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RESEARCH PAPER

The Effect of Polymer Coating Systems on the Preparation, Tableting, and Dissolution Properties of Sustained-Release Drug Pellets

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ABSTRACT

The preparation of sustained-release (SR) drug pellets and their tablets was evaluated. Pellets containing indomethacin, pseudoephedrine hydrochloride (P-HCl), or pseudoephedrine (P) base were prepared by spraying a mixture of drug, Eudragit® S-100 resins, dibutyl sebacate, and alcohol onto nonpareil seeds via the Wurster-column process. The oven-dried drug/Eudragit S-100 (DS) pellets were coated with different levels of Eudragit RS and Eudragit S-100 acrylic resins. Tablets containing P-HCl or P-base SR pellets, microcrystalline cellulose, and Methocel® K4M were compressed. The solubility of the drug entity in the polymer solution was found to be the most critical factor affecting the yield and the physical properties of the resultant DS pellets. Dissolution studies of Eudragit RS coated drug pellets demonstrated that the release profiles depended not only on the physicochemical properties of the drug, particularly aqueous solubility, but also on the coating levels. The release rate profiles of the matrix tablets can be modified by varying the types of P-HCl or P-base SR pellets in the formulation. The release of drug from the matrix tablets is primarily matrix controlled.

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INTRODUCTION

The use of acrylic resins in controlling the release of drug has become important in the formulation of pharmaceuticals. The use of Eudragit® acrylic resins as a polymer system to prepare sustained-release (SR) formulations via the fluidized-bed process has been demonstrated (1,2). In earlier studies, indomethacin (water insoluble) and pseudoephedrine hydrochloride (water soluble) sustained-release pellets were successfully prepared via the Wurster-column process using three different types of Eudragit acrylic resins (3,4). It was found that aqueous solubility of the pseudoephedrine HCL affected the in vitro dissolution profiles of the resultant drug/Eudragit S-100 (DS) pellets. Consequently, the amounts and types of barrier coatings required for the coating of the DS pellets were also affected by the aqueous solubility of pseudoephedrine HCl (3). In order to further investigate the processing capability of this layering process, pseudoephedrine base (slightly water soluble) was used in the present study to produce sustained-release drug pellets using the same Wurster-column process. The effect of the nature of drug on the release profiles of the finished pellets was examined. Furthermore, the effect of the barrier coatings (Eudragit RS and Eudragit S-100) on the release profiles of the coated pellets was studied. The optimization of the drug layering and coating processes via the Wurster column to produce sustained-release drug pellets is presented.

Tableting of microcapsules or sustained-release drug pellets offers a convenient method for formulating coated drug particles into a dosage form (5,6). Depending on the selection of excipients, drug release profiles of the compressed drug pellets can be faster or slower (7,8). The second objective of the present study is to identify an appropriate tablet formulation to deliver sustained-release drug pellets. The initial formulation approach was based on the hydroxypropyl methylcellulose sustained-release technology (9). Matrix tablets were prepared by direct compression of a mixture of sustained-release drug pellets, hydroxypropyl methylcellulose, and other excipients. The influence of the types of drug pellets and excipients upon release characteristics of tablets of micropellets was also investigated.

MATERIALS AND METHODS

Materials

Indomethacin (Industrie Chimiche Parmaceutiche Italiane) and pseudoephedrine hydrochloride (Granes Chemicals, NJ) were USP grade. Pseudoephedrine base was a gift from Knoll Fine Chemical Company (Parsippany, NJ). Talc (Charles B. Crystal Company, NY), 18–20 mesh nonpareil seeds (Ingredients Technology Corporation, Pennsauken, NJ), and alcohol were USP grade. Dibutyl sebacate (Union Camp, OH), polyethylene glycol 8000 (Carbox-8000 Fluke, Union Carbide Corporation), diethyl phthalate (Eastman Chemical Products, Inc., TN), microcrystalline cellulose (Avicel PH-101, FMC, Philadelphia, PA), and Methocel® K4M (Dow Chemical, Midland, MI) 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.

Preparation of Drug, Eudragit S-100, Dibutyl Sebacate, and Alcohol Slurry

Preparation for the pseudoephedrine HCl slurry and indomethacin slurry are reported elsewhere (3,4,10). The method used for the preparation of the indomethacin slurry was utilized to prepare the pseudoephedrine base slurry.

Preparation of Drug/Eudragit S-100 Pellets (DS Pellets)

Preparation for the pseudoephedrine HCl (PS) and indomethacin/Eudragit S-100 pellets is reported elsewhere (3,4,10). The method used for the preparation of indomethacin/Eudragit S-100 (IS) pellets was utilized to prepare the pseudoephedrine base/Eudragit S-100 (PBS) pellets.

Preparation of Sustained-Release Drug Pellets

Seven hundred grams of DS pellets 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 different types of acrylic resins. The amount of polymer applied during the intermediate portion of the run could be calculated by monitoring the weight of the coating solution that was applied. Appropriate samples were collected for testing and evaluation. All these samples were dried for 24 hr at room temperature to remove residual solvent from the coated pellets. The coating parameters are reported elsewhere (3). The specific formulations utilized for the coating operation of these three different types of DS pellets are given in Table 1.

Table 1

Composition of Coating Formulas for Three Different Types of Sustained-Release Drug Pellets

Formula No.	Types of drug, Eudragit S-100 Pellets	Coating Composition and Level: Eudragit RS/PEG[a] (10:1) [% w/w]	Eudragit RS/DEP[b] (10:1) [% w/w]	Eudragit S-100/DBS[c] (10:1) [% w/w]
1	Indomethacin	0.5, 1.0	None	None
2	Pseudoephedrine HCl	None	3, 5, 7, 8	None
3	Pseudoephedrine HCl	None	8	2
4	Pseudoephedrine base	None	3, 5, 7, 8	None
5	Pseudoephedrine base	None	8	2

[a]PEG: polyethylene glycol.
[b]DEP: diethyl phthalate.
[c]DBS: dibutyl sebacate.

Preparation of Sustained-Release Matrix Tablets

Tablets containing pseudoephedrine (HCl or base) SR pellets (equivalent to 200 mg of pseudoephedrine HCl or base, 50% w/w), an appropriate amount of microcrystalline cellulose (Avicel PH-101, 13.2% w/w), and Methocel K4M (36.8% w/w) were made by direct compression using a Carver press equipped with a 1.27-cm diameter, flat-face punch. Compression force was varied from 500 to 1500 lb to prepare 4 batches of tablets. The formulations are given in Table 2.

Dissolution Testing

Drug release was studied using USP apparatus II (rotating paddle) at 37°C and 100 rpm agitation speed with 900 ml of phosphate buffers (pH 6.5 or pH 7.2). Samples were removed at suitable time intervals. The collected samples were assayed spectrophotometrically at 257 nm for pseudoephedrine HCl or base content and at 318 nm for indomethacin content. Triplicate samples were assayed and the mean values are reported.

RESULTS AND DISCUSSION

Effect of the Physical Properties of the Drug Entity on the Processing Capability of the Wurster-Column Process to Produce Drug/Eudragit S-100 Pellets

Three model drug compounds showed different solubilities in the formula amount of Eudragit S-100 resins, dibutyl sebacate, and alcohol solution. The formula amount of pseudoephedrine base (300 g) was completely dissolved in the polymer solution, whereas only 86% of the formula amount of pseudoephedrine HCl was solubilized in the polymer solution. Seven percent of indomethacin was solubilized in the polymer solution and the remaining portion of drug powder (93%) was suspended in the polymer solution to yield a drug slurry.

Table 2

Composition of Four Batches of 200 mg Pseudoephedrine (HCl or Base) Sustained-Release Tablets

Formula No.	Types of Pellets Used for Compression
6	Pseudoephedrine HCl/Eudragit S-100 pellets
7	Pseudoephedrine base/Eudragit S-100 pellets
8	Pseudoephedrine HCl/Eudragit S-100 pellets coated with 8% of Eudragit RS/DEP coating (formula 2)
9	Pseudoephedrine base/Eudragit 2-100 pellets coated with 8% of Eudragit RS/DEP coating (formula 4)

It is well established in the literature that it is much easier to load drug onto the substrate using a drug/polymer solution than using a drug/polymer slurry (11). It was found that the solubility of the drug entity in the polymer solution had a profound effect on the processing capability of the Wurster-column process to produce DS pellets. It affected the yield and the physical properties of the resultant DS pellets. Pseudoephedrine base, which was completely dissolved in the polymer solution, provided the most trouble-free process to produce pseudoephedrine base/Eudragit S-100 (PBS) pellets. The formula amount of drug/polymer solution was applied onto the nonpareil seeds via the Wurster-column process to yield 2 batches of PBS pellets with acceptable yield (98.8%). Pseudoephedrine HCl, having 86% solubility in the polymer solution and the remaining portion (14%) of the drug powder in micronized form, also gave a trouble-free process. Six batches of pseudoephedrine HCl/Eudragit S-100 (PS) pellets were successfully prepared with acceptable yield (98.4%). As the solubility of the drug entity in the polymer solution decreased, as in the case with indomethacin (7% solubility), the processing parameters of the layering process became a critical factor affecting the outcome of the drug-loading process. Since 93% of the formula amount of indomethacin remained as drug powder suspended in the slurry, the indomethacin, Eudragit S-100, DBS, and alcohol slurry had to be passed through the Colloid mill to ensure a uniform distribution of drug powder in the resultant slurry. In addition, the slurry needed to be constantly stirred during the entire layering process to avoid settling of the drug powder in the slurry, which in turn led to blockage of the spraying nozzle and caused disruption of the layering process.

The overall yield of 5 batches of indomethacin/Eudragit S-100 (IS) pellets was 89.3%, which was slightly lower than the other two types of DS pellets (PBS and PS). It was found that the overall yield of IS pellets could be improved by controlling the overall particle size distribution and the particle diameter of the drug entity in this layering process. It was found that only the micronized indomethacin powder was suitable for the layering process to produce IS pellets with an acceptable yield of 98.2% (10).

Effect of Physical Properties of Drug Entity on the In Vitro Release Rate of Drug from the Drug/Eudragit S-100 Pellets

Aqueous solubility of the drug entity was found to affect the in vitro dissolution profiles of the resultant DS pellets. Indomethacin is practically insoluble in water (0.4 mg/100 ml), whereas pseudoephedrine HCl is the most soluble in water (>200 g/100 ml) as compared to pseudoephedrine base (1g/100 ml). Figure 1 shows a plot of cumulative percentage of drug released from three different types of DS pellets in pH 6.5 phosphate buffer. The release rate profile of the IS pellets was significantly lower than PBS or PS pellets. This indicated that the IS pellets exhibited sustained-release characteristics. Forty-four percent of the total drug content was released at the end of 8 hr (Fig. 1). Studies conducted at pH 7.2, phosphate buffer, showed a much faster release of indomethacin from the IS pellets. For instance, 96% of the drug content was released at the 45-min interval. The reason for the difference in release rate profiles of the IS pellets in two different pH phosphate buffers was attributed to the enteric effect of Eudragit S-100 resins on the release rate profile of the IS pellets (4).

It was also found that the particle size of indomethacin powder used for the preparation of IS pellets influenced the release profiles of the resultant drug pellets. The release rate of the indomethacin from the IS pellets was found to be related to the particle size of indomethacin used for the layering process of drug pellets. Finer particle sizes of indomethacin yielded IS pellets with the faster in vitro release-rate profile (10).

Data demonstrated that Eudragit S-100 resin could be used effectively as an enteric polymer for the drug pellets containing the water-insoluble indomethacin. The release of pseudoephedrine HCl and pseudoephedrine base from the DS pellets in pH 6.5 phosphate buffer

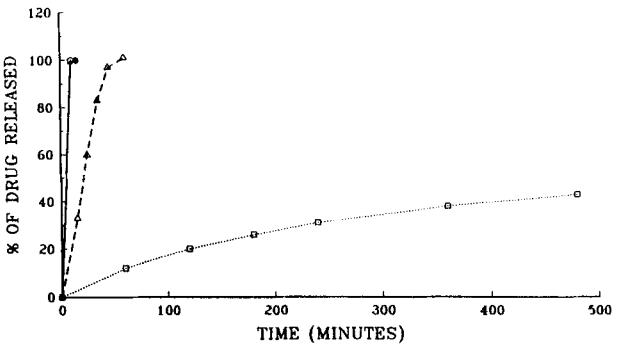

Figure 1. Release profiles of drug from three different types of drug/Eudragit S-100 pellets in pH 6.5 and pH 7.2 phosphate buffers. (*) pseudoephedrine HCl/Eudragit S-100 pellets in pH 6.5 buffer (data from Ref. 3); (○) pseudoephedrine base/Eudragit S-100 pellets in pH 6.5 buffer; (□) indomethacin/Eudragit S-100 pellets in pH 6.5 buffer (data from Ref. 4); (Δ) indomethacin/Eudragit S-100 pellets in pH 7.2 buffer (data from Ref. 4).

was far more rapid as compared to IS pellets (Fig. 1). Ninety-eight percent of drug was released at the 5-min interval. Eudragit S-100 acrylic resins did not provide any retardation to the release of pseudoephedrine HCl or pseudoephedrine base from the drug matrix pellets. Its primary function was to bind drug onto the substrate (nonpareil seeds). Since both pseudoephedrine HCl and pseudoephedrine base were solubilized in the polymer solution, the deposition of drug/polymer matrix onto the substrate could yield a matrix layer with drug particles dispersed uniformly in the Eudragit S-100 acrylic resins (Fig. 2). Drug particles would be interconnected with each other to form a network of drug–polymer matrix. Pseudoephedrine HCl (water soluble) and pseudoephedrine base (slightly water soluble), embedded on the surface of matrix pellets, released rapidly upon contacting the dissolution medium. As the drug started dissolving, microporous channels may have been created in the drug matrix. Consequently, the dissolution medium could rapidly penetrate into the inner matrix to dissolve embedded drug molecules. On the other hand, indomethacin particles, being insoluble in the polymer solution, deposited as drug particles in the drug/Eudragit S-100 matrix layer. Indomethacin particles (practically water insoluble), embedded on the surface of matrix pellets, released slowly upon contacting the dissolution medium. It would take a much longer time to solubilize indomethacin particles in the drug matrix layer to create microporous channels for dissolution medium to penetrate into the inner matrix. Therefore, the dissolution process for indomethacin from the drug matrix was significantly slower than pseudoephedrine HCl and pseudoephedrine base.

Effect of Film Thickness on Release Profile

Three different types of DS pellets coated with the same coating formula (Eudragit RS:Plasticizer; 10:1) were subjected to dissolution testing using pH 6.5 phosphate buffer. Both PS and PBS pellets were coated with the same levels of coating of the same coating formula (Eudragit RS:DEP; 10:1) to assess the effect of film thickness on release profile. IS pellets were coated with lower levels of coating (Eudragit RS:PEG; 10:1). The release rate profiles of the sustained-release drug pellets depended on the coating level of the final product. As the coating thickness increased, a decrease in the release rates of the coated drug pellets was observed (Fig. 3). At the higher coating levels (8% coating), pseudoephedrine HCl sustained-release pellets released 52% of the drug in 30 min, whereas those pellets coated to weight

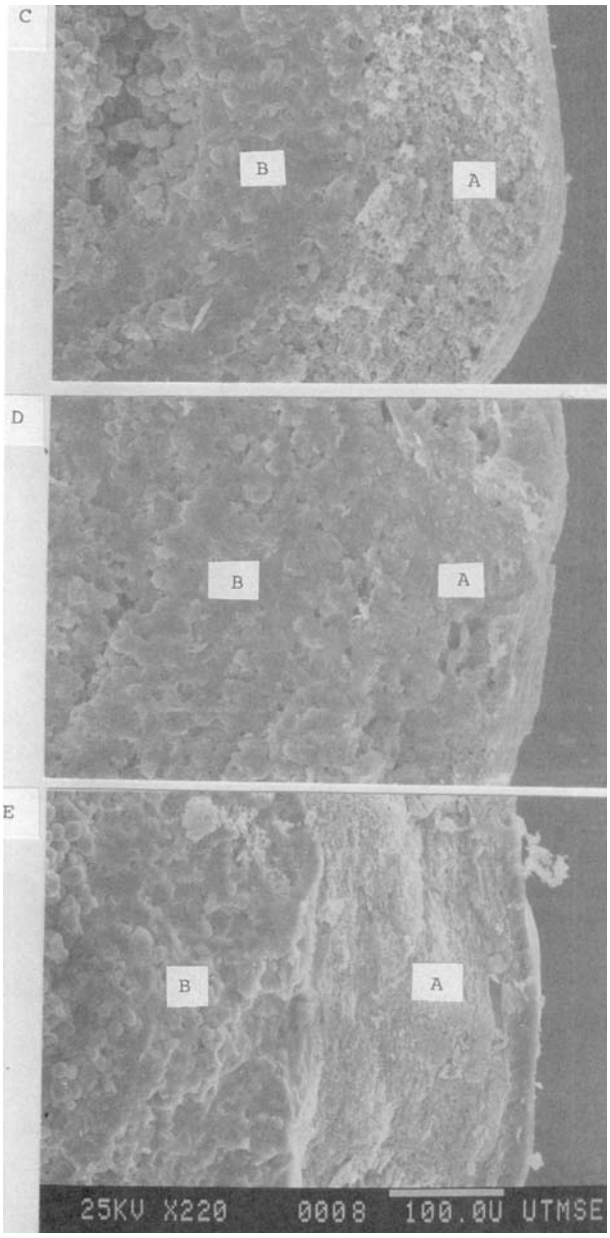

Figure 2. Scanning electron micrographs of cross section of three different types of drug/Eudragit S-100 pellets. (A) drug matrix layer; (B) nonpareil seed layer; (C) indomethacin/Eudragit S-100 pellets; (D) pseudoephedrine HCl/Eudragit S-100 pellets; (E) pseudoephedrine base/Eudragit S-100 pellets.

increase of 3% released 92% of the drug. Similar trends were also observed with pseudoephedrine base sustained-release pellets coated with the same coating formula (Fig. 3). For the same coating level, such as 8%, pseudoephedrine base sustained-release pellets show a

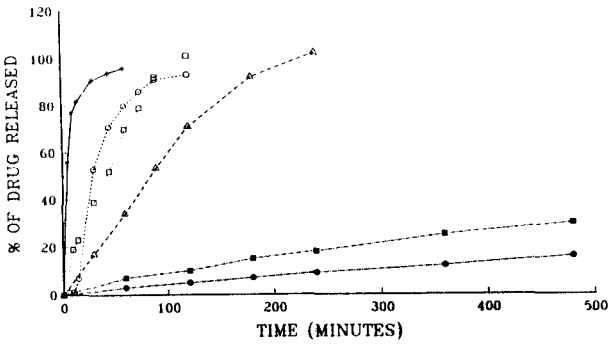

Figure 3. Effect of coating thickness on the release profiles of three types of sustained-release drug pellets in pH 6.5 phosphate buffer (Eudragit RS/DEP coating). (*) 3%—pseudoephedrine HCl (data from Ref. 3); (○) 8%—pseudoephedrine HCl (data from Ref. 3); (□) 3%—pseudoephedrine base; (Δ) 8%—pseudoephedrine base; (■) 0.5%—indomethacin (Eudragit RS/PEG coating); (●) 1.0%—indomethacin (Eudragit RS/PEG coating).

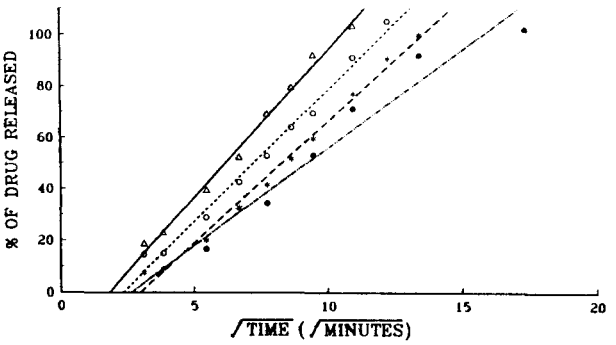

Figure 4. Release kinetics of pseudoephedrine base sustained-release pellets assuming Higuchi matrix release in pH 6.5 phosphate buffer (Eudragit RS/DEP coating). (Δ) 3% (R^2 = 0.9960); (○) 5% (R^2 = 0.9923); (*) 7% (R^2 = 0.9953); (●) 8% (R^2 = 0.9972).

much slower release profile compared to the pseudoephedrine HCl sustained-release pellets. Since pseudoephedrine base is less soluble than pseudoephedrine HCl, the difference in aqueous solubility may account for this observation. The integrity of the coating was well preserved throughout the dissolution experiments for these two types of sustained-release drug pellets. Even when the drug was completely depleted from a pellet, the shell remained intact. The drug release appeared to follow first-order kinetics for pseudoephedrine HCl sustained-release pellets. Increasing the coating level decreased the initial release rate but had no significant effect on the first-order release stage (3). However, the drug release for pseudoephedrine base sustained-release pellets appeared to follow matrix release kinetics rather than the first-order kinetics (Fig. 4). As the aqueous solubility of the substrate further decreased, such as practically water-insoluble indomethacin, the coating levels required to achieve a similar release profile were significantly reduced. For instance, indomethacin sustained-release pellets coated with 1% Eudragit RS coating exhibited a much slower dissolution profile as compared to the 8% Eudragit RS coated pseudoephedrine HCl or base sustained-release pellets (Fig. 3).

Highly water-soluble and alcohol-soluble drugs, such as pseudoephedrine HCl and pseudoephedrine base, generally require higher coating levels than poorly water-soluble and poorly alcohol-soluble compound (indomethacin). This behavior is partially attributed to the different rate of migration of species during the coating process as reported by Bodmeier (12). During film-coating deposition, highly alcohol-soluble pseudoephedrine HCl or base dissolve in the sprayed droplets and remain embedded in the Eudragit RS film after the evaporation of alcohol. As more and more layers of film are deposited to constitute the coating wall material, the migration of drug diminishes until a coating film devoid of drug is produced. Since the presence of drug in the inner parts of the coating leads to a porous structure during dissolution, a thicker coat is required to generate a specific release profile than would be the case with poorly alcohol-soluble indomethacin.

Effect of an Overcoat on the Release Profiles

Agglomeration of pellets to form soft lumps upon storage at or above room temperature was observed for the drug pellets coated with Eudragit RS acrylic resins (3). The tendency to form soft lumps upon storage was found directly proportional to the coating level of Eudragit RS resins. IS pellets coated with a 1% Eudragit RS resin level did not show any lumping of pellets upon storage at room temperature. However, pseudoephedrine HCl or base pellets that required 8% of Eudragit RS level to attain the desirable release profiles showed severe lumping of pellets. The formation of these soft lumps was minimized by applying an overcoat of Eudragit S-100/DBS film (2%) onto the PS or PBS pellets. The overcoat also contributed to the reduction of the rate of drug release from the coated drug pellets (Fig. 5).

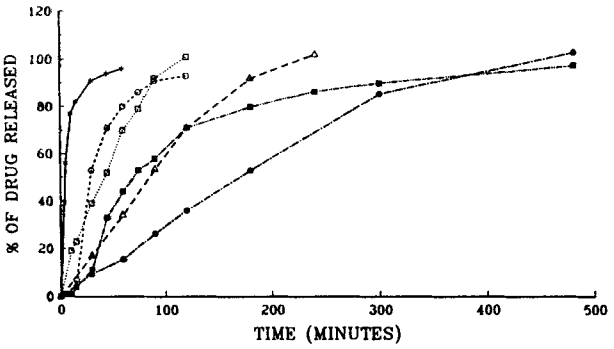

Figure 5. Effect of overcoat on the release profiles of two types of sustained-release drug pellets in pH 6.5 phosphate buffer (Eudragit RS/DEP coating). (*) 3%—pseudoephedrine HCl (data from Ref. 3); (○) 8%—pseudoephedrine HCl (data from Ref. 3); (■) 8% + 2% Eudragit S-100 coating—pseudoephedrine HCl (data from Ref. 3); (□) 3%—pseudoephedrine base; (Δ) 8%—pseudoephedrine base; (●) 8% + 2% Eudragit S-100 coating—pseudoephedrine base.

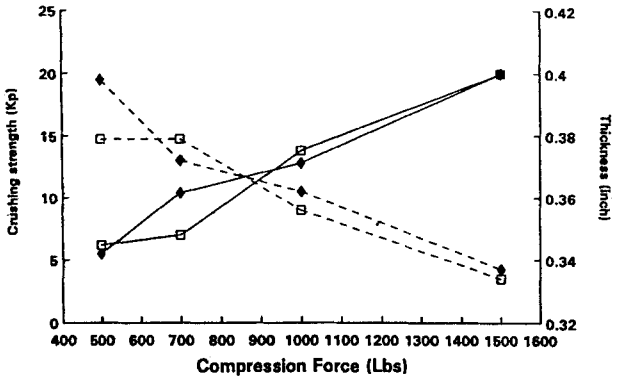

Figure 6. Effect of compression force on the crushing strength and thickness of tableted pseudoephedrine HCl/Eudragit S-100 pellets. (□) formula A; (◆) formula B; (. . . .) thickness; (____) crushing strength.

Tablet Properties of Sustained-Release Drug Pellets with Excipients

Dissolution profiles of pseudoephedrine HCl and base sustained-release pellets (Fig. 3) indicated that the 8% Eudragit RS/DEP coatings did not provide an effective coating barrier as compared to the 1% Eudragit RS/PEG coated indomethacin pellets. One way to improve the sustained-release characteristics of the pseudoephedrine HCl or base sustained-release pellets was to incorporate these coated drug pellets into a matrix tablet formulation. Two prototypes of matrix tablets were used for the feasibility screening test. Formula A called for a composition of 50% of drug pellets, 40% of Methocel K4M, and 10% of microcrystalline cellulose (MCC); whereas formula B used a composition of 50% of drug pellets, 36.7% of Methocel K4M, and 13.3% of MCC. Matrix tablets were compressed using 4 different compression forces (500, 700, 1000, and 1500 lb) and were submerged in water for 24 hr to observe the swelling characteristics. The compression force affecting the thickness and crushing strength of matrix tablets was not significantly different between the two formulations, as indicated in Fig. 6. Both matrix tablet formulations showed an increase in tablet crushing strength and a decrease in tablet thickness with an increase in compression force. However, observation of the swelling characteristics of the matrix tablets in water indicated that formula B exhibited better swelling behavior than formula A. Tablets of formula B compressed at 1000 lb and 1500 lb of compression force remained intact and swelled evenly during the entire swelling test, whereas among 4 types of tablets of formula A, only tablets compressed at 1500 lb of compression force remained intact. Considering the compression and swelling data, matrix tablets of formula B compressed at 1000 lb of compression force were selected for the subsequent compression study of pseudoephedrine HCl or base sustained-release pellets.

Effect of Types of Sustained-Release Drug Pellets on the Release Profiles of the Matrix Tablets

The matrix tablets containing PS or PBS pellets showed dissolution profiles significantly slower than those of the PS or PBS pellets (Fig. 7). The sustained-release characteristics of the matrix tablets was primarily controlled by the Methocel K4M and MCC gel structure, since the pseudoephedrine HCl or base/Eudragit S-100 pellets previously showed no retardation of drug release (95% of drug content released at 5 min). In addition, the solubility of drug entity apparently affected the release patterns of the matrix tablets. Tablets containing PBS pellets showed a slower release rate profile compared to the tablets containing PS pellets. The mean dissolution time of 50% drug released for pseudoephedrine HCl and pseudoephedrine base matrix tablets were 157 min and 428 min, respectively. As the matrix tablets are exposed to aqueous fluid, the tablet surface becomes wet and the polymer starts to partially hydrate to form a gel layer. There follows an expansion of the gel layer when water permeates into the tablet increasing the thickness of the gel layer, and soluble

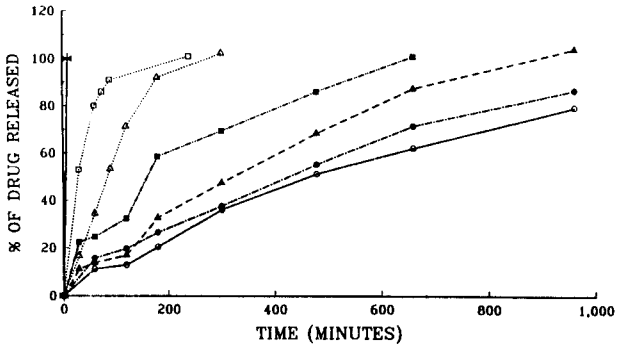

Figure 7. Release profiles of drug from 4 different batches of matrix tablets in pH 6.5 phosphate buffer. (*) pseudoephedrine HCl/Eudragit S-100 pellets (data from Ref. 3); (—) pseudoephedrine base/Eudragit S-100 pellets; (□) 8% Eudragit RS coated pseudoephedrine HCl pellets (data from Ref. 3); (Δ) 8% Eudragit RS coated pseudoephedrine base pellets; (■) tablets containing pseudoephedrine HCl/Eudragit S-100 pellets; (●) tablets containing pseudoephedrine base/Eudragit S-100 pellets; (▲) tablets containing 8% Eudragit RS coated pseudoephedrine HCl pellets; (○) tablets containing 8% Eudragit RS coated pseudoephedrine base pellets.

drug diffuses through the gel barrier. Since pseudoephedrine base is less soluble than pseudoephedrine HCl, it will require longer time for the incoming dissolution medium to solubilize the pseudoephedrine base in the drug/Eudragit S-100 matrix layer compared to the more water-soluble pseudoephedrine HCl. Subsequently, the release of pseudoephedrine base from the matrix tablets was slower than the pseudoephedrine HCl.

The release profiles of the matrix tablets were further affected by the types of pseudoephedrine HCl or base sustained-release pellets (8% Eudragit RS/DEP coating) used in the matrix tablet formulation. Matrix tablets containing Eudragit RS coated drug pellets exhibited significantly slower release profiles as compared to those of the Eudragit RS coated drug pellets (Fig. 7). The data indicated that the sustained-release characteristics of this type of matrix tablets was controlled by both the Methocel K4M and MCC gel structure (major factor) and the Eudragit RS coated PS or PBS pellets (minor factor). Furthermore, matrix tablets containing Eudragit RS coated PS pellets exhibited a slower release profile as compared to the matrix tablets containing uncoated PS pellets (Fig. 7). The data indicated that the release patterns of the matrix tablets can be altered by incorporating different types of pseudoephedrine HCl or base sustained-release pellets.

All 4 types of matrix tablets showed an initial burst effect at the first hour of the dissolution test (Fig. 7). This phenomenon might be attributed to the excessive buildup of drug on the surface of the matrix tablet. This can be examined as follows: during the compression process, some of the pseudoephedrine sustained-release pellets located at the surface of the tablet might be partially damaged and may have provided a small portion of drug for the initial burst effect.

By plotting the percentage of drug released versus the square root of time, drug releases from the matrix tablets followed the Higuchi model for all 4 types of matrix tablets (Fig. 8). The release kinetics of this formulation approach was in agreement with the literature that the hydroxypropylmethylcellulose (HPMC) matrix tablets followed matrix release (13,14).

CONCLUSION

The manufacture of sustained-release drug pellets using the Wurster-column process is relatively simple and reproducible. The solubility of the drug entity in the polymer solution was found to be the most critical factor affecting the yield and the physical properties of the resultant drug/Eudragit S-100 pellets. As the solubility of the drug entity decreased in the polymer solution, the overall particle size distribution and particle diameter of the drug entity were found to be the critical factors affecting the layering process. Only micronized drug pow-

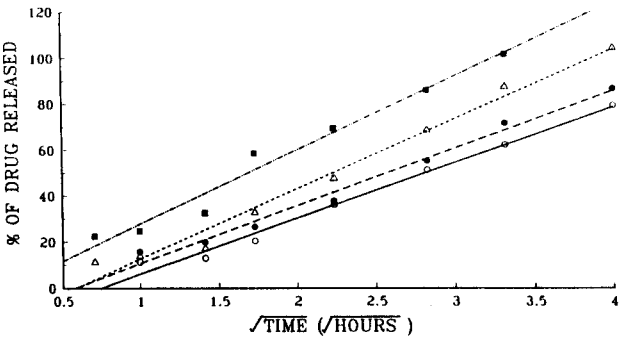

Figure 8. Release kinetics of 4 batches of matrix tablets assuming Higuchi matrix release in pH 6.5 phosphate buffer. (■) tablets containing pseudoephedrine HCL/Eudragit S-100 pellets (R^2 = 0.9864); (●) tablets containing pseudoephedrine base/Eudragit S-100 pellets (R^2 = 0.9933); (Δ) tablets containing 8% Eudragit RS coated pseudoephedrine HCl pellets (R^2 = 0.9912); (○) tablets containing 8% Eudragit RS coated pseudoephedrine base pellets (R^2 = 0.9939).

der was found suitable for the layering process. Aqueous solubility of the drug entity was found to affect the in vitro dissolution profiles of the resultant drug pellets. Dissolution studies of Eudragit RS coated drug pellets demonstrated that the release profiles depended not only on the physicochemical properties of the drug, particularly solubility, but also on the coating levels. The concentration of the polymers is the determining factor in controlling the release rate. An overcoat of Eudragit S-100 resin can eliminate the formation of soft lumps that are commonly observed with higher levels of Eudragit RS coated drug pellets. The overcoat also contributes to the retardation of drug release from the coated drug pellets.

Pseudoephedrine HCl or base sustained-release tablets can be prepared using Methocel K4M, MCC, and an appropriate type of pseudoephedrine HCl or base sustained-release pellets. The release profiles of Eudragit RS coated drug pellets were extended by the matrix tablet formulation. The release patterns of the matrix tablets can be altered by incorporating different types of pseudoephedrine HCl or base sustained-release pellets.

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