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COMMUNICATION

Controlled-Release Behavior of Diphenhydramine Hydrochloride Loaded Neutral Microgranules and Coated Using Ethylcellulose Water Dispersion

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ABSTRACT

The development of a loading method of a water-soluble drug using aqueous binding solution to produce microgranules that were then coated with an aqueous ethylcellulose dispersion to sustain drug release is described. The results, in terms of drug used, showed that besides the fluidized bed parameters, the amount of drug dissolved in the binder solution plays an important role in obtaining a satisfying result during the spraying process. Thus, it seems necessary to determine the critical concentration above which the material started to adhere to the interior of the fluidization column, and the possibility of drug layering onto carrier material is aggravated. ANOVA of the time parameter for release of 63.2% of total drug (td) value showed significant influence of ethylcellulose (Aquacoat ECD-30) and dibutyl sebacate concentration on diphenhydramine hydrochloride (DPH) release. The dissolution rate decreased with an increase in polymer concentration. The diffusional exponent n *of the Peppas equation indicated that the DPH release kinetic was non-Fickian but approached Fickian diffusion, particularly at higher coating levels.*

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INTRODUCTION

Today, the use of coated microgranules is one of the numerous advances in formulation of sustained release drug. Coated microgranules allow decreased frequency of dosing and thus minimize the side effects of the drug and ensure good dispersion of the drug throughout the stomach, avoiding local irritation of the gastric mucosa. However, the coating procedure usually needs an organic polymer solution. The role and advantage of solvent use in the film-formation process have been reported (1–5). However, the organic solvents have many disadvantages, such as environmental pollution and toxicity caused by evaporation solvent and carcinogenicity. Coating method using aqueous colloidal polymeric dispersion or water-soluble polymers have been developed to eliminate these disadvantages, but they are still rarely used because of slow water evaporation. However, the use of neutral microgranules is the subject of many recent research articles (6,7).

The aim of this work was to study the release behavior of diphenhydramine hydrochloride (DPH) from a neutral microgranules used as a material carrier. The drug was layered to the surface of the microgranules using aqueous polyvinylpyrrolidone K30. Thus obtained, the microgranules were coated with ethylcellulose (EC, Aquacoat ECD-30, FMC Europe S.A., Brussels) films containing the lipophilic plasticizer dibutyl sebacate (DBS).

MATERIALS AND METHODS

Materials

The following materials were used as received: DPH (Cooper, Melun, France), polyvinylpyrrolidone K30 (ISP-Chimie/Aughedinger, Stuttgart, Germany), EC aqueous dispersion (Aquacoat ECD-30, FMC Europe S.A.), DBS (Prolabo, France), and neutral microgranules (710–810 μm, Seppic, France).

Methods

The loading solution was prepared by dissolving the drug in an adequate quantity of distilled water using a magnetic stirrer. Polyvinylpyrrolidone was then slowly dispersed into the solution and was stirred until completely dissolved. For coating dispersion, 400 g of Aquacoat ECD-30 was diluted in a beaker with 400 g of water using a magnetic stirrer. Different percentages of DBS (30, 35, and 40% w/w), calculated on the basis of dry powder of EC, were incorporated into a stirred dispersion. The layering conditions of DPH on neutral microgranules were as follows: fluidized bed coater (glatt GS3 Wurster method) fill charge, 500 g neutral microgranules, inlet air temperature 78–80°C, outlet air temperature 66–67°C, granule bed temperature 60–62°C, atomizing pressure 3 bars, rotating, spraying rate 9 ml/min, spray nozzle orifice 1, and drying time 5 min. The microgranules thus obtained were coated in the same granulator: fill charge, 500 g coated DPH microgranules, inlet air temperature 50–51°C, outlet air temperature 38–40°C, granule bed temperature 42–45°C, atomizing pressure 2 bars, rotating, spraying rate 6.5 ml/min, spray nozzle orifice 1, and drying time 5 min.

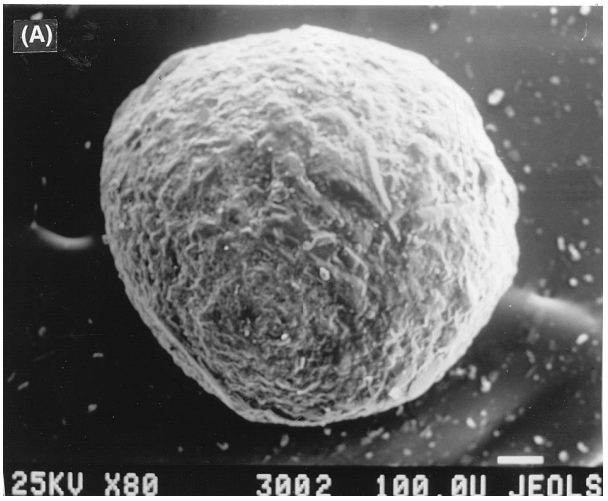
The dissolution test was carried out using USP XXX dissolution apparatus 1 (type Dissolutest, Prolabo). Six samples from each formulation were tested using 1000 ml of simulated gastric fluid (pH 1.2) at 37°C and with a stirring rate of 100 rpm. The drug release was determined by a spectrophotometer at 253-nm wavelength.

A Joele scanning electron microscope (JSM-35CF, Joele) was used to observe the surface morphology of the neutral microgranules with or without drug and coated microgranules before and after the end of dissolution.

Release data were expressed from *b* and *td* parameters to the equation developed by Weibull. It is an empirical equation proposed by Rosin et al. (8) and then by Weibull (9) and frequently abridged by RRSBW. It was modified and applied for the first time by Langerbucher (10) to describe the dissolution curves of pharmaceutical drug. Parameters of Weibull allow comparison between formulations and give a global approach of dissolution kinetic without specifying the release mechanism. Thus, in an attempt to describe the mechanism of drug release, the dissolution data were analyzed using equations introduced by Peppas (11).

RESULTS AND DISCUSSION

Preliminary attempts of loading the drug onto neutral microgranules demonstrated that outside fluidized bed parameters, the amount of drug dissolved in a binder solution plays an important role in obtaining a satisfying result during the spraying process. It was observed that 4% of drug dissolved in a binder solution (w/w) was the maximum concentration necessary to obtain acceptable spraying conditions. Above 4%, the drug concentration caused sticking and disturbance in the fluidization process. A probable cause of this disadvantage may be the higher viscosity of the resulting solution with an increasing amount of drug dissolved in the preparation. Higher viscosity probably causes an increasing strain on the pumping unit and increased difficulty in atomization of



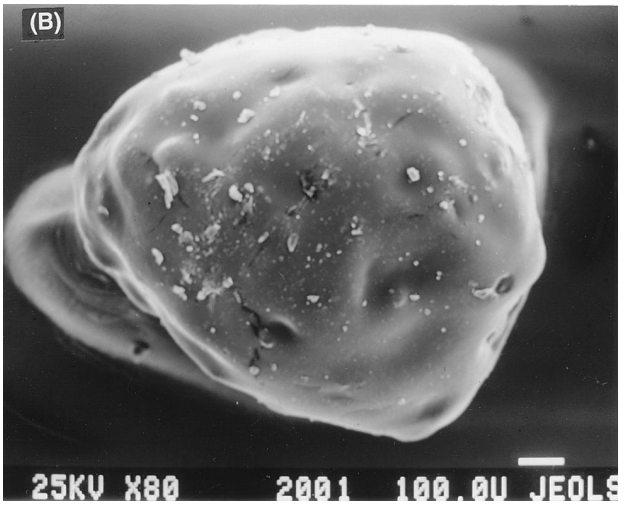
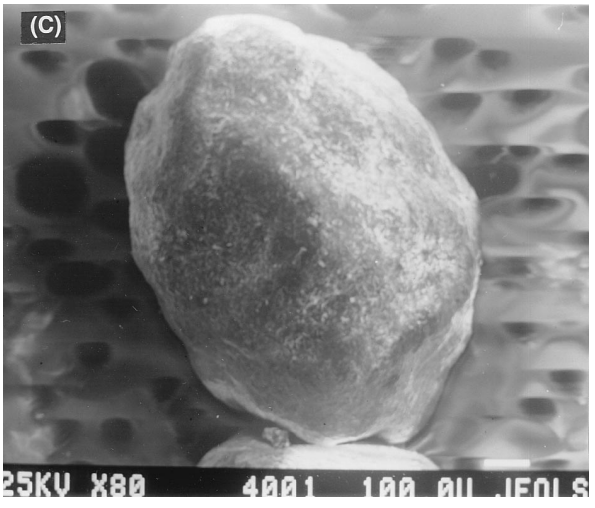
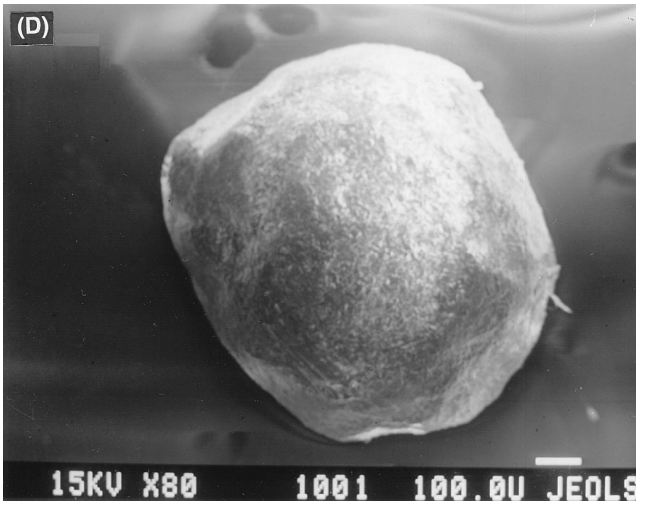


Figure 1. SEM photographs of neutral microgranules without (A) and with (B) drug.





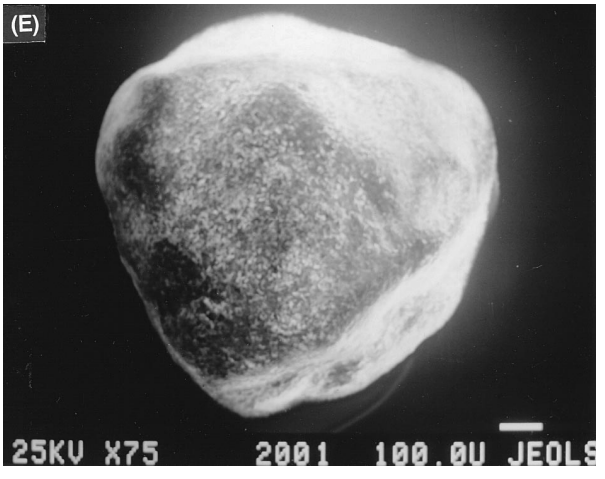


Figure 2. SEM photographs obtained from coated microgranules using (C) DBS 30% and EC 12%, (D) DBS 35% and EC 12%, and (E) DBS 40% and EC 12%.

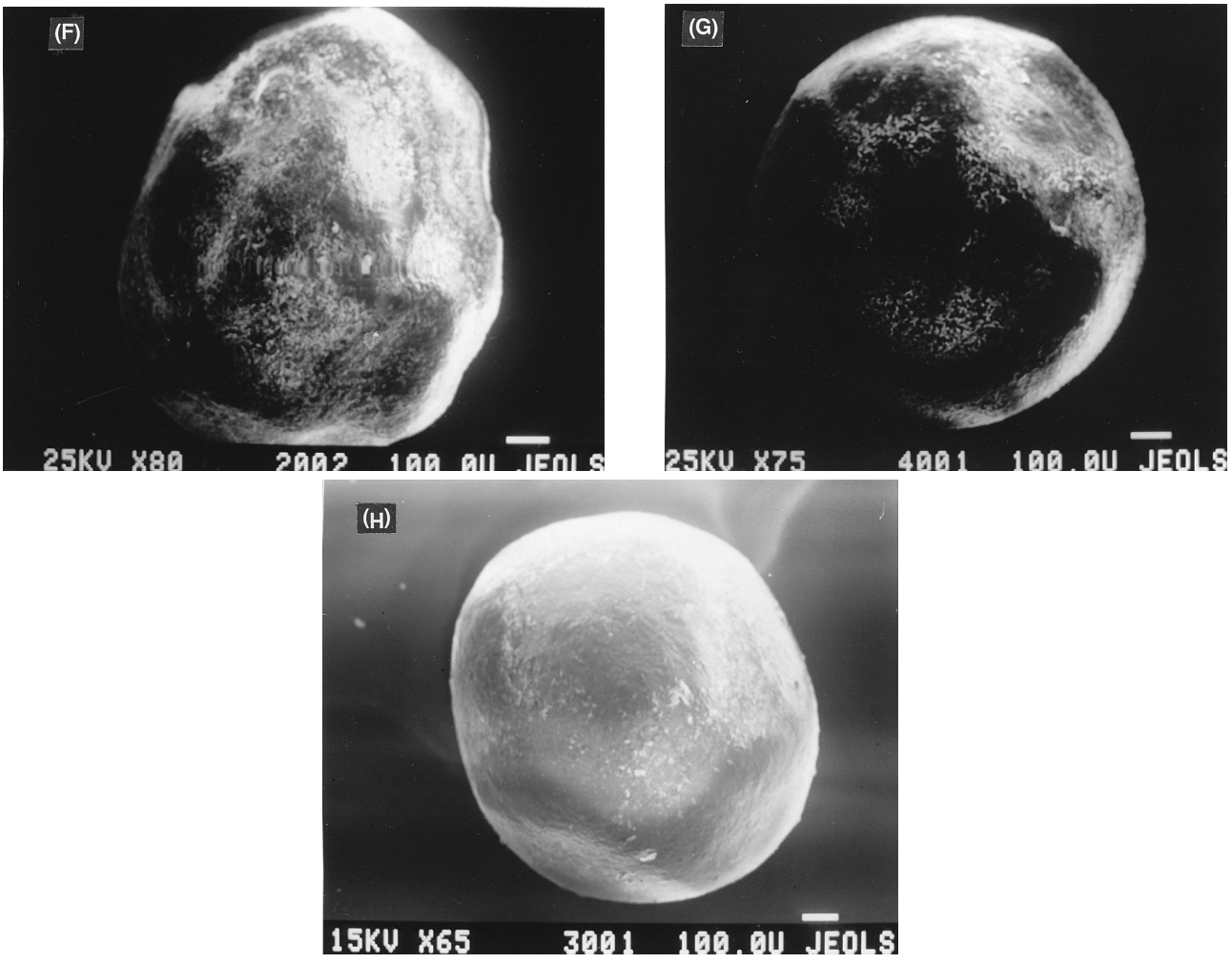


Figure 3. SEM photographs obtained from coated microgranules at end of drug dissolution using (F) DBS 30% and EC 12%, (G) DBS 35% and EC 12%, and (H) DBS 40% and EC 12%.

the spraying solution. These results confirmed earlier findings (12) that a water-soluble drug dissolved in a binder solution can affect and increase the viscosity of the resultant solution. It is necessary to determine the maximum concentration above which conditions of drug layering become impossible.

After optimization of the process, four batches were manufactured under identical spraying conditions to validate the method. Release profiles obtained were almost identical with complete drug release in 3 min and confirmed that the adapted process parameter gave good results with great reproducibility. These finding demonstrated that it is possible to reach, with the range tested, satisfactory results without using an organic solvent. However, despite the good results obtained, it was noted that at the end of the dissolution time, total drug release from all batches ranging from 88% to 92% was compared with the theoretical amount (100% of pure drug). This difference is difficult to explain because of the great number of different operating parameters used (13). This is probably due to the abrasive action of microgranules during the spraying process. After drug layering, the surface morphology of the microgranules without drug [Fig. 1(A)] and those containing the drug [Fig. 1(B)] were examined by a scanning electron microscopic (SEM). These results showed that the microgranule without drug had a rough surface, whereas those with drug had a smooth surface completely covered with drug, which confirms feasibility of the technique used.

On the other hand, the surface structure of some coated microgranules was examined by SEM photographs before and after the end of dissolution. Figure

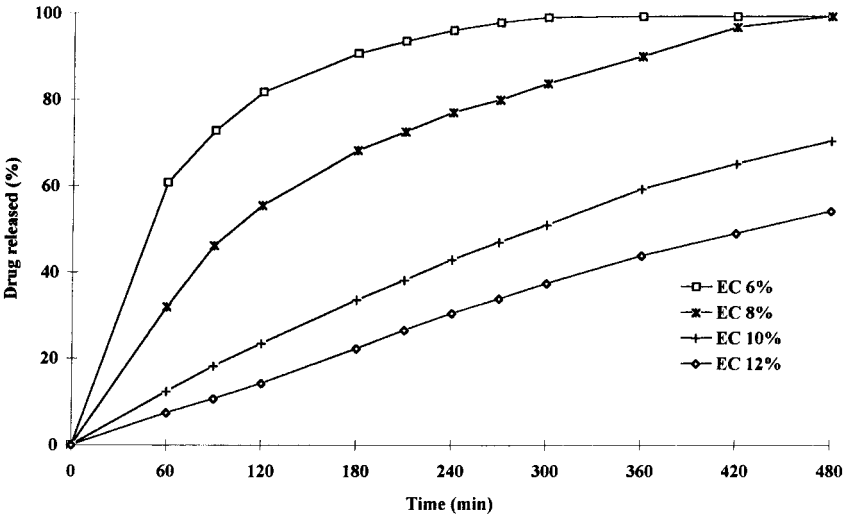


Figure 4. Dissolution profiles of DPH as a function of applied EC coating level containing 30% plasticizer.

2(C)–(E) showed coated microgranules before dissolution, whereas in Fig. 3(F)–(H), the same microgranule at the end of dissolution can be seen. The different external morphology observed between Figs. 1(B) and 2(C)–(E) indicates that surfaces of coated microgranules were completely coated with EC film. These results confirmed the benefit of optimization of the process. It was observed that coated microgranules retain their shape even at the end of drug dissolution [Fig. 3(F)–(H)]. This finding indicated no degradation of polymer film during complete release of drug. Polymer film protected the neutral microgranule which retained the shape. These results suggest that the drug release mechanism is followed by diffusion through the plasticized film. This observation is similar to that observed by Moroni and Ghebre-Selassie (14) on the release of DPH from tablets containing poly(oxyethylene) homopolymers. The authors concluded that this phenomena probably exists because DPH produces locally a high ionic concentration in the hydrated layer of tablets and delays polymer dissolution until most of the drug is depleted.

The release profiles are represented individually (Figs. 4–6) to simplify comparative study of the results. As expected, analysis of these curves showed that drug re-

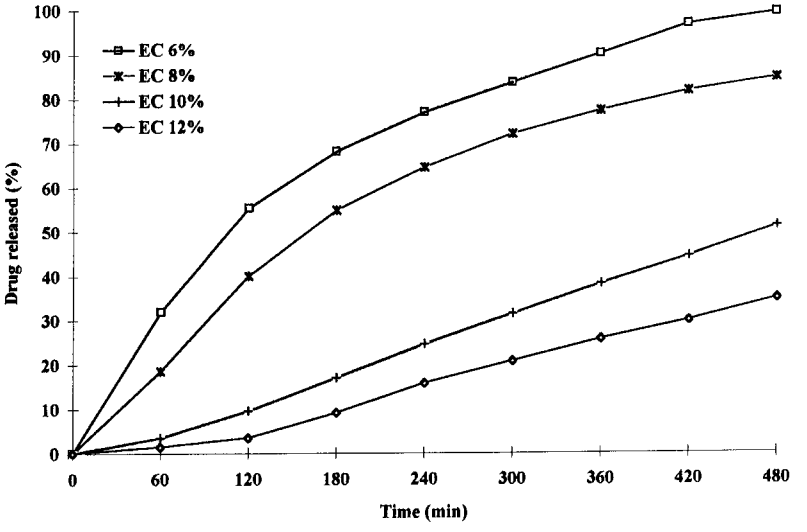


Figure 5. Dissolution profiles of DPH as a function of applied EC coating level containing 35% plasticizer.

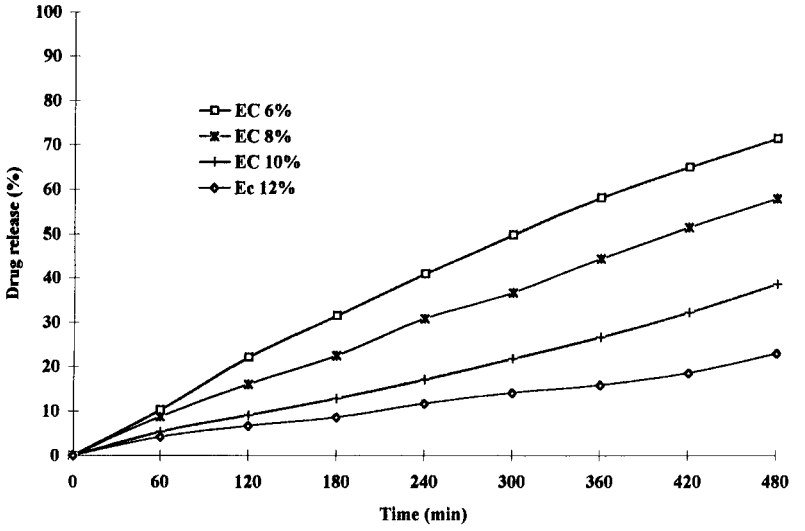


Figure 6. Dissolution profiles of DPH as a function of applied EC coating level containing 40% plasticizer.

leased and dissolution rate depends on coating level and DBS concentration. There is a direct correlation between coating level and DBS concentration on the drug dissolution rate. Dissolution rate gradually decreased as the amount of coating applied increased. Comparison of dissolution curves with an equal percentage of EC deposited showed that release rate of DPH was slower with an increase of plasticizer. However, three formulas showed different release behavior by changing EC and DBS concentrations. As can be seen in Fig. 6, the drug release can be described by zero-order kinetic for all coating levels, whereas Figs. 4 and 5 show that only at higher coating level (10–12%), the zero-order kinetic was achieved. The other coating level (6–8%) behaved differently.

All data were treated by using the Weibull equation. A good linear relationship of the dissolution profile was obtained between 10 and 80%. Linear correlation coefficients obtained for all formulation ranged from 0.98 to 0.99. Because no significant differences were observed between *b* values, *Td* values were used and compared by means of ANOVA to estimate statistically the effects of EC and DBS concentrations on drug release. Results of these analyses are given in Table 1. The high value of F experimental compared with F theoretical (Snedecor factor) showed significant influence of EC and DBS concentration on DPH release and confirmed mentioned observations that dissolution rate decreases with an increase of polymer and DBS concentration. Interaction observed between concentrations of polymer and DBS showed that the effect of coating level on release rate depends on DBS concentrations. When a smaller concentration of plasticizer was used, the reduction of release rate with increased EC concentrations was more influenced (Figs. 4–6).

To better understand the dissolution mechanism, we used Peppas equation in which the release exponent (*n*) characterizes diffusion mechanism. Linearity of the dissolution profile, between 10 and 70% for all formulation, was verified with correlation coefficients greater than 0.98. Table 2 presents diffusional exponents of *n* and

Table 1

F Values of ANOVA

Factors study	F Experimental	F Theoretical	$\alpha = 0.05$
Concentration DBS	1361	$F_{2}^{2}{}_{4} = 3.4$	
Concentration EC	2153	$F_{2}^{3}{}_{4} = 3.0$	
DBS × EC (Interaction)	36	$F_{2}^{6}{}_{4} = 2.5$	

Table 2

Value of Diffusional Exponent n, *Based on Equation* $M_t/M_\infty = k\ t_n$

DBS (%)	← 30 →				← 35 →				← 40 →			
EC %	6	8	10	12	6	8	10	12	6	8	10	12
(*n*)	0.70	0.77	1.04	0.91	0.84	0.96	1.01	0.83	0.92	0.94	0.97	0.95
R^2	0.98	0.98	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.98	0.99

their correlation coefficients, calculated by the least-square method. Except for a coating level of 10%, which corresponds to super case II diffusion transport mechanism, the *n* values for all formulation ranged from 0.70 to 0.97 (Table 2), which indicated that the DPH release kinetic was non-Fickian but approached Fickian diffusion, particularly at higher coating level.

CONCLUSION

Our investigation indicated that the amount of drug dissolved in a binder solution plays an important role in obtaining a satisfying result during the spraying process. It was observed that coated microgranules retain their shape even at the end of drug dissolution. This observation followed the trend that the spraying process depends not only on fluid bed parameters but also on the amount and solubility of drug used (15). ANOVA of *td* value showed significant influence of EC and DBS concentration on DPH release. It confirmed the earlier finding that dissolution rate decreased with an increase in polymer concentration. In addition, we noted that reduction of release rate with increased EC concentrations was more influenced when a smaller concentration of plasticizer was used. The diffusional exponent *n* of the Peppas equation indicated that DPH release kinetic is non-Fickian but approached Fickian diffusion, particularly at higher coating levels.

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