

Formulation and evaluation of controlled release diltiazem pellets using Eudragit NE40

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Abstract

A release controlling film coat around diltiazem pellets was developed with Eudragit NE40 and the effects of percent drug layering, pH and stirring speed of dissolution media on drug release were also evaluated. Diltiazem HCL aqueous solutions were applied onto inert pellets to produce drug pellets, which were subsequently coated with aqueous polymer dispersion using bottom spray Fluidized-bed coater. Coated pellets were cured at 37°C for 24 h. The release profile of coated pellets was found to be inversely proportional to the thickness of the polymer coat and desirable controlled release characteristics could be achieved by manipulating the coating levels. The percent drug layering onto inert pellets had no effect on the release rate of coated pellets. Moreover, diltiazem HCL release was fairly independent of pH and stirring speed.

Keywords: Controlled release pellets, coating, Eudragit, diltiazem, fluidized-bed.

Introduction

Oral multiparticulate controlled release dosage forms such as coated pellets are usually preferred over unit dosage forms due to lesser risk of dose dumping, lesser local irritation and lesser variations in gastric emptying. Advances in fluidized-bed coating systems and aqueous polymer coating systems have also played key role in promoting multi-unit dosage forms (Bechgaard *et al.*, 1982; Sharge *et al.*, 1999).

Some aqueous coating systems have been described to possess pH-dependent properties, but most are little affected by the pH of the dissolution media. The current United States Pharmacopeia (US Pharmacopeia) only lists three controlled release coatings namely cellulose acetate, ethylcellulose and methacrylic acid copolymers that function as a rate controlling membrane. Although other coatings exist but these three are widely accepted (Savage and Rhodes, 1995). An aqueous commercial coating dispersion system Eudragit NE40 was used as coating and drug release rate controlling agent for a highly water-soluble drug, diltiazem HCL. Eudragit NE40 is based on poly (ethyl acrylate-methyl methacrylate) esters without functional group and has pH independent permeability characteristics and reproducible results (Li *et al.*, 1991).

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Diltiazem HCL is a calcium channel blocker and has short half-life that necessitates frequent administration of doses to maintain steady-state plasma levels.

The primary objective of the present study was to formulate diltiazem pellets with controlled release characteristics using bottom spray coating system. The effects of drug layering, pH and stirring speed of dissolution media on drug release profiles were also investigated.

Materials and Methods

Diltiazem HCL (Reddy Pharma Singapore), Eudragit NE40D (Rohm Pharma, Germany), lactose monohydrate BP (HMS, Holland), microcrystalline cellulose (Avicel PH 10, FMC corporation, USA), polyvinylpyrrolidone (K30, USA), talc BP (Merek) and all other chemicals used were analytical grade.

Preparation of Drug Pellets

Inert pellets (1.0-18 mm) were first prepared by extrusion-spheronization method using Standard formula; lactose: Avicel:water (1:1:0.9) and were used for drug pellets. The drug (20 % w/v) was first dissolved in a binder solution (2 % w/v, K30) and talc (2 % w/v) was then added to the drug solution with continuous stirring before and during the application onto 150 g inert pellets to produce drug pellets containing 10 % , 20 % and 30 % diltiazem using bottom-spray fluidized bed coater under the operating conditions shown below.

Inlet air temperature	55-60°C
Atomizing air pressure	0.6 bar
Spray rate	2.0-2.5 ml/min
Spray nozzle diameter	0.8 mm

Coating of drug Pellets

For aqueous polymer coating, 150 g of diltiazem pellets (20 %) were used. An aqueous dispersion of Eudragit NE40 was used and obtained commercially. Prior to coating, the polymer was diluted to 10 % w/v with distilled water. A small quantity of talc (2 % w/v) was added into the coating mixture as an anti-adherent. The mixture was stirred using a magnetic stirrer prior to and throughout the coating process. Coating was performed onto drug pellets under similar operating conditions shown above except the inlet air temperature was maintained at 25-30 °C. Five coating levels of NE40 dispersion were examined and based on theoretical weight gained of 3, 4, 5, 6 and 7 %. The coated pellets were cured in an oven equipped with an air circulating fan at 37°C for 24 h and stored in an airtight container before initiating dissolution studies.

Influence of % drug layering on drug release

The drug pellets containing 10 %, 20 % and 30 % of diltiazem were subsequently coated with NE40 dispersion to the same thickness with a theoretical weight gained of 5 % using similar coating procedures as mentioned above.

Dissolution studies

The in vitro dissolution of all the coated pellets was determined using the USP apparatus II (Sotax AT7, Switzerland). The test was performed in 900 ml distilled water as the dissolution medium with the temperature maintained at 37.0 ± 0.5 °C, while the stirring speed was set at 100 rpm. Samples of about 5ml volume each were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h with an automated fraction collector (SDX, Malaysia). At the end of 10 h, the pellets were crushed in the dissolution vessels to obtain homogeneous dispersion and stirring continued for another 15 min. Samples were then collected and then analyzed for drug content. This reading represented the total amount of drug dissolved and was used to determine the percentage of drug release at the different sampling intervals. Diltiazem HCL content sample was analyzed directly or after dilution with the dissolution medium at 237 nm using an UV spectrophotometer (Hitachi U2000, Tokyo, Japan). Triplicate readings of each type of coated pellets was used in the data analysis. Moreover, the release profiles of drug pellets (20 %) coated with 5 % NE40 dispersion were also determined at pH 1, 4 and 7 and at various stirring speed using water as dissolution media.

Scanning Electron Microscopy (SEM)

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

Results and Discussion

Influence of coating levels and % drug layering on drug release

Fig. 1 shows the drug release profiles of diltiazem pellets, which were coated at various coating levels with NE40 dispersion. The rate of drug release was controlled by the coat and could be varied in a predictable manner by varying the thickness of the coat. As the coat thickness was increased from 3 % to 7 % the rate of drug release was decreased accordingly being inversely proportional to the thickness of the polymer coat. The thicker the coat, the would be the diffusional pathlength during passage of the molecules across the coat and thus the drug release was delayed. Similar inverse relationship between thickness of polymer coat and the rate of drug release has been reported (Ghebre- Sellassie, 1987; Govender et al., 1997; Schultz and Kleinebudde, 1997).

Fig. 2 shows that percent drug layering had no remarkable effect on the release rate of the coated pellets. The release rates of these coated pellets were found to be almost similar and virtually independent of drug layering. These findings are in accord with those obtained by

Rekhi *et al.* (1995) in which drug release from Surelease coated beads were found independent of drug layering. An examination of the release profiles of the coated pellets containing 10-30 % diltiazem revealed that a major portion of the drug (70-75 %) was released in a relatively constant rate over 6 h reflecting typical zero order release kinetics. The non-linearity of the later part of the plots was due to a declining drug concentration left in the pellets and constant rate of drug release could no longer be maintained. The release rate constants, based on zero order kinetics calculated from the initial part of the plots are given in Table 1 with the corresponding values of R^2 . The values showed that release rates were closely similar, being independent of the % of drug layered. Moreover, the high R^2 values indicated that the % released was increased linearly over time for up to 75 % of the total drug.

Fig. 3 shows the drug release from coated diltiazem pellets in pH 1, 4 and pH 7. At the two lower pH, the release profiles were essentially similar. At pH 7, there was a slight decrease in the rate of drug release, especially during the initial part of dissolution study (1 to 6 h). These results indicate that the release of diltiazem HCL from the coated pellets was slightly affected by the pH of dissolution media. Polymeric coatings with pH independent permeability may give rise to pH-dependent drug release profile due to differences in solubility of the drug in various pH values. Compared to present study, drug release from pellets coated with Eudragit NE30D was reported to be highly dependent on the pH of the dissolution media due to pH-dependent solubility of the drug (Amighi *et al.*, 1998). Moreover, the coated pellets were also evaluated at different stirring speed in the dissolution media as shown in Fig.4 indicating the release profiles were almost superimposable and found to be independent of rate of agitation.

Table 1. Release rate constants and regression coefficients of 5% NE40-coated pellets

% Drug layering	Rate constant, K (%/h)	R^2	% Drug released for calculation of rate
10	12.58	0.9837	0-75
20	12.59	0.9902	0-75
30	11.88	0.9944	0-75

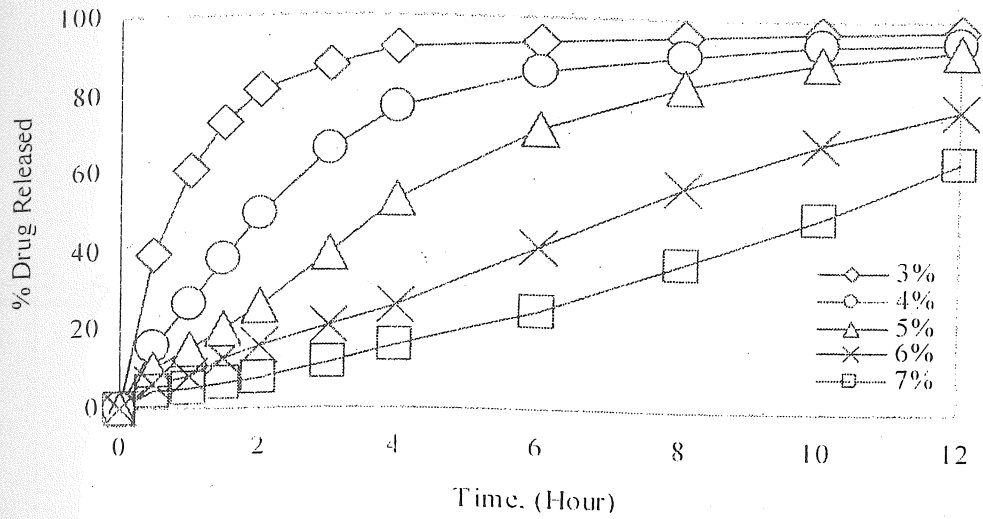


Fig. 1. Influence of various coating levels of NE40 on in vitro diltiazem HCl release from coated pellets

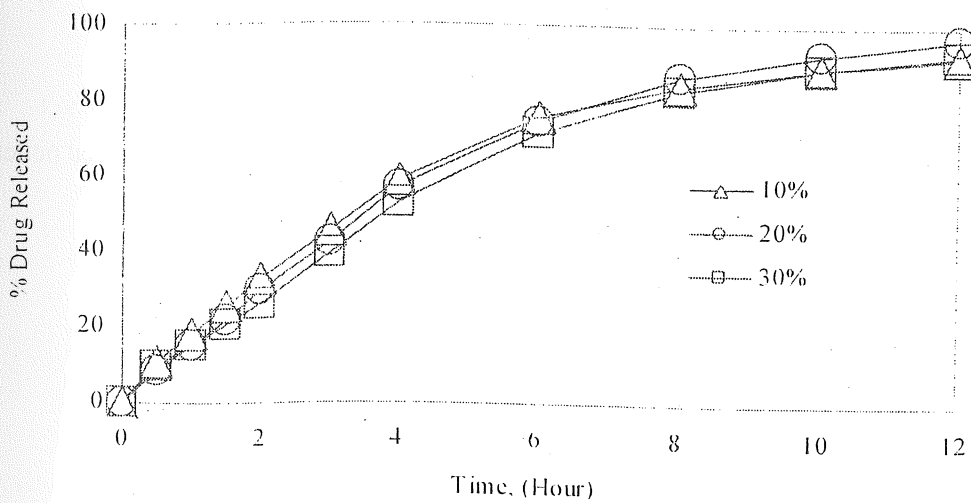


Fig. 2. Influence of % drug layering (10-30%) on in vitro diltiazem HCl release from 5% NE40-coated pellets

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20	12.59	0.9902	0-75
30	11.88	0.9944	0-75

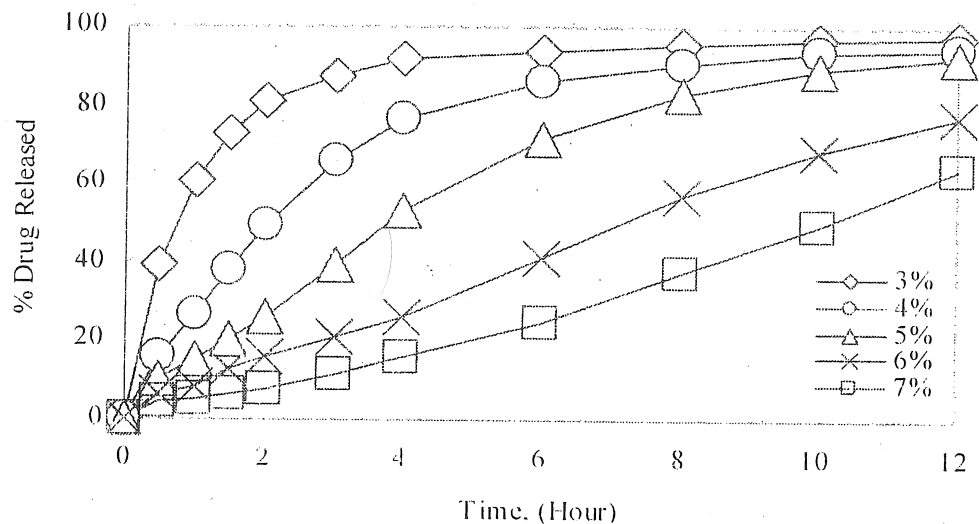


Fig. 1. Influence of various coating levels of NE40 on in vitro diltiazem HCl release from coated pellets

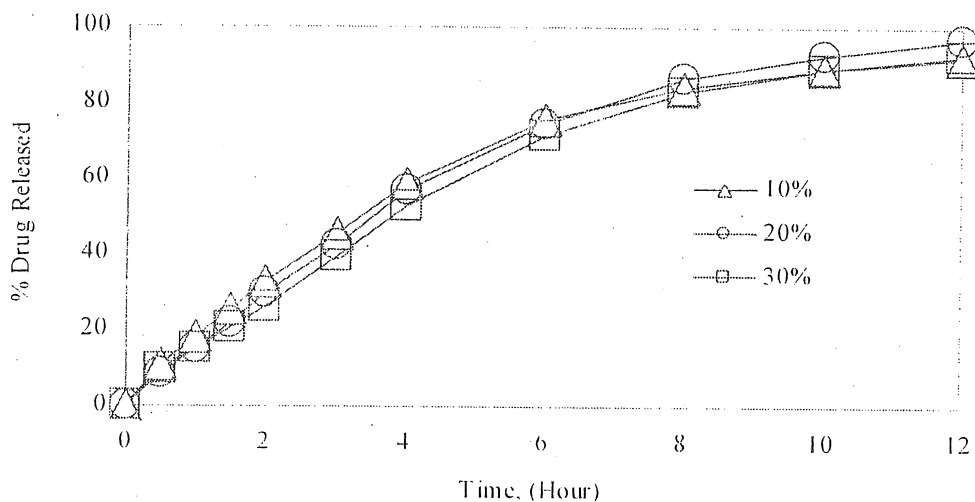


Fig. 2. Influence of % drug layering (10-30%) on in vitro diltiazem HCl release from 5% NE40-coated pellets

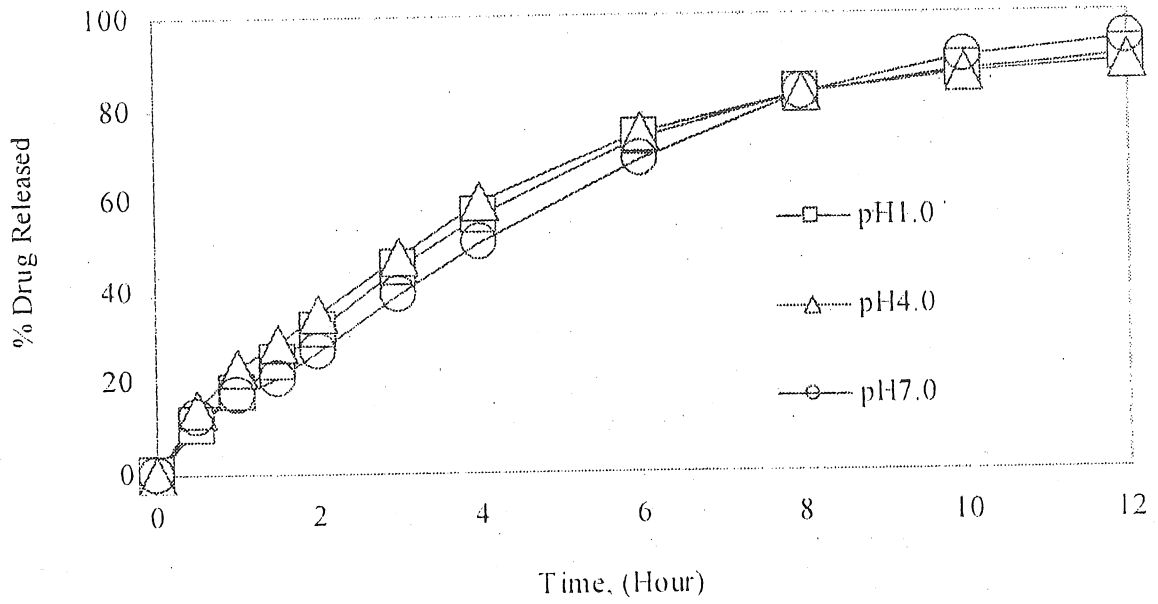


Fig. 3. Influence of pH on in vitro diltiazem HCl release from coated pellets

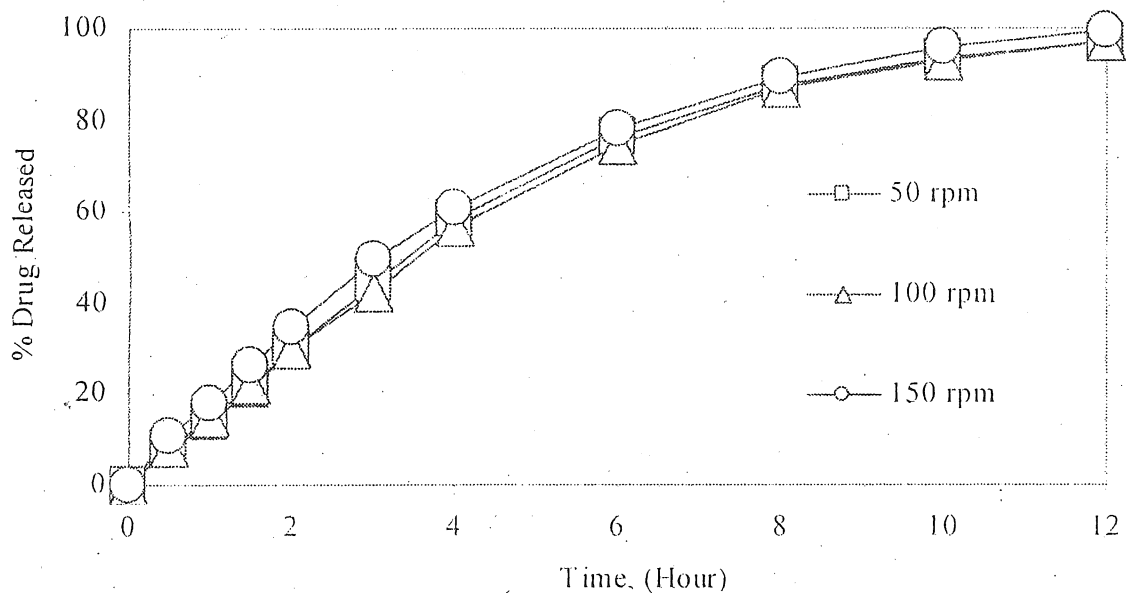


Fig. 4. Influence of stirring speeds on in vitro diltiazem HCl release from coated pellets

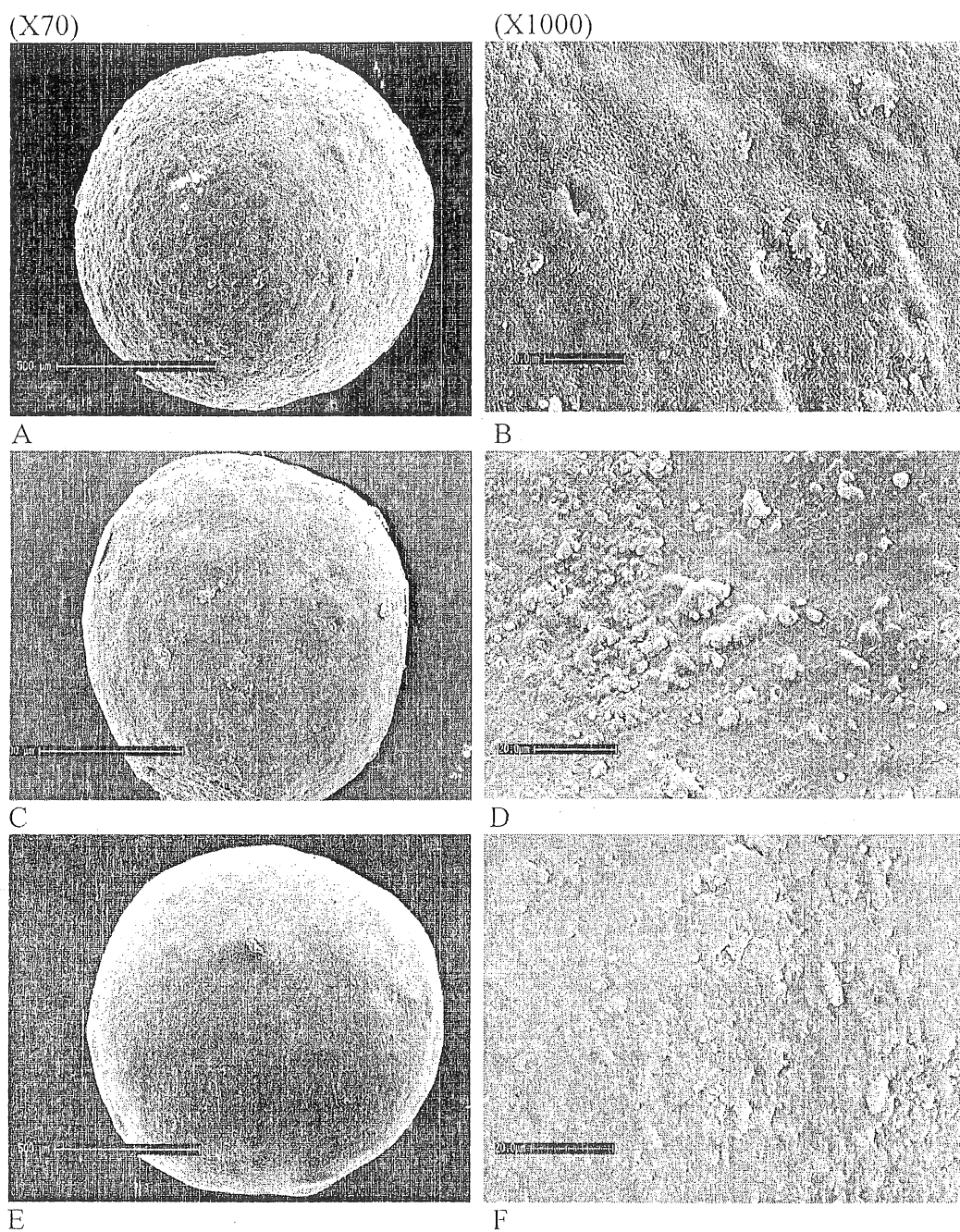


Fig. 5. Scanning electron photomicrographs of (A & B) drug pellets, (C & D) 3 % coated pellet and (E & F) 7% coated pellets

SEM evaluation of pellets

Drug pellets (20 %) and coated pellets were examined under scanning electron microscopy at both low (x70) and high (x1000) magnifications. The electron photomicrographs are shown in Fig. 5, both drug pellets and coated pellets at low magnification appeared to exist as spherical discrete units whilst the surface morphology of the drug pellets appeared to be visibly different from that of coated pellets at high magnification. The surface of drug pellets was continuous but granular compared to smooth and homogenous surface of coated pellets. The surface of pellets coated with NE40 at 7 % coating levels was more compact, continuous and uniform while pellets coated at 3 % at coating levels had a rough surface with uncoated patches (Fig. 5 B, D and F).

Conclusion

Controlled release pellets of diltiazem HCL were prepared by coating drug pellets with Eudragit NE40 dispersion using fluidized bed coater. The coated pellets were found to provide desirable controlled release rates during 12 h testing interval and the release rate could be varied in a predictable manner by varying the coat thickness. The manufacturing conditions used were reproducible between the batches of the coated pellets. Diltiazem HCL release was fairly independent of pH, stirring speed and percent drug layering.

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