin (water insoluble) exhibited a much slower release rate profile indicating that the beadlets exhibited sustained release characteristics.[4] Pseudoephedrine hydrochloride (water soluble), embedded on the surface of matrix beadlets, released rapidly upon contacting the dissolution medium. As the drug started dissolving, microporus channels may have been created in the drug matrix. Consequently, the dissolution medium could penetrate into the inner matrix rapidly to solubize embedded drug molecules. Eudragit® S-100, even though it was established to be an effective enteric resin in a

Table VIII

Composition of Free Films Prepared Using Different Combinations of Eudragit® RS and Plasticizers

Resin (Part)	Plasticizers		Description of the Free Film*
	Water Insoluble(Part)	Water Soluble (Part)	
Eudragit RS (10)	DEP (1)	-	Flexible but Tacky Films
Eudragit RS (10)	DEP (1.5)	-	More Flexible but Tacky Films
Eudragit RS (10)	DEP (2)	-	More Flexible but Tackier Films
Eudragit RS (10)	DEP (2.5)	-	Excellent, Continuous, Flexible but Tackier Films
Eudragit RS (10)	-	PEG-8000(1)	Brittle films but not Tacky
Eudragit RS (10)	-	PEG-8000(2)	Relatively flexible films.
Eudragit RS (10)	-	-	Discontinuous, powdery films.

* Free Films - samples were prepared by pouring dispersion in a petric dish and allowing the solvent to evaporate over 14 hours at room temperature or at 50°C. Film characteristics were determined by physical and mechanical observation. Visual examination and physical touching of the films were carried out to evaluate the tackiness and flexibility of the films. Film fragments were removed from the petri dish with the aid of a spatula to evaluate the strength of the films.

DEP: Diethyl phthalate

PEG-8000: Polyethylene glycol

similar formulation prepared with a water insoluble drug[4], cannot prevent or retard drug diffusion through a "leaky" microporus matrix. The rationale of utilizing Eudragit® S-100 in this layering process to yield a controlled release drug matrix for a water soluble drug apparently may not be a feasible means to accomplish the task.

Effect of Relative Ratio of Eudragit® Resins to the Placticizers on the Quality of Film-Coating.

It should be pointed out that the technique of free film study of Eudragit® resin and plasticizers was adopted as a screening procedure to select the appropriate type Eudragit® resin/plasticizer film for the initial experiments. As can be seen in Table VIII, free films of different combinations of Eudragit® RS and plasticizer casted on a petri dish, indicate that Eudragit® RS/DEP (10:2.5) gives the most flexible film. As the concentration of DEP increased in the film, a more flexible film resulted. However, the tackiness of the film also increased. With the same ratio of Eudragit® RS to the plasticizer, such as 10:2, the combination of Eudragit® RS/DEP yielded a more flexible but tackier film as compared to the combination of Eudragit® RS/PEG. In terms of flexibility of the resultant film, DEP (water insoluble plasticizer) seems to be a better plasticizer than PEG (water soluble plasticizer) to plasticize Eudragit® RS resin. Eudragit® RS alone (without any plastizier) mixed with alcohol yielded a discontinuous, powdery fragment of film. Data indicated that it was necessary to incorporate plasticizer to Eudragit® RS resin to yield a flexible continuous film. This finding was in agreement with Rohm Pharm's recommendation. The manufacturer strongly recommended the use of a plasticizer with Eudragit® RS resin to yield a flexible film[6].

It was reported in the literature that the processing parameters of the coating process, the tackiness of the liquid or

suspension and the coating formulation could effect the quality of the film coating deposited onto the substrate[8-13]. In an ideal coating process, each layer of coating is applied uniformly and is dried completely before beadlets are recycled for further coating. The coated beadlet should remain as a single unit throughout the entire coating process. Consequently, the entire coating process should yield little or no agglomeration. The surface of drug-coated beadlets should appear smooth and continuous. Whereas, if the coating process or coating formulation is not optimized, the disposition of the polymer film onto the substrate would fail to spread uniformly leaving an imperfect film. The tendency of beadlets to form agglomerate would also increase in these circumstances[12-14].

In our study, the tendency of beadlets to agglomerate in the coating process is used as a guideline to evaluate the coating formulation of Eudragit® RS and plasticizers. The best coating formulation should yield the leastest number of agglomerates. Three sets of experiments were conducted to evaluate the three different coating formulations using Eduragit® RS and plasticizers (PEG or DEP). To study the effect of types of plasticizer on the coating formulation, the ratio of Eudragit® RS to plasticizer (either DEP or PEG) of 10:1 was selected for coating experiments. The coating formulation of Eudragit® RS/DEP (10:1) gave a more flexible film in the free film study (Table VIII) than the coating formulation of Eudragit® RS/PEG (10:1). The ratio of 10:1 of Eudragit® to plasticizer was selected based on the Rohm Pharma's recommendation[6].

To study the effect of the amount of plasticizer on the coating formulation, the coating formulation of Eudragit® RS/DEP (10:2) was selected to compare with the coating formulation of Eudragit® RS/DEP (10:1).

The quality of film coatings obtained from the actual Wurster column coating process utilizing these three different coating formulations were in agreement with the results generated from the free film casted on a petri disk. The success of the coating formulation in the coating process is directly related to the tackiness of the Eudragit® film. The most trouble free coating formulation was observed with the combinaton of Eudragit® RS/PEG (10:1) applied onto the beadlets. This coating formulation yielded little or no agglomeration. This coating formulation showed the least in flexibility but the least in tackiness in the free film study. Whereas the coating formulation using the combination of Eudragit® RS/DEP (10:1) yielded more agglomerates, indicating that this formulation was far less desirable as compared to the Eudragit® RS/PEG (10:1) formulation. The worst coating formulation was observed when the combination of Eudragit® RS/DEP (10:2) was utilized for the coating. This coating formulation exhibited an excellent, flexible but tackier film in the free film study. In order to continue the coating process, an intermittent spray cycle was utilized to complete the coating process. The resultant coated product contained the highest number of agglomerates as compared to the other two coating formulations. These data seem to imply

that one should be cautious in selecting and applying the information generated from the casting of free films of Eudragit® RS and plasticizer. It was apparent that the degree of tackiness rather than the flexibility of the Eudragit® film is much more indicative in predicting the success of the coating formulation in the coating process. Owing to the inherent tacky nature of acrylic resins, one should always conduct actual coating experiment to evaluate the film formation of a particular acrylic resin/plasticizer system.

Effect of Film Thickness on Release Profile.

The release rate profiles of the pseudoephedrine hydrochloride sustained release beadlets depend, to a greater extent, on the coating level of the final product. As the coating thickness increased, a decrease in the release rates of the coated beadlets was observed (Figure 1 and 2). For instance, at the higher coating levels, such as 8% coating, pseudoephedrine hydrochloride sustained release beadlets [Eudragit® RS/DEP (10:1)] released 52% of the drug in 30 minutes, whereas those beadlets coated to weight increases of 3% and 5% released 92% and 78% of the drug, respectively. The integrity of the coating was well preserved throughout the dissolution experiments; even when the drug was completely depleted from a beadlet, the shell remained intact. In addition, as the level of coating thickness increased, the drug was released after a lag time, which became larger in proportion to the thickness of the Eudragit® RS

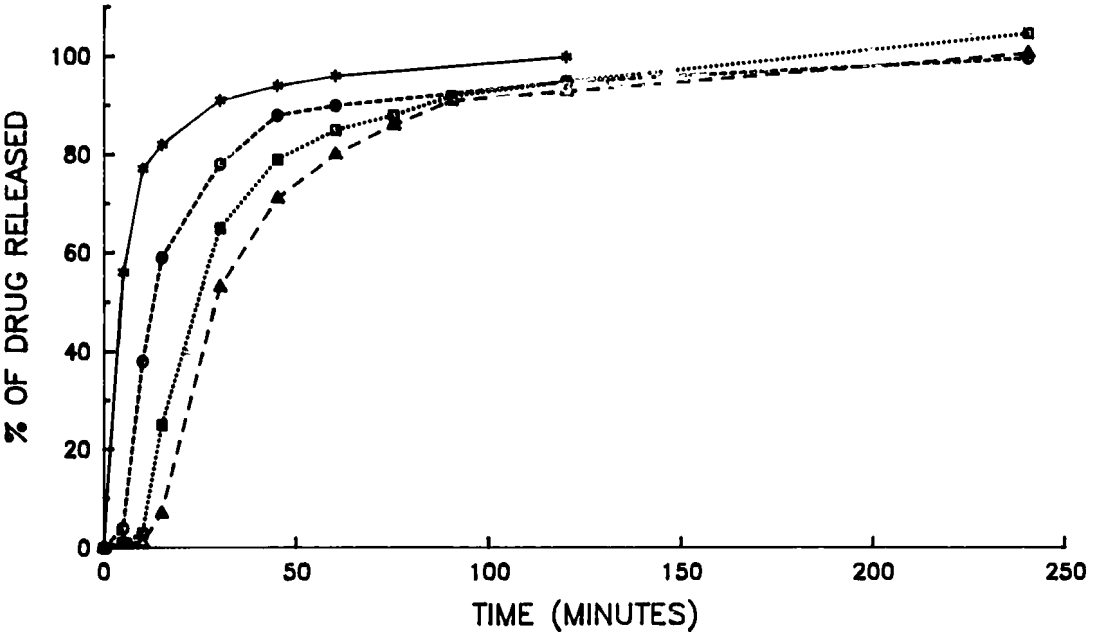

Figure 1. Effect of coating thickness on the release profile of pseudoephedrine HCl sustained release beadlets in pH 6.5 phosphate buffer (Eudragit RS:DEP::10:1). Coating: ✱ ,3%; ○ ,5%; □ ,7%;△,8%.

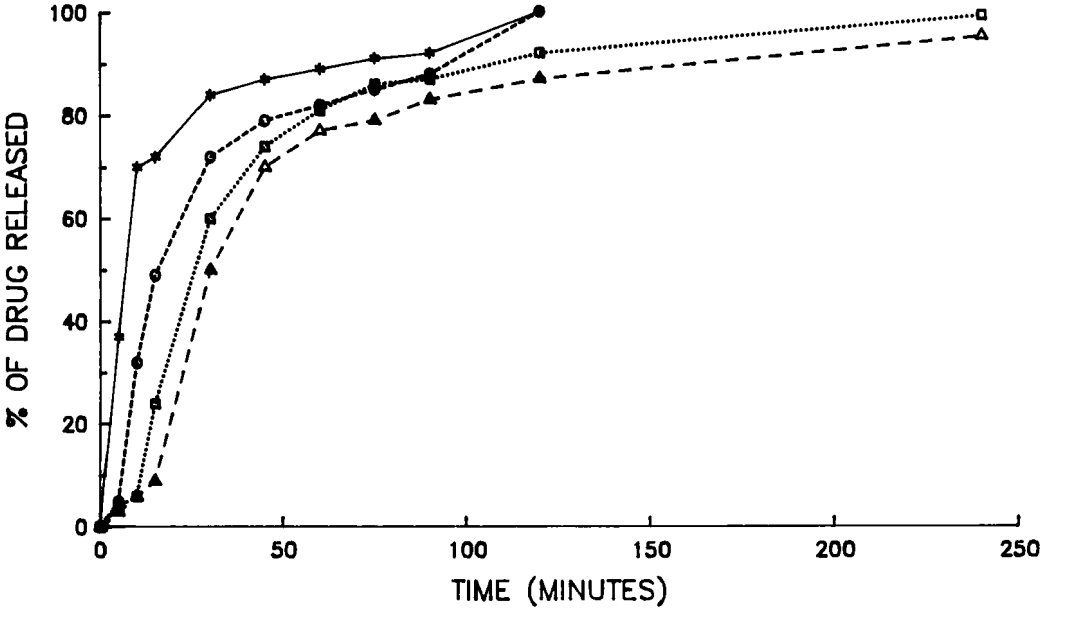

Figure 2. Effect of coating thickness on the release profile of pseudoephedrine HCl sustained release beadlets in pH 6.5 phosphate buffer (Eudragit RS:PEG::10:1). Coating: ✱ ,3%; ○ ,5%; □ ,7%;△,8%.

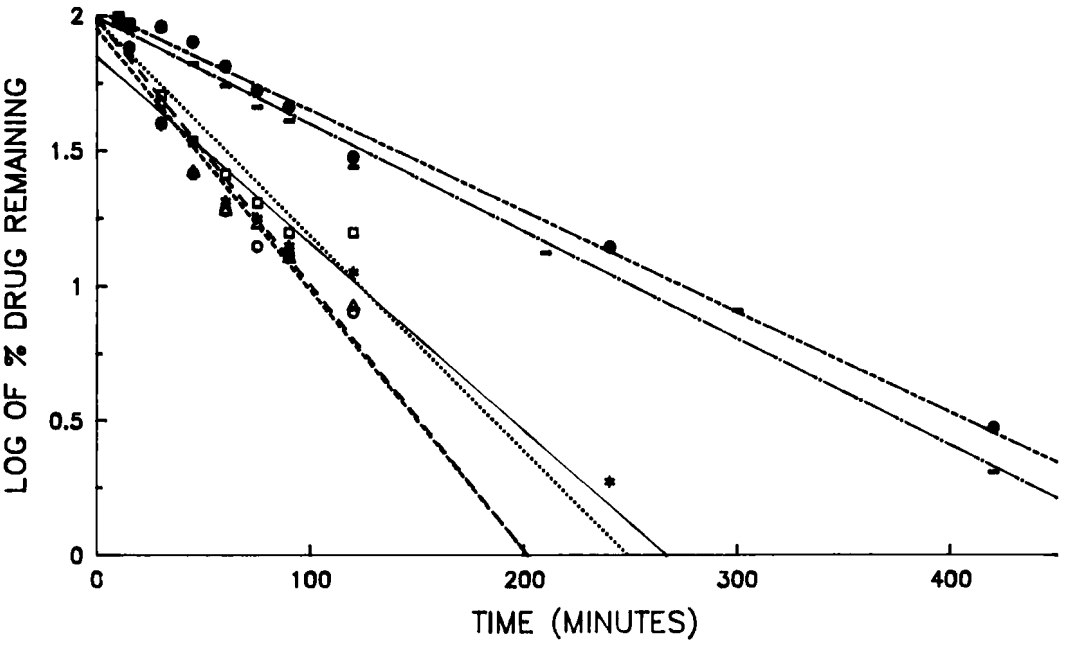

Figure 3. Release rate profile of pseudoephedrine from sustained release beadlets plotted assuming first order release kinetics in pH 6.5 phosphate buffer (Eudragit RS:DEP::10:1). Coating: ▬ ,7%; ✳ ,8%; □ ,8%+2% Eudragit S-100/DBS. (Eudragit RS:PEG::10:1) Coating: ● ,7%; ○ ,8%; △ ,8%+2% Eudragit S-100/DBS.

coating. The drug release appeared to follow first order kinetics. Increasing the coating level decreased the initial release rate, but had no great effect on the first order release stage (Figure 3).

Effect of the Amount and Types of Plasticizers to the Eudragit® Resin on the Release Rate Profiles of the Coated Beadlets.

As can be seen from Figure 4, the beadlets coated with a lower level of DEP (Eudragit RS:DEP::10:1) showed a slower dissolution profile as compared to the beadlets coated with the

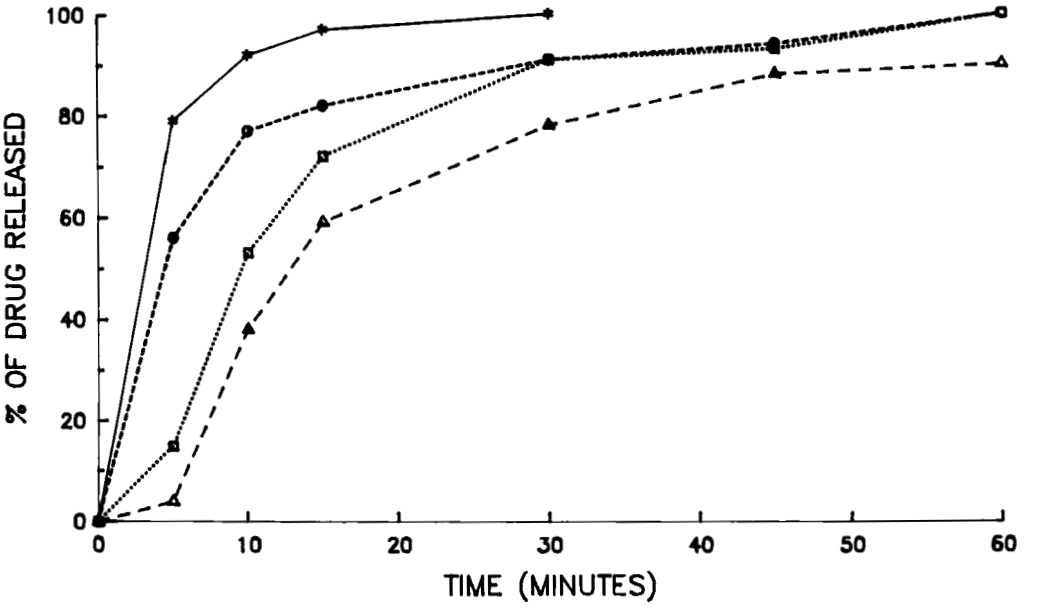

Figure 4. Effect of relative ratio of Eudragit RS to plasticizers (DEP) in the final film on release profile in pH 6.5 phosphate buffer (Eudragit RS:DEP::10:1). Coating: ○, 3%; △, 5%. (Eudragit RS:DEP::10:2) Coating: ✱, 3%; □, 5%.

same level of coating thickness but a higher level of DEP (Eudragit® RS:DEP::10:2). Based on the Null hypothesis[15], the difference in the release rate profiles of these two coating formulations was significant at the 5% level ($P<0.05$). This phenomenon may be attributed to the fact that the higher level of plasticizers lead to excessive softening of the polymer film. Consequently, beadlet agglomeration, sticking, and poor fluidization problems resulted during coating. A similar finding was reported by Chang, et al.[2]. It is hypothesized that the process of disposition of barrier coating onto the substrate would be disrupted by the agglomeration of beadlets, which in

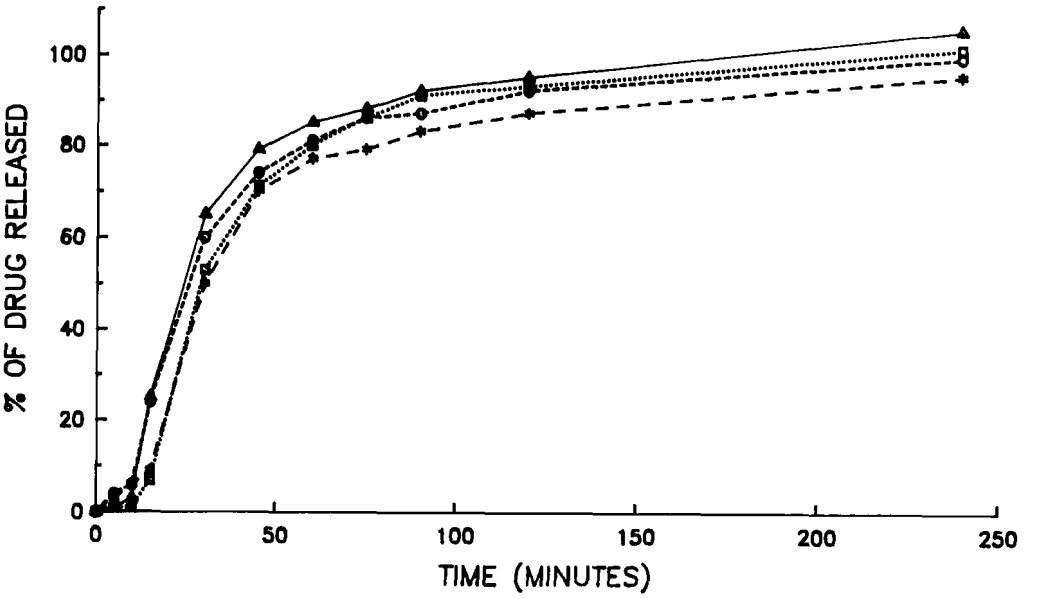

Figure 5. Effect of types of plasticizers in the final film on release profile in pH 6.5 phosphate buffer (Eudragit RS:plasticizer::10:1). Coating: Δ,7%(DEP); o,7%(PEG); □,8%(DEP); ✳,8%(PEG).

turn, would lead to the disposition of imperfect film. Consequently, a faster release of drug through the imperfect membrane may account for the difference in the release rate profiles of these two coating formulations.

With the same level of plasticizers (Eudragit® RS:DEP or PEG::10:1), the release rate of pseudoephedrine HCl from the coated beadlets was not effected by the type of plasticizers (Figure 5). Based on the Null statistical hypothesis[15], the difference in the release rate profiles of these two formulations was not significant at the 5% level ($P>0.05$). It is hypothesized that the coating formulation of these beadlets may account for this finding. Since the coating formulation containing PEG

showed the lowest number of agglomerates, it is hypothesized that the film deposition onto the substrate is applied uniformly during the coating process. The better film deposition of the same coating thickness may compensate for the water soluble nature of PEG as compared to the water insoluble nature of DEP.

Effect of a Precoat and Overcoat on the Release Profiles.

Agglomeration of beadlets to form soft lumps upon storage at or above room temperature was observed for the beadlets coated with Eudragit® formulations. As the Eudragit® coating levels increased, these soft lumps tend to be harder and are much more difficult to separate. The use of hydrophilic polymer overcoats to prevent lumping of particles has been reported in the literature.[3,11,16] The formation of these lumps can be minimized by the application of an overcoat of Eudragit® S-100/DBS film. The overcoat (1 to 2%), not only can prevent the formation of soft lumps, but can also contribute to reduce the rate of drug release at the lower pH dissolution media (below pH 7.0) (Figure 6). The extent of the reduction of drug release was far more effective for the overcoat as compared to the same level of Eudragit RS/DEP coating in pH 6.5 phosphate buffer (Figure 6). The enteric nature of Eudragit® S-100/DBS coating (use as an overcoat) seems to be very effective in retarding the drug release from the coated beadlets. Eudragit® S-100, being enteric in nature, can provide a barrier coating to retard drug release from media ranging from pH 1.0 to 6.5.[6,7,17] Only when the pH of

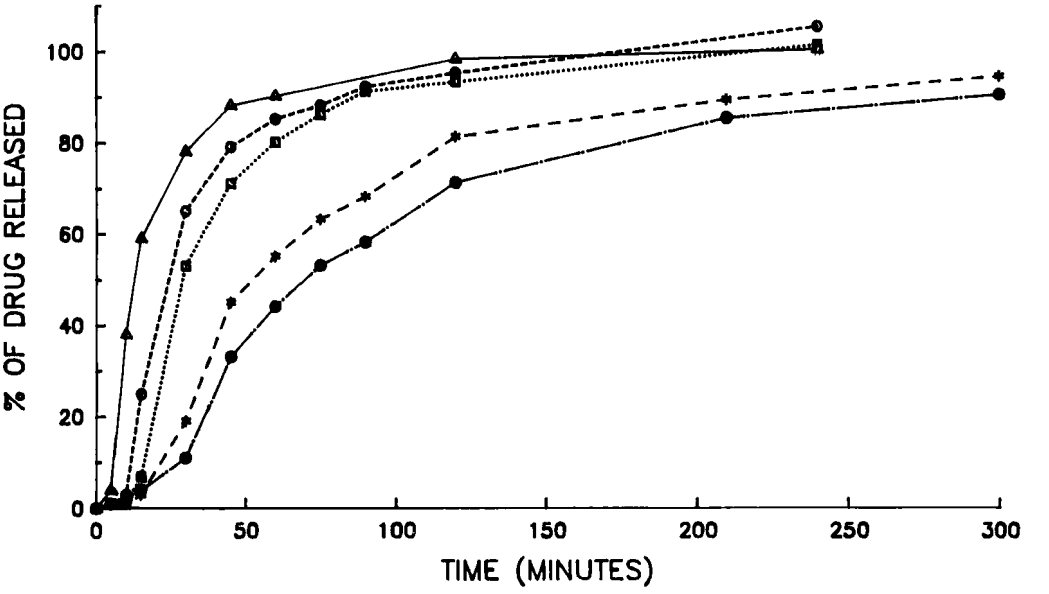

Figure 6. Effect of an overcoat of Eudragit S-100/DBS film on the release profile in pH 6.5 phosphate buffer [(Eudragit RS:DEP::10:1) Coating: △,5%; ○,7%; □,8%; ✱,8%+1% Eudragit S-100/DBS; ● ,8%+2% Eudragit S-100/DBS].

the dissolution environment approaches 7.0 or above, then the Eudragit® S-100 film will start dissolving and provide a faster release of drug. The Eudragit® S-100 overcoat may be a good means to prevent dose dumping in the upper G.I. tract (where the pH ranges from 3.0 to 6.0), but also may provide for the complete release of drug in the lower region of the G.I. tract (pH ranging from 7.0 to 8.0). However, it would require an in-vivo study to verify the performance of this formulation approach. PS beadlets coated with 2% Eudragit® S-100/DBS film (as a Precoat), then followed with 8% Eudragit® RS/DEP coating, did not show the same extent in retarding drug release from the beadlets in pH 6.5

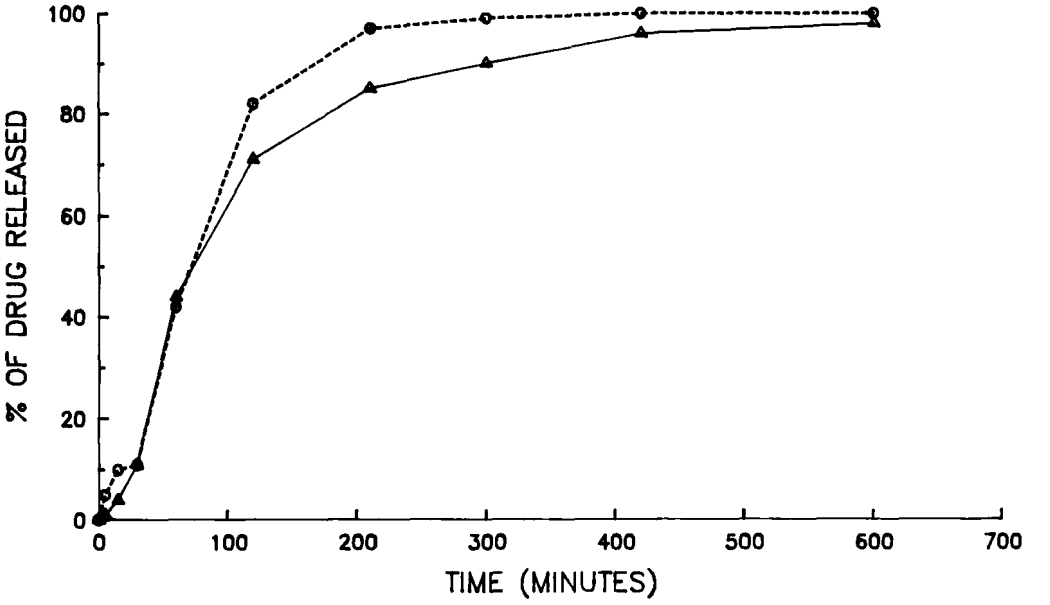

Figure 7. Effect of a precoat and an overcoat of Eudragit S-100/ DBS film on the release profile in pH 6.5 phosphate buffer. Δ ,8% Eudragit RS:DEP::10:1+2% Eudragit S-100/ DBS (overcoat); O ,2% Eudragit S-100 (precoat)+8% Eudragit RS:DEP::10:1.

phosphate buffer (Figure 7) or prevent the formation of soft lumps of beadlets. Data seems to indicate the order of application of Eudragit® S-100/DBS film can be a critical step in achieving the desired in-vitro release profile of the coated beadlets. Beadlets, which were coated with an appropriate amount of Eudragit® RS/DEP or PEG coating (pH independent, diffusion controlled resin), then followed with an overcoat of Eudragit® S-100/DBS (pH dependent resin), provide in-vitro sustained release profiles as compared to the marketed sustained release product (Figure 8). However, the release rate profiles of the

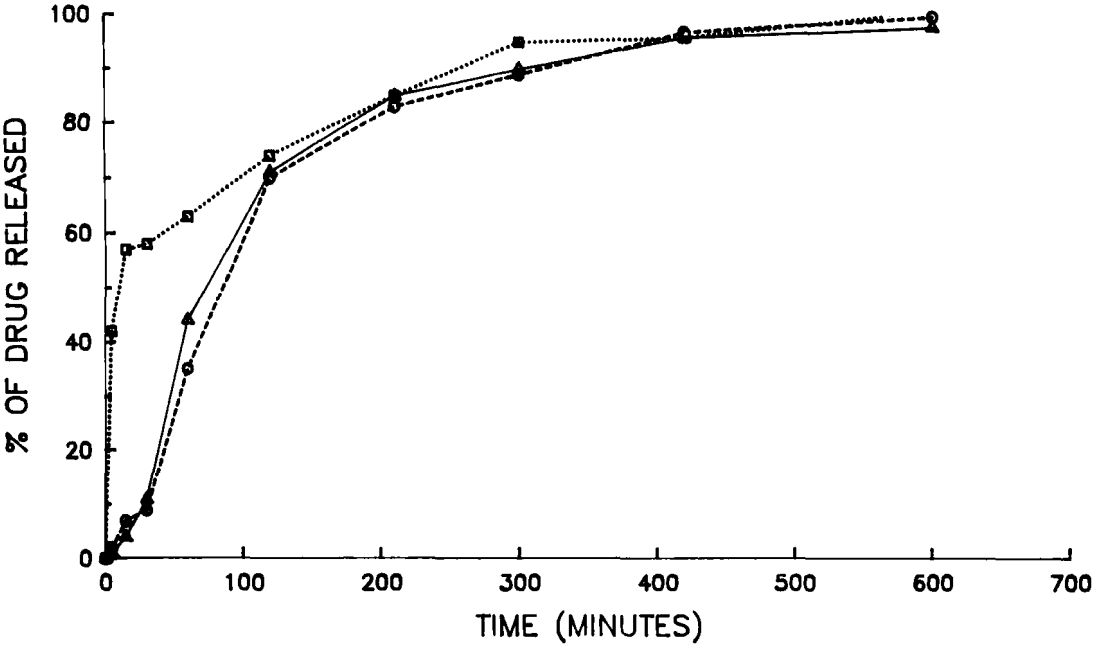

Figure 8. Release rate profiles of pseudoephedrine HCl sustained release beadlets and Sudafed 12 hours capsule in pH 6.5 phosphate buffer. Coating: □,Sudafed 12 hours capsule; Δ,8% Eudragit RS:DEP::10:1+2% Eudragit S-100:DBS; o,8% Eudragit RS:PEG::10:1+2% Eudragit S-100:DBS.

two experimental formulations were much slower than the commercial product in the first 100 minutes.

Effect of Dissolution Medium on Release Profiles.

Figure 9 shows the effect of dissolution media pH on the release of pseudoephedrine hydrochloride from beadlets coated with 8% Eudragit® RS/DEP plus 2% Eudragit® S-100/DBS (overcoat) coating. The release rate of drug from the coated beadlets, which contained an overcoat of Eudragit® S-100/DBS (2%), showed slight increases in release rates as a function of pH of the

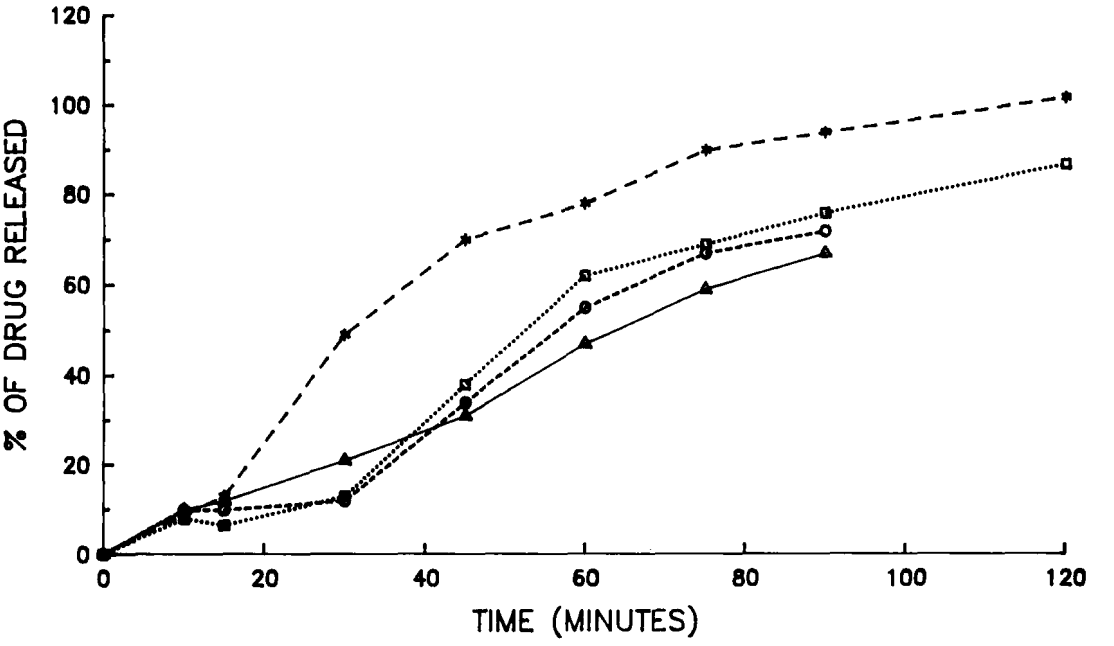

Figure 9. Effect of pH of dissolution medium on release rate profile of pseudoephedrine HCl S.R. beadlets(Coating: 8% Eudragit RS:DEP::10:1+2% Eudragit S-100:DBS::10:1). pH: △,1.2; ○,3.0; □,5.0; ✳,7.25.

dissolution media (from pH 1.2 to 5.0). However, the release rate of drug from the coated beadlets increased drastically at pH 7.2 as compared to the data of pH 5.0 (Figure 9). The difference in release rate profiles from pH 5.0 to pH 7.2 may be attributed to the overcoat of Eudragit® S-100/DBS coating. At lower pH dissolution media, such as pH 3.0 or 5.0, the overcoat of Eudragit® S-100 resin acts as an enteric polymer to retard drug release. At pH 7.2 phosphate buffer, the overcoat of Eudragit® S-100/DBS film starts dissolving and allows rapid release of drug from the coated beadlets.

CONCLUSION

In-vitro dissolution studies of pseudoephedrine hydrochloride sustained release beadlets which were coated with different combinations of plasticizers and Eudragit® RS resins indicated that the release profiles of the drug are influenced by a number of factors. The coating levels, types of resins and types of plasticizers in the film play a major role in determining the release rate profiles of the drug from the coated beadlets. The pH of the dissolution media and the use of an overcoat are two other factors which may effect the nature of the filmcoat and the release profiles of the beadlets. An overcoat of Eudragit® S-100 resin can eliminate the formation of soft lumps which are commonly observed on storage with Eudragit® RS coated beadlets. In addition, it also contributes to retard drug release from the coated beadlets in dissolution media ranging from pH 1.2 to 6.5.

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