Drug Development and Industrial Pharmacy, 31:339–347, 2005

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1081/DDC-200054307

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Eudragit NE40–Drug Mixed Coating System for Controlling Drug Release of Core Pellets

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ABSTRACT This study was aimed at developing a controlled-release coating system around core pellets with aqueous dispersion, along with some water channeling agents. Core pellets of diltiazem were prepared using the extrusion-spheronization technique and subsequently coated with aqueous dispersion of Eudragit NE40 alone, or drug–polymer mixtures using bottom-spray fluidized bed coater. The lag time in drug release profiles increased as the coating levels of Eudragit NE40 were increased, whereas no lag time was observed in core pellets coated with drug–polymer mixtures. Mixed coating at the 7% level exhibited comparatively better release profiles and provided desirable release rates during the 12-hour testing interval. Diltiazem HCl release from mixed coating was fairly independent of pH and drug loading. Curing of coated pellets was found to be an essential step for stable drug release profiles. The selection of core size range had remarkable effect on drug release rate and was considerably reduced by using greater core size.

KEYWORDS Diltiazem, Eudragit, Extrusion-spheronization technique, Fluidized bed coating, Controlled-release pellets

INTRODUCTION

One of the commonly used methods for the preparation of controlled-release pellets involves the extrusion-spheronization process followed by coating with a water-insoluble polymer film using a fluidized bed coating system. It is generally recognized that this technique produces evenly coated pellets with uniform thickness. The process of air suspension or bottom spray coater is preferably used for coating matrix pellets/core pellets or drug-layered pellets. The aqueous-based copolymer is characterized by short processing times, economical production, and reproducible results (Eudragit Data Sheet, 1989; Ghebre-Sellassie et al., 1986). Therefore, an aqueous coating system can preferably be usable in fluidized bed coater. In general, curing of coated pellets reduces the drug release and provides the stable release profiles (Wesseling & Bodmeier, 2001). Eudragit NE40, a nonbiodegradable copolymer containing 40% solid content in aqueous dispersion has molecular weight of about

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800,000. Due to its very low minimum film forming temperature (5°C), soft and flexible films can be prepared at room temperature without addition of any plasticizer (Lehmann, 1989). The tackiness of various polymers films were investigated and was in the order of Eudragit NE30D>RS 30D>RL 30D>Aquacoat (Wesseling et al., 1999).

This study was conducted to develop a release controlling film coat around diltiazem core pellets with Eudragit NE40 (NE40) alone or in mixed form. Diltiazem core pellets were prepared with a rotary extruder and spheronizer, whereas polymer coats were produced using a bottom spray coater. In vitro dissolution test was used for comparison of drug release profiles of various coated pellets. The effect of temperature, size ranges of core pellets, and pH of the dissolution media on the release behavior were also examined. In addition, the surface morphology of the coated pellets was examined with scanning electron photographs.

MATERIALS AND METHODS

Materials

Diltiazem HCl (Reddy Pharma, Singapore), Eudragit NE40D (Rohm Pharma, Darmstadt, Germany), lactose monohydrate BP (HMS, Holland), microcrystalline cellulose (Avicel PH 101, FMC Corporation, Princeton, NJ), and talc BP (Merck, Darmstadt, Germany).

Preparation of Core Pellets

Avicel and lactose were first blended in a Kenwood planetary mixer for 5 min then diltiazem HCl dissolved in the required amount of water was poured into the powder mixture. The wet mass was further mixed for 10 min and was fed between two contra-rotating rollers of a rotary extruder (Alexanderwerk, Remscheid, Germany). The extrudates were cut into smaller cylinders by the knife fixed inside one of the rollers and further processed using a 22.5-cm Spheronizer (G. B. Caleva Ltd., Dorset, UK) fitted with a cross-hatched plate rotated at 1000 rpm for 15 min. After spheronization, the pellets were dried in a fluid bed drier at 60°C for 15 min. The dried pellets were screened to obtain mesh fraction of 0.8–1.0 mm, 1.0–1.18 mm and 1.18–1.25 mm. The formulae of core pellets are shown in Table 1.

TABLE 1 Formulae of Diltiazem Core Pellets

	Core pellets	
Ingredients	10%	20%
Diltiazem HCl (g)	50	100
Avicel PH 101 (g)	250	250
Lactose (g)	200	150
Water (g)	200	160

Influence of NE40 Coating on Drug Release

For aqueous polymer coating, 150 g of core pellets (1.0–1.18 mm) containing 10 and 20% diltiazem were used. A 10% w/v NE40 dispersion was prepared by mixing 25 mL of NE40 and talc (2 g) in distilled water to make the volume up to 100 mL, and the dispersion was agitated throughout the coating process. Five coating levels of NE40 dispersion were applied and based on theoretical weight gains of 3, 4, 5, 6, and 7%. All the coating processes were performed using an Aeromatic AG Strea 1 fluidized bed coater and operated under the following conditions.

Inlet air temperature	30–35°C
Atomizing air pressure	0.6 bar
Spray rate	2.0–2.5 mL/min
Spray nozzle diameter	0.8 mm

The coated pellets were transferred to a paper-lined tray, cured overnight in an oven with an air-circulating fan at 37°C and stored in a desiccator before initiating dissolution studies.

Influence of Drug–Polymer Mixed Coating on Drug Release

In this part of study, only 20% core pellets (150 g) were chosen for drug–polymer mixed coating. Diltiazem HCl powder in 15, 20, and 25% of the total polymer content was used for modifying the permeability of the NE40 film. Various drug–polymer mixtures were prepared separately by dissolving the required amount of diltiazem (1.5, 2.0, 2.5 g) in about 50 mL of distilled water prior to the addition of NE40 (25 mL) and talc (2% w/v). The volume of the mixtures was made up to 100 mL and was stirred using a magnetic stirrer prior to and throughout the coating process. Drug–polymer mixtures were then separately

sprayed at 7% coating level on core pellets. In addition, 20% cores pellets with sieve fractions 0.8–1.0 and 1.25–1.4 mm were separately coated with drug–polymer mixtures (containing 25% diltiazem) at 7% coating level. The coated pellets were transferred to a paper-lined tray and cured in the same manner as stated previously.

Influence of Thermal Treatment on Drug Release

A batch of 20% core pellets (1.0–1.18 mm) was coated with drug–polymer mixture containing 25% diltiazem and the coated pellets were divided into two parts, one part was kept as such in a desiccator (uncured pellets), and the small portions of other part were kept in an oven at 37, 50, and 60°C for 24 hr to evaluate the effects of thermal treatment on drug release. The treated pellets were then allowed to cool at room temperature in a desiccator.

Dissolution Studies

Predetermined weights of coated pellets were used for the dissolution studies using USP apparatus II (Sotex AT7, Switzerland). The test was performed in 900 mL distilled water maintained at 37±0.5°C and stirring speed of 100 rpm. Samples (5 mL) were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hr with an automated fraction collector (SDX, Penang, Malaysia) equipped with a piston pump. The drug content in each sample was analyzed directly or diluted with the release medium at 237 nm using an UV spectrophotometer (Hitachi U2000, Tokyo, Japan). The cumulative percentage of drug released was calculated, and the mean of triplicate readings of each type of coated pellets was used in the data analysis. Moreover, dissolution profiles of various coated pellets having standard deviation within ±2% were included in results and discussion. The release profiles of core pellets (20%) coated with drug–polymer mixture containing 25% diltiazem were also determined at pH 1 and 7.

Scanning Electron Microscopy

The surface views of the pellets were recorded using a scanning electron microscope (Leica Cambridge S-360, Cambridge, UK). The coated pellets were mounted onto stubs using double-sided adhesive tape. The mounted samples were sputter coated (Polron Sc 515, New Haven, East Sussex, UK) with gold palladium under an argon atmosphere and examined at 15 kV accelerating voltage.

RESULTS AND DISCUSSION

In preparation of core pellets, low proportions of highly water-soluble drug in the formulation did not produce any serious problem compared with higher drug content. As the percentage of drug increased from 20 to 30%, both extrusion and spheronization became very difficult to control due to imbalance of granulating liquid required for proper plasticity of the wet mass. Optimum wetting could not be achieved by inclusion of more than 50% Avicel component and lowering the amount of lactose. Therefore, abnormal shapes such as ellipsoids and cylinders with rounded end were formed.

A polymeric membrane provide a certain amount of resistance to drug diffusion from the drug reservoir to the surrounding medium. The driving force of such systems is the concentration gradient of drug molecules between the reservoir and the medium. The drug entity from film-coated dosage forms may be transported through a hydrated swollen film or a network of capillaries filled with the dissolution media. Dissolution studies indicated that several factors would affect drug release from the coated pellets. Some of the more fundamental parameters such as coating thickness, drug loading, pH of the dissolution medium, curing time and temperature, storage time, and water-soluble additives may affect the nature of polymeric film, and hence, the release rate of pellets.

Influence of Eudragit NE40 Coating on Drug Release

Drug release of coated pellets depends to a greater extent on coating levels of the polymeric dispersion applied on core pellets shown in Fig. 1. A faster release was observed with 3% compared with 7% coating levels. The release rate from the coated pellets seemed to be inversely proportional to the thickness of the polymer coat. A similar inverse relationship between the thickness of polymer coat and the rate of drug release has been reported (Govender & Dangor, 1997;

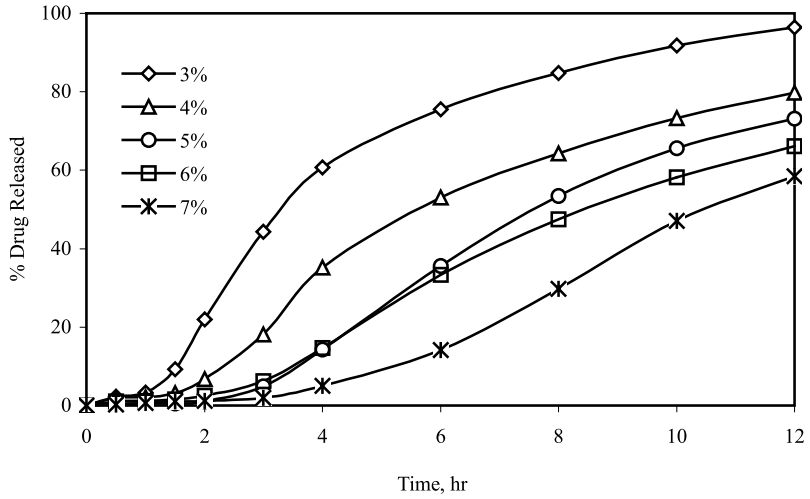

FIGURE 1 **Influence of Various Coating Levels on In Vitro Diltiazem HCl Release from Core Pellets (20%) Coated with Eudragit NE40 Dispersion.**

Govender et al., 1995; Li et al., 1991). A closer examination of release profile of 5–7% coated pellets shows that the drug was released after a lag time, which became longer as the level of coating thickness was increased. In addition, drug release from 7% coated pellets was initiated after 2 hr lag time. Similar release profiles of coated pellets using 10% core pellets were also obtained (results not shown), indicating that percent drug loading had no effect on the drug release rate. Because the coating of core pellets with NE40 dispersion alone could not achieve the drug release at a desirable rate; therefore, instead of using any other water-soluble material as a channeling agent, drug powder was incorporated in the polymeric dispersion to improve the drug release characteristics.

Influence of Drug–Polymer Mixed Coating on Drug Release

Incorporating a water-soluble material into the nonsoluble coat provides a simple method of modifying its permeability, and hence, the rate of drug release from the coated pellets. Thus, drug itself was investigated as a possible channeling agent for modifying the permeability of the membrane coat.

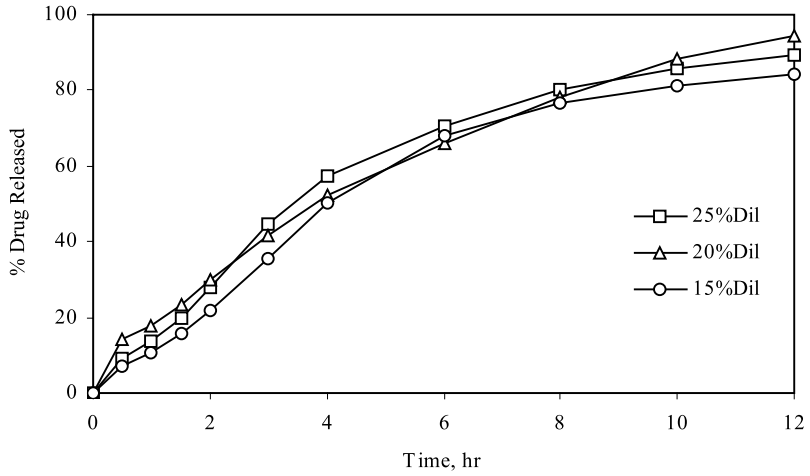

FIGURE 2 **Influence of Mixed Coating on In Vitro Drug Release from Core Pellets Coated with 7% Drug–Polymer Mixtures Containing Various Percentages of Diltiazem (Dil).**

TABLE 2 Drug Release Rate Constants K and Regression Coefficients R^2 of Coated Pellets Obtained from Data Corresponding to 0–8 hr

Coated pellets containing diltiazem in mixed film	Zero order		First order	
	K_1/h	R^2	K_2/h	R^2
15%	10.2	0.9764	0.9277	0.9847
20%	9.4	0.9559	0.6574	0.9827
25%	10.4	0.9669	0.8437	0.9825

Drug release profiles from core pellets coated with drug–polymer mixtures containing 15, 20, and 25% diltiazem powder with respect to 7% NE40 are shown in Fig. 2. The drug release characteristics were apparently changed from the core pellets coated with NE40 dispersion alone (Fig. 1). The drug was released gradually without any lag time and the extent of drug release was also improved. More than 90% drug was released in about 12 hr compared with less than 60% drug released from pellets coated with NE40 dispersion alone. This rise in the release rate was clearly due to pore formation within the coating film, which provided channels for rapid penetration of dissolution media. The dissolution data of coated pellets containing 15–25% diltiazem were also fitted using zero-order and first-order kinetic models. The release rate constants (K) and regression coefficient (R^2) of coated pellets obtained from data corresponding to 0–8 hr are compared in Table 2. The model with higher R^2 value was considered to be the more appropriate model for the dissolution data. Higher R^2 values were obtained for first-order plot compared with zero order, and hence, the release of coated pellets can be ascribed by first-order kinetics. It is also evident that no apparent difference in the release rate constants of coated pellets was observed with the inclusion of various percentages of drug. Therefore, drug–polymer mixtures containing 15–25% diltiazem were equally beneficial in controlling drug release at 7% coating level and were found to be effective in avoiding lag time observed in the pellets coated with NE40 dispersion alone.

However, as the percentage of diltiazem in the drug–polymer mixture was increased from 25 to 30% or above, the drug release rate of the coated pellets was greatly enhanced (result not shown) and was unable to achieve desirable drug release rate. This is due to the fact that the release controlling film around the core pellets was too weak to withstand the pressure of dissolution media. Therefore, the film was ruptured due to increase in its porosity, which resulted in an almost 100% release in about 3–4 hr. Such findings could be related with almost immediate drug release from salbutamol-coated pellets using a mixture of Eudragit RS30 and a small amount of drug (Govender et al., 1995). In contrast, Li et al. (1990) found a slight increase in drug release rates from pellets coated with a mixture of ethylcellulose and theophylline. The reason for such behavior could be due to the difference in the solubility of drug and permeability of various polymers used.

No evidence of interaction between drug and polymer has been observed during preliminary differential scanning calorimetry studies of coated pellets. Diltiazem, a highly water-soluble drug was entrapped by water-insoluble polymeric film and appeared as mixed outermost film around the cores. When the coated pellets contacted the dissolution medium, the whole amount of diltiazem in the mixed film would be leached out and provide channels for penetration of more fluid inside the core. Also, there are less chances of movement of drug from the core pellets to the outermost film in the absence of dissolution medium, and hence, it would not affect the release kinetics or modify the film.

Influence of Thermal Treatment on Drug Release

Heating time and temperature, as well as storage at higher temperature, can affect the coalescence process for the latex films around the pellets and tablets. Generally, thermal treatment or curing may reduce the drug release, which result in stable drug release profiles (Wesseling & Bodmeier, 2001). Figure 3 illustrates the release profiles of treated pellets at different temperatures. Pellets treated at 50 and 60°C showed comparable release profiles but were both slightly slower than those thermally treated at 37°C. In

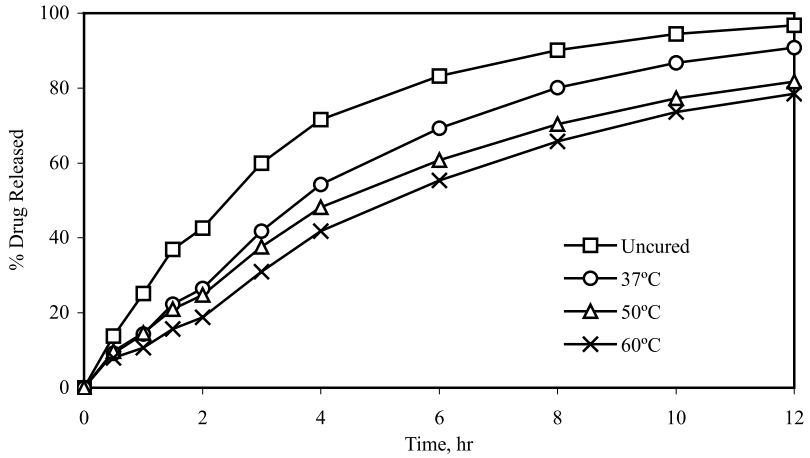

FIGURE 3 **Influence of Thermal Treatment on In Vitro Diltiazem HCl Release from Core Pellets Coated with 7% Drug–Polymer Mixture.**

comparison, the untreated pellets showed faster rate of drug release compared with the thermally treated pellets. It appeared that as the treatment temperature was increased, there was a corresponding decrease in the rate of drug release. Upon curing at various temperatures studied, there was still polymer chain movements and further coalescence of the polymer particles in the coat formed, and at 60°C, complete film formation was achieved after 24 hr (Gilligan & Po, 1991). Thereafter, further increase in the curing temperature did not cause any further changes in the film structure and provides a stable release profile (Wesseling & Bodmeier, 2001). The influence of the curing temperature on the rate of drug release could be attributed to its effect on the film formation. When the polymer particles were deposited on the pellet surface during coating, interdiffusion of the polymer chains among adjacent polymer particles would lead to formation of an integral film around the drug pellets. However, the movements of the polymer chains, and hence, the film formation process depends on temperature, which must be maintained above the minimum film formation temperature (MFT) or the glass transition temperature (Tg). The coating temperature of NE40 in this study was well above the MFT (5°C) and did not require any plasticizer to reduce MFT or Tg. Therefore, the process was completed without interruption. As the coating temperature was lowered to 25°C, the pellets were sticky and agglomerated in groups, but did not affect the coating process. The pellets were defluidized at higher coating temperatures due to electrostatic charges developed on the surface of core pellets. The flow properties of these pellets were badly affected due to agglomeration of pellets in a single mass, and the coating process was practically impossible to proceed above 40°C. However, when the pellets were cooled down to room temperature, the free-flowing properties were reinstated.

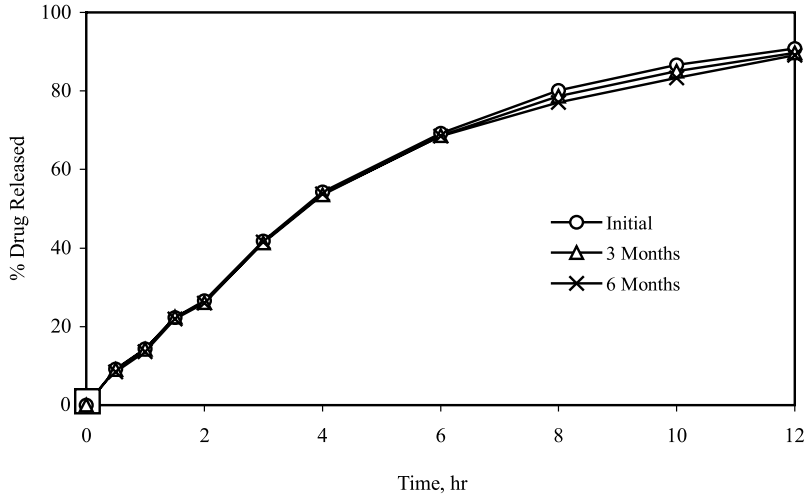

FIGURE 4 **Influence of Storage at 37°C on Drug Release Profiles of Core Pellets Coated With 7% Drug-Polymer Mixture.**

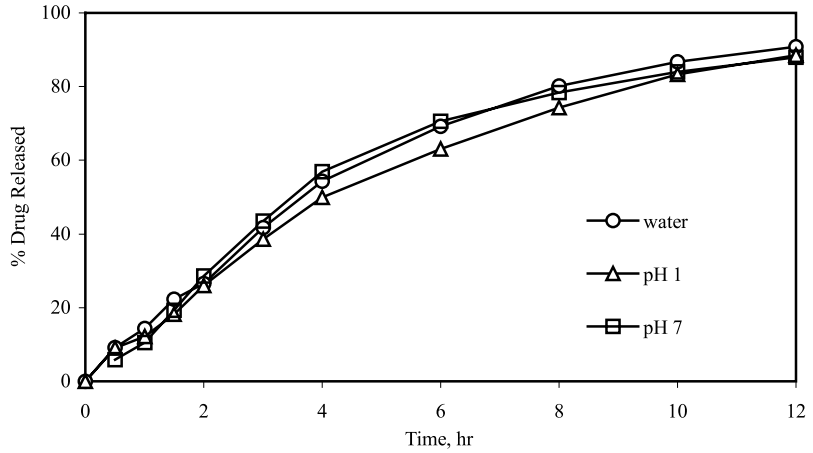

FIGURE 5 **Influence of pH on In Vitro Diltiazem HCl Release from Core Pellets Coated with 7% Drug–Polymer Mixture.**

Therefore, the phenomenon of agglomeration during the coating process was different at low or high temperatures. The groups of coated pellets were also agglomerated in an airtight bottle upon storage at 40°C, but such undesirable effects could be avoided by mixing certain amounts of antiadherent with the coated pellets.

The drug release of coated pellets initially and after 3 and 6 months of storage at 37°C in an oven indicated a negligible change in the dissolution profiles (Fig. 4), and the rate of drug release seemed to be stable during 6 mo of storage. As these coated pellets were cured at 37°C for 24 hr, therefore, negligible changes were observed in the release profiles.

Influence of pH on Drug Release

Dissolution testing in distilled or deionized water is useful only for initial development of dosage forms. Polymeric coatings with pH-independent permeability may give rise to pH-dependent drug release profile due to difference in drug solubility at various pH values. Therefore, for the variable environment of gastrointestinal tract, the drug release characteristics are evaluated at different pH. Drug release from pellets coated with 7% drug–polymer mixture in pH 1 and pH 7 are presented in Fig. 5. The release profiles at two different pH dissolution media were comparable and slight differences in their release rates were found. This could be attributed to fairly pH-independent water solubility of diltiazem. The solubility of saturated diltiazem solution is comparatively greater at pH 4.8 (678 mg/mL) compared with lower solubility in 0.1M HCl (588 mg/mL) (McCelland et al., 1991). In the same way, such differences in the solubility seemed to appear in the coated pellets, which contained about 25% of diltiazem, with respect to the outermost release-controlling membrane. At pH 1, diltiazem from the outer film layer was slowly discharged from

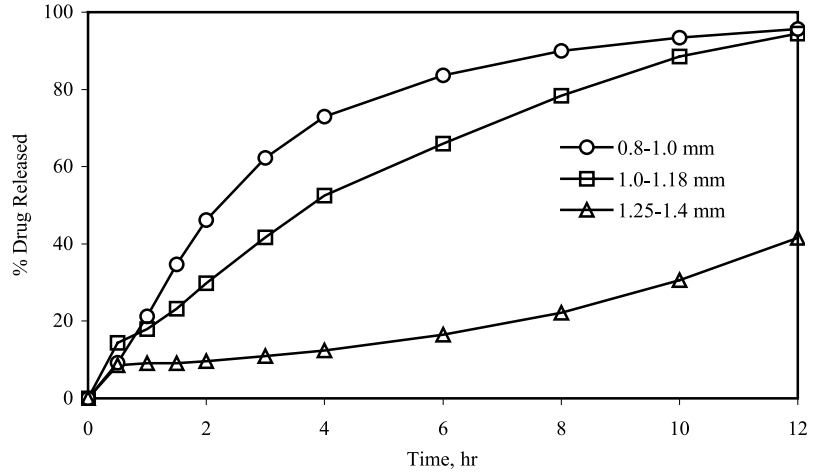

FIGURE 6 **Influence of Various Core Sizes on In Vitro Diltiazem HCl Release from Core Pellets Coated with 7% Drug–Polymer Mixtures.**

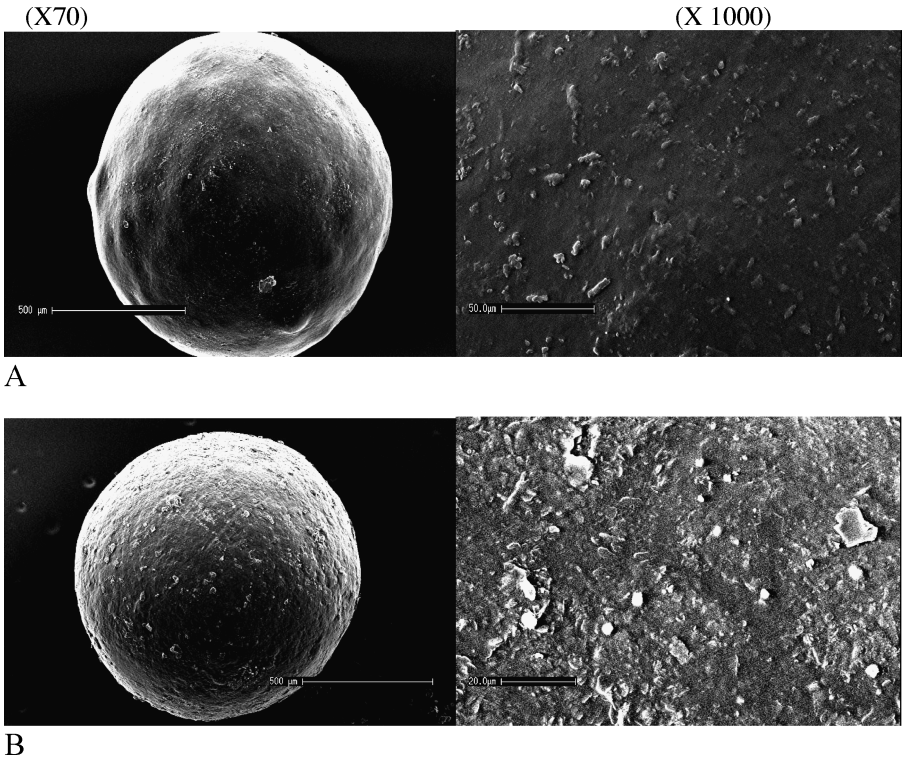

FIGURE 7 **SEM of (A) Pellets Coated with NE40 Dispersion and (B) Pellets Coated with 7% Drug–Polymer Mixture.**

0.1M HCl due to common ion effect of chloride in both drug and dissolution medium. The results are consistent with those of Mathir et al. (1997), who also reported pH-independent release of chlorpheniramine maleate from pellets coated with aqueous dispersion of Eudragit NE30.

Influence of Core Size on Drug Release

Two batches having different mesh sizes with a narrow size distribution of core pellets 0.8–1.0 mm and 1.25–1.40 mm were coated separately with 7% drug–polymer mixtures. A significant difference in the release profiles is shown in Fig. 6. The results were not unexpected and evidenced that the larger size pellets displayed significantly slower release rate when compared with smaller size pellets. To achieve similar release profiles, the smaller pellets would require more quantity of drug–polymer mixtures for coatings that in turn would consume more time for processing. Because the release characteristics of drug are greatly affected by altering the initial mesh size, selection of initial pellet size is an essential prerequisite for product development.

Morphology of Coated Pellets

Scanning electron microscopy (SEM) of coated pellets was also employed to evaluate the performance of the coating system and aqueous-based coating formulations used in this study. The pellets coated with 7% NE40 dispersion and drug–polymer mixture at both lower ($\times 70$) and higher ($\times 1000$) magnifications are shown in Fig. 7. The surface of coated pellets with NE40 alone was comparatively smoother than the surface of pellet coated with drug–polymer mixture. This might be due to the presence of diltiazem powder scattered in the mixed film and appeared as white tiny particles on the surface of the pellet. These particles would act as entrance or exit points for the dissolution medium after rapid release of drug from the mixed film.

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