# Development and *in Vitro-in Vivo* Evaluation of a Multiparticulate Sustained Release Formulation of Diltiazem

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***Purpose.*** To develop and evaluate the *in vitro/in vivo* performance of diltiazem sustained release pellets that were prepared by the Wurster column process. ***Methods.*** Pellets containing diltiazem were prepared by spraying a slurry of micronized diltiazem hydrochloride, pharmaceutical glaze and alcohol onto an appropriate mesh fraction of nonpareil seeds using the Wurster column. A two-step drug layering process was used to increase drug loading from 60% to 75%. The oven-dried diltiazem basic pellets were coated with ethylcellulose/dibutyl sebacate coating solution to yield diltiazem sustained release pellets. An open, randomized Latin square, three-way crossover clinical study was used to evaluate the *in vivo* performance of the coated product. ***Results.*** Altering the mesh fraction of the starting nonpareil seeds for this layering process was found to affect the release characteristics of drug from the pellets. An oven-drying step was required to stabilize the diltiazem basic pellets. The thicker the drug loading layer the longer the oven drying is needed to stabilize the pellets. The diltiazem sustained release pellets produced by these methods displayed sustained release dissolution profiles both *in vitro* and *in vivo*. Diltiazem basic pellets coated with a 0.6% ethylcellulose/dibutyl sebacate coating showed a different rate of absorption (lower $C_{max}$ and higher $T_{max}$) and the same extent of absorption as compared to Cardizem® tablets. ***Conclusions.*** Clinical data confirmed that this formulation approach is an effective means to produce a diltiazem sustained release product.

KEY WORDS: Sustained release; diltiazem; *in vitro; in vivo;* ethylcellulose.

## INTRODUCTION

Diltiazem hydrochloride is a calcium channel blocker widely used for the treatment of angina pectoris, arrhythmia and hypertension (1). Diltiazem has a relatively short half-life of two to seven h and is usually administered three to four times daily in the form of an immediate release formulation. Given its chronic use and its pharmacokinetic and pharmacodynamic properties, diltiazem is potentially a good candidate for sustained release formulations. Recently, different formulation approaches have been attempted to develop sustained release preparations to extend clinical effects and reduce dosing frequency to improve patient compliance (2–5). This report describes a method to prepare multiparticulate sustained release diltiazem pellets using the fluidized-bed coating process. An enteric polymer (shellac) was used as a binder in a layering process to yield the diltiazem basic pellets. The effect of drug loading on the physical properties of the diltiazem basic pellets is reported. The resultant diltiazem basic pellets were coated with the barrier coating of ethylcellulose to yield the diltiazem sustained release pellets. The *in vivo* performances of this formulation approach also were investigated.

## MATERIALS AND METHODS

### Chemicals

Diltiazem Hydrochloride USP (Orion Corp. Limited, Espoo, Finland); Nonpareil Seeds: 25/30, 35/40, and 40/50 mesh fraction (Crompton & Knowles Corporation, Mahwah, NJ); Pharmaceutical Glaze NF (Regular bleached shellac, 4 lb. cut; William Zinsser & Co. Inc., Somerset, NJ); SD 35A alcohol (Fisher Scientific, Fair Lawn, NJ); Ethylcellulose NF (Ethocel standard 10, Dow Chemical Company, Midland, MI); and Dibutyl Sebacate (Union Camp, Ohio) were purchased and used as received. Cardizem® tablets (60 mg) were used as received (Marion Merrell Dow Inc., Kansas City, MO). All reagents were analytical grade.

### Preparation of Diltiazem Basic Pellets

Pellets containing diltiazem hydrochloride were prepared by spraying a slurry of micronized diltiazem hydrochloride, pharmaceutical glaze, and SD 35A alcohol onto an appropriate mesh fraction of nonpareil seeds using the Wurster column process (Aeromatic Strea-1 Coater, Niro-Aeromatic, Inc., Columbia, MD). The resultant drug pellets were defined as the diltiazem basic pellets. The solids content of the drug and polymer slurry was 37.8% (w/w). The diltiazem basic pellets were then tray-dried at 70°C for either 24 h (one-step process) or 48 h (two-step process). The formulation for the one-step process used to prepare diltiazem basic pellets is shown in Table I. A two-step layering process was also investigated. In this procedure, 300 g of diltiazem basic pellets from the one-step process were recharged into the Wurster column and were layered with the same amount of drug and polymer slurry as described in the one-step process to yield 1,250 g of the final diltiazem basic pellets. The formulations are shown in Table I.

### Preparation of Diltiazem Sustained Release Pellets

Seven hundred grams of diltiazem basic pellets were coated with the predetermined amount of ethylcellulose/dibutyl sebacate (DBS) coatings to achieve the theoretical percentage weight gain of coatings in an Aeromatic Strea-1 Coater (Wurster insert) to yield the diltiazem sustained release pellets. The resultant coated pellets were dried either in the Wurster column for an additional 20 min or tray-dried at 70°C for 24 h. The resultant coated drug pellets were defined as the diltiazem sustained release pellets. The coating formulation was composed of 4.4% of ethylcellulose, 1.1% of DBS, and 94.5% of SD 35A alcohol. The selection of the

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Table I. The amount of ingredients used to prepare diltiazem basic pellets by Wurster column process.

| Ingredients | One-step process Weight (g) | Formulation 1[a] (%) | Formulation 2[b] (%) | Formulation 3[b] (%) |
|---|---|---|---|---|
| Diltiazem HCl (Micronized) | 750 | 60.00 | 74.85 | 74.85 |
| Nonpareil Seeds | | | | |
| 25/30 (Mesh) | 300 | 24.00 | – | – |
| 35/40 (Mesh) | – | – | 5.30 | – |
| 40/50 (Mesh) | – | – | – | 5.30 |
| Pharmaceutical Glaze (Solid) | 200 | 16.00 | 19.85 | 19.85 |
| Total | 1250 | 100.0 | 100.0 | 100.0 |

[a] One-step process.
[b] Two-step process.

ratio of ethylcellulose to DBS was based on the results from the dissolution data. The dissolution data from the preliminary coating experiments using the same level of ethylcellulose/DBS coating plasticized with 10, 20, and 25% of DBS in relation to the weight of ethylcellulose indicated that diltiazem sustained release pellets coated with 25% of DBS showed the most retardation of drug dissolution. In addition, DBS has been reported to be a good plasticizer for ethylcellulose films (6,7). Therefore, DBS was selected in a ratio of 4:1 of ethylcellulose to DBS for the coating experiments. The operating parameters of the Aeromatic S-1 Coater for the coating process are as follows. The inlet temperature was maintained between 46 to 50°C to provide an outlet temperature of 30 to 35°C. The flow rate of the coating solution was maintained at 6 to 7 g per min. A 0.8 mm Schlick nozzle was used for the coating experiments. The two batches of diltiazem sustained release pellets used for the clinical study were prepared by spraying 64 g and 77 g of the ethylcellulose/DBS (5.5% w/w) solution onto 700 g of diltiazem basic pellets of formulation 2 to yield formulations A and B, respectively.

### *In Vitro* Studies

Dissolution tests were performed using the paddle method (USP XXII, 50 rpm, 37°C) in 900 ml of phosphate buffer. Sample weights of either diltiazem basic pellets or diltiazem sustained release pellets containing 120 mg of diltiazem hydrochloride were used for the dissolution studies. The pH 3 phosphate buffer was used for the diltiazem basic pel-lets (Dissolution method A). A different dissolution medium was used for the diltiazem sustained release pellets. The pH 3 phosphate buffer was used from zero to 3.5 h and then the pH was changed to 7.4 by addition of 5 N sodium hydroxide solution (Dissolution method B). In addition, the pH profiles of the diltiazem sustained release pellets were determined using various phosphate buffers including pH values of 1.2, 3, 5, and 7.4. Samples were withdrawn from the dissolution vessels at preselected time intervals and were assayed spectrophotometrically at 257 nm for diltiazem hydrochloride content. Each determination was carried out in six replicates.

### *In Vivo* Studies and Pharmacokinetic Analysis

Nine healthy male subjects (ages 19 to 45 years; weight, 70 to 81 kg) participated after giving informed consent. This was an open, randomized Latin square, three-way crossover of single doses of Cardizem® tablets (2 × 60 mg tablet) and two different sustained release formulations of diltiazem hydrochloride (120 mg capsule) with a one-week interval between dosing. Each subject received a total of three single doses of diltiazem hydrochloride in a period of three weeks. The drug was administered at 8:00 a.m. with 240 ml of water. Subjects were fasted overnight and for 4 h after dosing.

Venous blood samples (10 ml) were collected in heparinized vacutainers at 0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10, 12, 16, and 24 h after dosing. Plasma was separated by centrifugation at 3000 rpm and stored at −15°C. All of the samples were analyzed within one week of their collection.

Diltiazem was quantified in plasma by a HPLC method. The column was an Altex Utrasphere 3u C18, 4.6 mm i.d. × 7.5 cm. The mobile phase was a mixture of acetonitrile: phosphate buffer (34:66; pH 3.6) containing nonylamine and decyl-sodium sulfonate modifiers. The detection wavelength of 237 nm was used. The flow rate was 1.0 ml/min. The sensitivity of the method was 2.0 ng/ml. Linearity was assessed in the ranges 0 to 300 ng/ml. Interday and intraday assay precision and accuracy for the HPLC determinations of diltiazem in plasma were also performed and found to be acceptable.

Area under the curve (AUC) was calculated by the trapezoidal method. Pharmacokinetic parameters were evaluated by the General Linear Model of the SAS statistical program (SAS Institute Inc., Cary, NC) to determine if there were statistically significant ($p < 0.05$) differences between dosing groups. Bioavailability of each of the two formulations was determined relative to Cardizem® tablets. Statistical analysis appropriate for a Latin square three-way crossover design was performed, using a univariate analysis of variance (ANOVA).

## RESULTS AND DISCUSSION

### Effect of Variation in Size of Nonpareil Seeds on the Release Rate of Diltiazem Basic Pellets

Diltiazem basic pellets were successfully prepared using the fluidized-bed coating process. Depending on the drug load requirement, the drug content of the pellets could be varied from 60% by a one-step process to 75% by a two-step process. Altering the mesh fraction of the starting nonpareil seeds for the two-step layering process was found to affect

the release rate of drug from the diltiazem basic pellets. A greater drug load per unit volume of pellet was achieved by using the larger 35/40 mesh fraction of starting nonpareil seeds with an average particle diameter of 462 microns as compared to the batch prepared using the smaller 40/50 mesh fraction of nonpareil seeds with an average particle diameter of 364 microns. Table II shows that the average drug loading layer thickness of diltiazem basic pellet of formulation 2 (r = 527 microns) was 83% thicker than the pellets of formulation 3 (r = 287 microns). Table II shows that the specific surface area of the diltiazem basic pellets of formulation 2 (36.9 $cm^2/g$) was 72% lower than the pellets of formulation 3 (63.3 $cm^2/g$). These changes in physical characteristics of the diltiazem basic pellets affected the in vitro release characteristics. Figure 1 shows that since formulation 2 had a smaller specific surface area and a thicker drug loading layer exposed to the dissolution medium as compared to formulation 3, a much faster release rate of diltiazem hydrochloride from the pellets of formulation 3 was observed. The difference in the release rate profiles of these two formulations was significant at the 5% level ($p<0.05$) based on the *t*-test. The data indicated that the mesh size of the starting nonpareil seeds can be used to control the dissolution release rate of the diltiazem basic pellets. It should be pointed that the micronized diltiazem hydrochloride powder (average particle diameter of 8 microns) is water soluble and the formula amount of drug powder was completely dissolved in the dissolution medium within one min. Therefore, the release rate profiles of the three formulations exhibited in Figure 1 suggest retardation in drug dissolution. By plotting percentage of drug released from formulations 2 and 3 in pH 3 phosphate buffer versus square root of time, the data follow a release pattern with square root dependence. The correlation coefficient for formulations 2 an 3 was 0.978 and 0.967, respectively. Therefore drug release followed a typical matrix formulation as described by Higuchi.

Dissolution testing was used to discriminate between diltiazem basic pellets where drug loading layer was completely coalesced. Pellets displaying similar release profiles after exposure to heat were considered to be fully coalesced. It was found that an oven-drying step at 70°C for 24 h was required to stabilize the diltiazem basic pellets prepared by a one-step process. An additional twenty min of drying of the pellets in the Wurster column coater did not yield product with a constant dissolution profile. Dissolution data demonstrated that the non-oven dried sample produced by the one-step process (formulation 1) displayed a slower dissolution rate of drug as compared to the samples that were oven-dried

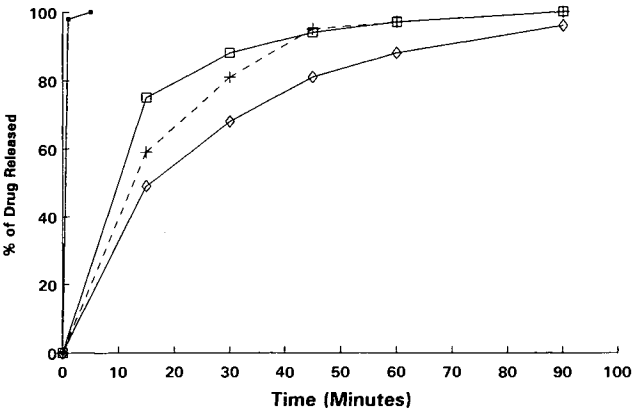


Fig. 1. Cumulative amount (%) of diltiazem hydrochloride released from three batches of diltiazem basic pellets in pH 3 phosphate buffer. (■) diltiazem powder; (□) Formulation 1 (one-step process); (+) Formulation 3 (specific surface area = 63.3 $cm^2/g$); (◇) Formulation 2 (specific surface area = 36.9 $cm^2/g$).

for 16 h and 24 h. The dissolution profiles of oven-dried samples did not change significantly after either 16 h or 24 h drying. The data indicated that diltiazem basic pellets were stabilized by the oven-drying step at 70°C for 24 h.

The time required for the oven drying cycle was found to be a function of the diameter of the diltiazem basic pellets. Dissolution data show that the diltiazem basic pellets of formulation 2, prepared by a two-step process, required a longer oven-drying period to stabilize the pellets. The dissolution profile of pellets that were dried for 24 h was much slower than the pellets that were dried for 48 h. However, the dissolution profile of the pellets dried for 48 h remained constant as compared to samples dried for 57 h and 90 h. The data indicated that diltiazem basic pellets by a two-step process required an oven drying of 48 h to stabilize drug loading layer.

### Effect of Coating Thickness on Release Profiles of Diltiazem Sustained Release Pellets

Formulation 2, exhibiting the thickest drug loading layer, smallest specific surface area and slowest release rate profile among the three types of the basic pellets, was selected as the model formulation for the coating experiments. The release rate profiles of the diltiazem sustained release pellets depend, to a greater extent, on the coating level of the product. As seen in Figure 2, when the coating thickness was increased, a decrease in the release rate of the coated pellets

**Table II.** Calculation of average drug loading layer thickness and specific surface area of three different formulations of diltiazem basic pellets.

| Formulation No. of Diltiazem Basic Pellets (DB) | Manufacturing Process | Ave. Particle Diameter of DB Pellets (D)–(I)(μm) | Ave. Particle Diameter of Non-pareil Seeds (II)(μm) | Ave. Drug load. Layer Thickness of DB Pellets [(I–II)/2 = III](μm) | True Density of DB Pellets (ρ) ($g/cm^3$) | Specific Surface Area (SA)* ($cm^2/g$) |
|---|---|---|---|---|---|---|
| 1 | One-step | 1255 | 657 | 299 | 1.161 | 41.18 |
| 2 | Two-step | 1515 | 462 | 527 | 1.073 | 36.88 |
| 3 | Two-step | 938 | 364 | 287 | 1.010 | 63.33 |

SA* = $6/(\rho D)$.
D = Average arithmetic diameter.

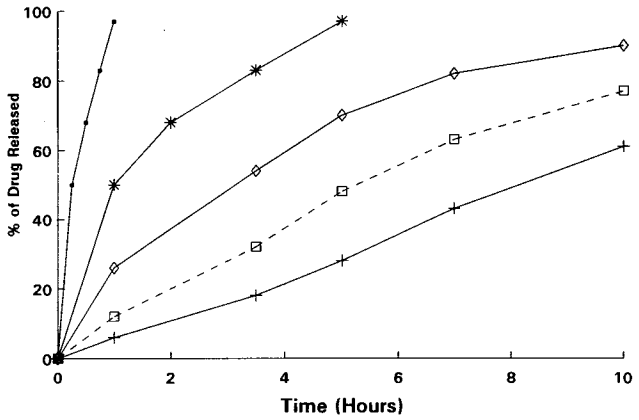


Fig. 2. Effect of coating thickness on the release profile of diltiazem sustained release pellets in pH 3 phosphate buffer from zero to 3.5 h and then the pH was changed to 7.4 (Dissolution method B). (■) diltiazem basic pellets (uncoated); (∗) Cardizem® Tablets; (◇) Formulation A (0.5% ethylcellulose/DBS coating); (□) Formulation B (0.6% ethylcellulose/DBS coating); (+) 1.0% ethylcellulose/DBS coating.

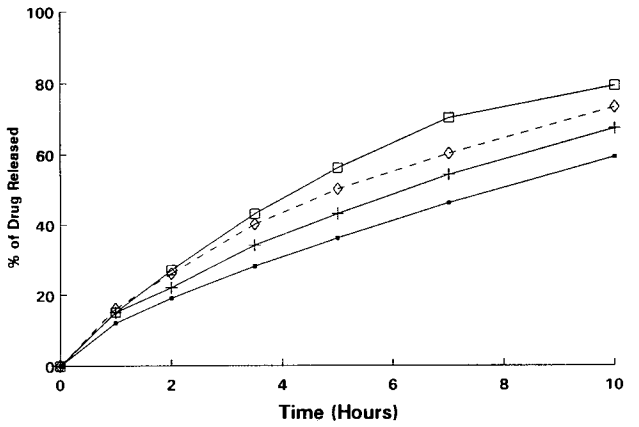


Fig. 3. Effect of pH of dissolution medium on the release rate profile of diltiazem sustained release pellets (0.6% ethylcellulose/DBS coating). (■) pH 1.2; (+) pH 3; (◇) pH 5; (□) pH 7.4.

was observed. It was found that the diltiazem sustained release pellets required an additional oven drying step at 70°C for 24 h to stabilize the ethylcellulose/DBS film. Diltiazem sustained release pellets dried in the Wurster column for additional 20 min, showed a much faster release rate profile as compared to the oven-dried diltiazem sustained release pellets (24 h). The data indicated that the ethylcellulose/DBS film was not cured during the 20 min of drying in the Wurster coater. The polymer film required 24 h of oven drying to allow the completion of the coalescence process. Therefore, the oven-dried diltiazem sustained release pellets showed a slower release profile since the coalesced ethylcellulose film provided a better barrier coating. The oven-dried diltiazem sustained release pellets that were coated with a 0.5% ethylcellulose/DBS coating also demonstrated a constant dissolution profile following storage at 50°C for three months.

### Effect of Dissolution Media pH on Release Profiles and Release Kinetics

Figure 3 shows the effect of dissolution media pH on the release rate of diltiazem hydrochloride from diltiazem sustained release pellets coated with 0.6% ethylcellulose/DBS coating. The release rate of drug from the diltiazem sustained release pellets showed a slight increase in release rate as the pH of the dissolution media was increased from pH 1.2 to 7.4. The increase in release rate may be attributed to the presence of the shellac in the diltiazem basic pellets. Shellac is insoluble in acidic conditions but soluble at alkaline conditions (8). As the pH of the dissolution media decreased to pH 1.2, the shellac in the drug loading layer acted as an enteric polymer to retard drug release of diltiazem hydrochloride in the acidic environment. As the pH of the dissolution media was increased, the enteric effect of shellac on the release rate of the diltiazem basic pellet was diminished since the shellac in the drug loading layer begins to dissolve and allows a more rapid release of drug from the diltiazem sustained release pellets.

Regardless of the coating level of either 0.5 or 0.6 or 1.0%, the release kinetics of the diltiazem sustained release pellets appeared to follow first order kinetics. Increasing the coating level decreased the initial release rate, but had no effect on the first order release rate. The correlation coefficients ($r^2$) for all three formulations ranged from 0.9727 to 0.9962. The data indicated that the release rate of drug was primarily controlled by the thickness of ethylcellulose film. The diffusion rate of drug through the ethylcellulose coating film governed the release rate of drug. The thicker the ethylcellulose film, the slower the rate of drug released from the pellets.

### *In Vivo* Studies

Diltiazem basic pellets of formulation 2, were coated with 0.5 and 0.6% of ethylcellulose/DBS coating to yield formulations A and B, respectively, for the clinical study. Two duplicate batches of formulations A and B were successfully prepared using the same coating process. The resultant diltiazem sustained release pellets showed similar *in vitro* dissolution profiles. The data indicated that the coating process was reproducible. Cardizem® 60 mg tablet was used as the reference standard for the study. Even though Cardizem® tablet is administrated as a conventional dosage form for 3 or 4 times daily, the *in vitro* dissolution profile of the

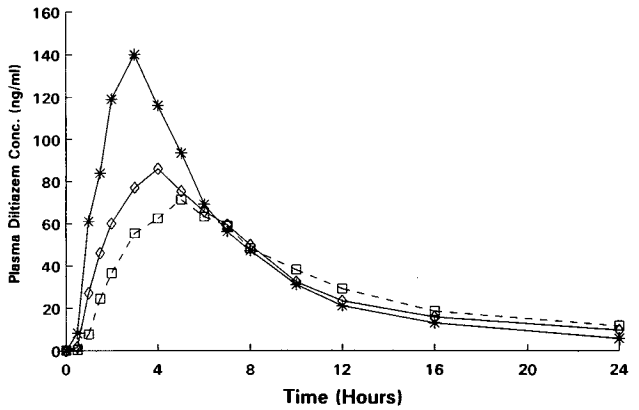


Fig. 4. Mean (n = 9) plasma concentrations of diltiazem. (∗) Cardizem® tablets; (◇) Formulation A; (□) Formulation B.

Table III. Pharmacokinetic parameters from *in vivo* clinical trial.

| Product | $C_{max}$ (ng/ml) | $T_{max}$ (h) | $AUC_{0-\infty}$ (ng-h/ml) | $K_{app}$ (L/h) | $T_{1/2}$ (h) |
|---|---|---|---|---|---|
| Cardizem® | 141.3 (68.7) | 3.1 (0.6) | 980 (506) | 0.155 (0.10) | 5.4 (1.8) |
| Formulation A | 89.0 (52.3)* | 3.2 (1.2) | 973 (641) | 0.096 (0.06)* | 10.0 (6.3)* |
| Formulation B | 73.2 (45.9)* | 5.0 (0.9)* | 949 (644) | 0.065 (0.02)* | 11.3 (2.7)* |

* Indicates $p < 0.05$.

tablet indicated that the formulation indeed is a controlled release dosage form. The Cardizem® tablet showed a sustained release profile as compared to the diltiazem basic pellets (Figure 2). Both of the experimental formulations A and B, exhibited a much slower dissolution profile as compared to the Cardizem® tablet (Figure 2).

Figure 4 shows the mean serum levels of nine fasted subjects following a single dose of diltiazem hydrochloride 120 mg as either Cardizem® tablet (60 mg per tablet) or the two experimental formulations. Pharmacokinetic parameters are listed in Table III. Formulation A, showed a different rate of absorption (lower $C_{max}$) as compared to the Cardizem® tablet. The extent of absorption of drug was equivalent to each other. Formulation B showed a slower *in vitro* release profile as compared to the formulation A, which demonstrated the same extent of absorption ($AUC_{0-\infty}$) but a different rate of absorption (lower $C_{max}$ and higher $T_{max}$) as compared to the Cardizem® tablet. When elimination parameters were compared, statistically significant differences were detected between the test formulations and the reference. The data clearly demonstrate that the rate of absorption of diltiazem was different between the test formulations and the Cardizem® tablets and indicate *in vivo* sustained release characteristics. Furthermore, as ethylcellulose/DBS coating level of diltiazem sustained release pellets was increased from 0.5% to 0.6%, the rate of absorption of formulation B (0.6% coating) was reduced as compared to formulation A (0.5% coating). Formulation B had a higher mean $T_{max}$ value of 5 h and a lower $C_{max}$ of 73.2 ng/ml compared to 3.2 h and 89.0 ng/ml for formulation A. The data implied that the rate of absorption of this formulation was controlled by the coating level of the ethylcellulose/DBS film of the coated pellets. Formulation B, which exhibited a different rate of absorption and the same extent of absorption, can probably be used as twice daily formulation as compared to the three times daily formulation of Cardizem® tablet. The *in vivo* data proved that the formulation approach presented in this paper indeed is a good means to prepare a sustained release diltiazem product.

In summary, the data indicated that diltiazem sustained release pellets can be prepared using the Wurster column process. The drug loading and release rate profile of the diltiazem basic pellets can be controlled by altering the mesh fraction of the starting nonpareil seeds. The duration of the oven-drying step was identified as a critical means to stabilize the diltiazem basic pellets. The rate of absorption of diltiazem hydrochloride from these formulations was controlled by the thickness of the ethylcellulose coating.

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