

Study of Crystallization of Endogenous Surfactant in Eudragit NE30D-Free Films and Its Influence on Drug-Release Properties of Controlled-Release Diphenhydramine HCl Pellets Coated with Eudragit NE30D

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ABSTRACT This study investigates the crystallization of the endogenous surfactant nonoxynol 100 in Eudragit NE30D-free films during storage and the influences of nonoxynol 100 on the dissolution of diphenhydramine hydrochloric acid (HCl) pellets coated with Eudragit NE30D before and after aging at ambient conditions. Polarizing light microscopy showed that when Eudragit NE30D-free films were stored at ambient conditions, off-white, flower-shaped crystals formed and increased in the polymer film as storage time increased. Also, x-ray diffraction showed polymer crystals in the aged free film. Thermogravimetric analysis showed no evidence of combined volatile molecules with the polymer molecules, and Fourier transformed infrared spectroscopy (FTIR) data suggested the same chemical composition of the polymer before and after phase separation. Further, from normal light microscopy, the appearance of the melting droplets in the polymer film indicated that the polymer molecules did not form the crystals. After the extraction of nonoxynol 100 by water, the free film formed by the water-extracted Eudragit NE30D was found free of the crystals after aging at the same conditions. The combination of the thermogravimetric analysis, FTIR, and microscopy showed that the origin of the crystals in dry Eudragit NE30D-free films came from nonoxynol 100, and not from the polymer molecules themselves. Monitoring by differential scanning calorimeter, it was found that the rates of crystallization of nonoxynol 100 were faster when the films were stored at 30 °C and 40 °C than when stored at ambient conditions and 45 °C. When stored at -5 °C, the crystallization rate was nearly zero. As the temperature got closer to melting temperature, the crystallization rate was very low because the system was in a thermodynamically disfavored state. The rate gradually increased and finally passed through a maximum as the crystallization temperature decreased. As the temperature kept decreasing, the crystallization rate became small again and eventually stopped because the system turned into a kinetically disfavored state. Because

the phase transition of nonoxynol 100 in Eudragit NE30D occurred at ambient conditions, its influence on the dissolution of diphenhydramine HCl pellets coated with Eudragit NE30D was studied. Three different levels of nonoxynol 100 were used in Eudragit NE30D dispersions to make 3 different batches of Eudragit NE30D film-coated, controlled-release diphenhydramine HCl pellets. The results showed the dissolution rate increased as the level of nonoxynol 100 increased in the coating formula. Compared to the commonly used water-soluble additive human peripheral mononuclear cell, nonoxynol 100 was more effective in enhancing the dissolution of diphenhydramine HCl from pellets coated with Eudragit NE30D. Further study showed that the phase separation of the surfactant during aging tends to stabilize or slightly increase dissolution rates at higher surfactant levels.

Key words: Eudragit NE30D, Endogenous Surfactant, Free Film, Diphenhydramine HCl Pellets

INTRODUCTION

Film coating has been widely used in controlled-release dosage forms. The long-term stability of these controlled-release dosage forms is one of the major concerns of pharmaceutical scientists (1-3).

Eudragit NE30D is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate. The chemical name of Eudragit NE 30 D is poly(ethylacrylate-methylmethacrylate)-dispersion 30%. The aging problem of Eudragit NE 30 D has been studied (4-6), and the decrease in dissolution resulting from aging has been found by Amighi and Moes (5). Eudragit NE30D polymer film is water insoluble, pH independent, water swellable, and water permeable. The water permeability of the polymer film is critical to drug dissolution profiles; it determines both the onset of drug release and the release rates of the drug products (7, 8). Besides ethyl acrylate and methyl

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methacrylate, the only component in the polymer latex dispersion is an endogenous surfactant: nonoxynol 100.

Nonoxynol 100 is a water-soluble, off-white solid with a melting point of 58°C to 59°C (9). The chemical name of nonoxynol is α -(4-nonylphenyl) ω -hydroxypoly-(oxy-1, 2-ethanediyl). The average number of ethylene oxide units (n) per molecule is indicated by the number that appears after nonoxynol. The manufacturer uses this surfactant to synthesize the polymer by emulsion polymerization (9), and it can be extracted from the polymer by water. In the manufacturer's information sheet, the amount of nonoxynol 100 is about 1.5% on the dry polymer basis. The surfactant has been observed to crystallize out from dry polymer films during storage. The influence of this surfactant's crystallization on drug release from matrices made with Eudragit NE30D has been studied by Gopferich and Lee (9), who have found that this surfactant and its crystallization have significant influence on drug release from matrices made by Eudragit NE30D (9). However, the potential influence of the surfactant on the drug release from controlled-release dosage forms film coated with Eudragit NE30D has not been investigated. Furthermore, a consistent reduction of the dissolution rates of the controlled-release dosage forms coated with Eudragit NE30D during their shelf lives have been observed (personal communication, Pfizer Global Research and Development, January 1999). Because Eudragit NE30D has been used in film coating for controlled release, it will be of great significance to reveal whether such reduction of drug release is caused by the phase separation of the surfactant.

To understand the effects of the endogenous surfactant on dissolution, studies were conducted to assess the impact of aging on the crystallization behavior of the surfactant in free film and the effect that surfactant crystallization that may have on drug release from the coated dosage forms. The study was carried out in 3 phases. First, the investigation sought information regarding the formation and rates of formation of the endogenous surfactant crystals on aging in Eudragit NE30D-free films under different storage conditions. The crystallization of the surfactant was studied by photomicroscopy, x-ray diffraction, thermogravimetric analysis(TGA), and Fourier transformed infrared spectroscopy(FTIR). Differential scanning

calorimeter(DSC) was used to measure the crystallization quantitatively. Second, the effect of the fresh surfactant on the dissolution rates of the controlled-release diphenhydramine hydrochloric acid (HCl) pellets coated with Eudragit NE30D was studied. Third, the influence of the surfactant on dissolution after aging was studied.

MATERIALS AND METHODS

Materials

Eudragit NE30D was supplied by Huls America Inc (Somerset, NJ). Nonoxynol 100 was supplied by Rhodia Inc (Cranbury, NJ). Diphenhydramine HCl was supplied by Parke-Davis Pharmaceutical Research (Holland, MI). Kaolin was supplied by Whittaker Clark & Daniels, Inc (South Plainfield, NJ). Sugar sphere pellets (16-18 mesh) were supplied by Paulaur Innovative Ingredient Specialists (Cranbury, NJ).

EXPERIMENTAL SECTION

Preparation and Storage of Free Films of Eudragit NE30D with 3 Levels of Nonoxynol 100

Two aqueous dispersions of Eudragit NE30D were prepared containing 5% and 10% nonoxynol 100 (calculated as percentage of the dry polymer). An original Eudragit NE30D dispersion and the above 2 dispersions (25 g) were poured into separate glass Petri dishes and dried at ambient conditions for 24 hours. After drying, the free films were lifted off the dishes and stored in ambient conditions for 2 days. Free film samples without additional nonoxynol 100 were stored at -5°C, ambient conditions, 30°C, 40°C, or 45°C, respectively, and 1 batch was cured at 60°C for 3 hours. The free film samples with 5% and 10% nonoxynol 100 were stored at ambient conditions for 2 months.

Preparation and Storage of Water-Extracted Eudragit NE30D-Free Films

Eudragit NE30D dispersion was freeze dried in a Virtis freeze dryer (Virtis, Gardiner, NY). The dried fine-polymer powder (15 g) was poured into a dissolution vessel with 900 mL of US Pharmacopeia (USP) water. The mixture was stirred with a dissolution paddle at 100 rpm for 24 hours in a 37°C water bath. The solid was filtered and soaked in fresh water for extraction for 7 repetitions. The above water-extracted solid was dissolved in acetone and poured into a glass Petri dish

and then dried under ambient conditions for 24 hours. The dried extracted film was stored under ambient conditions for 2 months.

Crystal Evaluation

Photomicroscopy

The film samples were examined at various time points using a Leitz Laborlux 12 Pol S optical microscope (Wild Leitz Ltd, Heerbrugg, Switzerland) fitted with a Sony Camera (Sony Corporation, Tokyo, Japan), a video printer (Sony Corporation, Tokyo, Japan). Crossed polarizers were used. Total magnification was X215.

Differential Scanning Calorimeter

A Perkin-Elmer DSC-7, Model DSC-7-719 (The Perkin-Elmer Corporation, Norwalk, CT) was used to examine the free film samples at various time points. Small pieces of free films (about 15 mg) were weighed and put into the sample pans with a hat configuration. The free films were heated from 25°C to 75°C with a heating rate of 5 °C/min and under the purge of nitrogen gas at 50 mL/min.

Thermogravimetric Analysis

A Perkin-Elmer TGA-7 (The Perkin-Elmer Corporation, Norwalk, CT) was used to determine whether volatile molecules combined with polymer molecules exist. That heating range was from 30°C to 200°C at 5°C/min. Nitrogen flow rate was 10 mL/min.

FTIR

A model 1725x FTIR spectrometer (The Perkin-Elmer Corporation, Norwalk, CT) was used to compare the chemical composition of the Eudragit NE30D films before and after aging.

X-ray Diffraction

A Rigaku Geigerflex x-ray diffractometer (PDE# 967-0402, Geigerflex, θ -2 θ goniometer, Copper K α arrange 15.42 nm, Rigaku USA, Danvers, MA) was used.

Preparation of Diphenhydramine HCl Layered Pellets

A batch of pellets (~ 400 g) was transferred into a fluidized-bed coating apparatus (Aeromatic Strea I, Aeromatic AG, Bubendorf, Switzerland) equipped for a bottom-spray coating in a Wurster column and coated with the solution of 171.3 g diphenhydramine HCl dissolved in 200 mL USP water. The inlet and outlet temperatures of the drying air were 58°C \pm 2°C and

Table 1. Coating Dispersion Formulations*

Number Coating Dispersions	
1	2% kaolin with Eudragit NE30D
2	2% kaolin and 5% nonoxynol 100 with Eudragit NE30D
3	2% kaolin and 10% nonoxynol 100 with Eudragit NE30D
4	2% kaolin and 4% HPMC with Eudragit NE30D
5	2% kaolin and 8% HPMC with Eudragit NE30D
6	2% kaolin and 12% HPMC with Eudragit NE30D

*All concentrations are expressed on the dry basis

48°C \pm 2°C, respectively. The drug solution was pumped at a flow rate of 1.5 mL/min for the first 20 minutes and 3 mL/min for the rest of the coating process under the pneumatic spraying pressure of 1 bar. The total spraying time was about 2 hours. Immediately after the diphenhydramine HCl solution was added and the layering completed, the drug-layered pellets were coated with 300 mL 5% water/water hydroxypropylmethyl cellulose (HPMC) solution. The inlet and outlet temperatures of the drying air and the pneumatic spraying pressure were used as above. The solution was sprayed at the flow rate of 2 mL/min. The total spraying time was about 2.5 hours. The diphenhydramine HCl-layered and HPMC-subcoated pellets were then dried in the same apparatus for 10 minutes at the above temperature. The drug content percentage of diphenhydramine HCl-layered and HPMC-subcoated pellets was determined by the drug content of 1 g of these pellets from an ultimate dissolution test.

Preparation of Coating Dispersions

Six coating dispersions containing 2% kaolin were prepared. Three levels of nonoxynol 100 and 3 levels of HPMC were compared. See Table 1. Kaolin was dispersed in water to mix with the required amount of acrylic aqueous dispersion. Different amounts of nonoxynol 100 or HPMC were dissolved in water to mix with the above dispersion and stirred for 30 minutes before being used in the coating process. Original Eudragit NE30D was compared to the original product with 5% and 10% additional nonoxynol 100.

Preparation of Coated Pellets

The above diphenhydramine HCl-layered and 3% HPMC-subcoated pellets (180 g) were transferred to the fluidized-bed coating apparatus, Aeromatic Strea I, configured for bottom-spray coating process in a Wurster column. The pellets were coated with Eudragit NE30D formulation until the desired film weight was deposited. The aqueous dispersion was continuously stirred to prevent sedimentation of insoluble particles.

The inlet and outlet temperatures of the drying air were $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ and $20^{\circ}\text{C} \pm 2^{\circ}\text{C}$, respectively. The coating dispersion was pumped at a flow rate of 1.5 mL/min at first 20 minutes and 3 mL/min for the rest of the time under the pneumatic spraying pressure of 1 bar. The total spraying time was about 50 minutes. Immediately after finishing the coating with Eudragit NE30D, 5% water/water HPMC solution was applied in the same apparatus with the same inlet, outlet temperatures, and pneumatic spraying pressure to achieve 2.5% water/water subcoat on the total pellets weight with a flow rate of 2 mL/min. A total spraying time of 35 minutes gave a 2.5% level HPMC overcoat. The coating levels of the coated pellets were determined by comparing drug-released pellets from the same weight of coated pellets and uncoated (only drug-layered and-subcoated) pellets in an ultimate dissolution test.

Dissolution Test of Diphenhydramine Tablets

The USP paddle method was chosen in this dissolution test. Dissolution medium was USP water and the volume was 900 mL. The dissolution medium was kept at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and the paddle speed was kept at 50 ± 2 rpm. Analytical wavelength was chosen at 258 nm; cell length was 1.00 cm. Six replicates were conducted for every dissolution test. Here relative standard deviation of any dissolution test after 6 hours is less than 2%; therefore, only the average of dissolution results will be reported in this article.

RESULTS AND DISCUSSION

Figure 1A, 1B, 1C, and 1D show the photographs taken by a polarizing light microscope for a fresh free film, a free film stored at room temperature for 20 days, a free film stored at room temperature for 8 months, and a water-extracted free film of Eudragit NE30D stored at room temperature for 2 months, respectively. It is interesting to note that the fresh free film of Eudragit NE30D presented in 1A does not contain any crystalline material; however, in 1B, with the increased storage time for 20 days at a room temperature, some single, flower-shaped crystals appeared. In 1C, when the storage time increased to 8 months, much more crystalline material appeared in the free film. Thus, it appeared that the observed crystallization in Eudragit NE30D-free film is a time-dependent process.

Eudragit NE30D is a polymer dispersion of ethyl acrylate and methyl methacrylate with the ratio 2:1. Besides ethyl acrylate and methyl methacrylate, the

only other component of the dispersion is nonoxynol 100. Therefore, the cause of the formation of the crystals might be either the result of the polymer molecules or the endogenous surfactant, nonoxynol 100. Nevertheless, the impurities introduced by potential contamination during preparation or storage might also cause such phase out and such possibility should also be examined.

Interestingly, Figure 1D, which was taken for the free film of extracted Eudragit NE30D stored at room temperature for 2 months, did not show any crystals that were observed in the aged free film. This observation provides strong evidence that the crystallization was formed by the endogenous surfactant of Eudragit NE30D dispersion, not from the polymer molecules themselves.

Another group of photomicroscopy analysis was conducted to characterize the melting properties of the crystals and the results are listed in Figure 2. Figure 2A shows a free film of Eudragit NE30D stored at room temperature for 20 days after curing at 45°C for 3 hours. Figure 2B shows the same free film heated in 52°C oven for 2 minutes; 2C shows the same free film heated in 52°C oven for 4 minutes. Both pictures 2A and 2B were taken under polarizing light microscope, whereas picture 2C was taken under nonpolarizing-light microscope. Comparing these 3 pictures, the melting point of the crystals appeared to be at about 52°C . In 2B, the crystals were in the midpoint of the melting process. After melting, droplets with a clear edge were seen when the picture was taken under a nonpolarizing light microscope. These droplets with a sharp edge indicate that the crystals that appeared in the free film of Eudragit NE30D were not the result of the partial crystallization of polymer molecules in Eudragit NE30D. If crystalline material was crystalline phase of polymer, the melting process should be the phase transition of the polymer between the crystalline phase and amorphous phase. Consequently, the crystalline phase of the polymer will fade away into the background, the amorphous phase of the polymer, and the sharp-edged droplets should not exist. Based on such evidence, the possibility of the partial crystallization of the polymer molecules in free film has been ruled out.

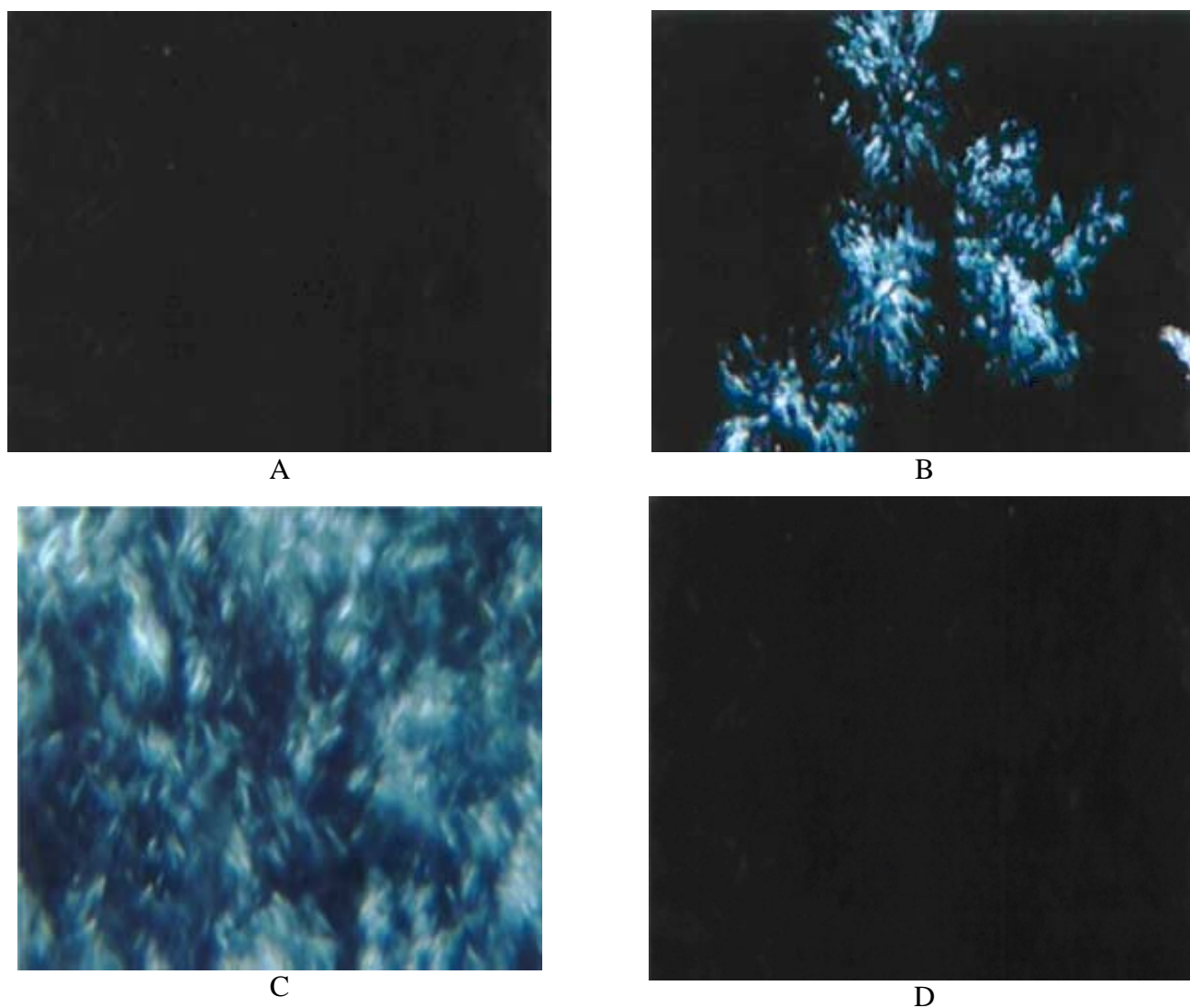


Figure 1. Polarizing light microscope analysis of fresh Eudragit NE30D free film.*

A, Fresh Eudragit NE30D free film sample. B, Eudragit NE30D, 45°C, 3 hours curing, stored at room temperature for 20 days. C, Eudragit NE30D 60°C, 3 hours curing, stored at room temperature for 8 months. D, Extracted Eudragit NE30free film stored at room temperature for 2 months.

***All images used polarizing light, X215 magnification, x 5 V.**



A



B



C

Figure 2. Polarizing-light microscope analysis of fresh Eudragit NE30D free films.*

A, Eudragit NE30D, 45°C, 3 hours curing, stored at room temperature for 20 days. B, Eudragit NE30D, 45°C, 3 hours curing, stored at room temperature for 20 days, then heated in 52 °C oven for 2 minutes; the picture was taken immediately. C, Eudragit NE30D, 45°C, 3 hours curing, stored at room temperature for 20 days, then heated in 52°C oven for 4 minutes; the picture was taken immediately.

*Both A and B used polarizing light, X215 magnification, x 5 V. C was taken with nonpolarizing light, X215 magnification, x 5 V.



A



B

Figure 3. Polarizing-light microscope analysis of Fresh Eudragit NE30D free films.*

A, Eudragit NE30D 60°C, 3 hours cured, stored at room temperature for 8 months. B, Eudragit NE30D 60°C, 3 hours curing, stored at room temperature for 8 months, 60°C oven for 30 minutes.

*Both used polarizing light, X215 magnification, x 5 V

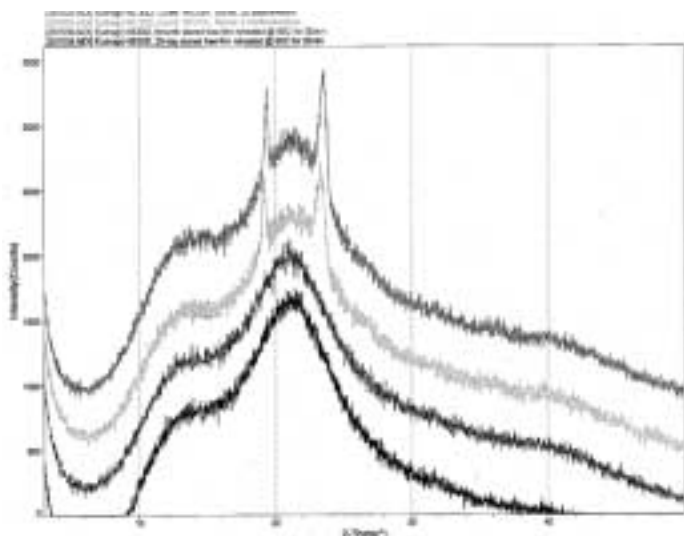


Figure 4. X-ray diffraction of Eudragit NE30D free films. Curve 1, 45°C, 3 hours curing, 20 days at a room temperature. Curve 2, 60°C, 1 hour curing, 8 months at room temperature. Curve 3, 60°C, 1 hour curing, 8 months at room temperature, 60°C reheated for 30 minutes. Curve 4, 45°C, 3 hours curing, 20 days at room temperature, 60°C reheated for 30 minutes.

We also compared Figure 3A-a 60°C, 3 hours-cured film of Eudragit NE30D stored at room temperature for 8 months-with Figure 3B, the same film as in Figure 3A but put into 60°C oven for 30 minutes. Figure 3B was taken immediately. After 8 months of storage, crystalline material was all over the polymer film. Similar to the melting process observed in Figure 2, all crystalline material disappeared in the film after being put into a 60°C oven for 30 minutes.

The x-ray analysis of the above free film samples was performed to verify that the white cloud observed is indeed a crystal and the results are displayed in Figure 4. From top to bottom, the first curve represents Eudragit NE30D-free film, 45°C, 3 hours cured, stored at room temperature for 20 days; the second curve represents Eudragit NE30D free film, 60°C, 3 hours cured, stored at room temperature for 8 months. Both curves show the existence of the crystalline material because of the sharp peaks in the curve and the results are consistent with those in polarizing-light photo microscopy analysis. The third curve and fourth curve represent the x-ray diffraction tests of the same samples in curve 1 and curve 2, respectively, but both samples have been reheated at 60°C for 30 minutes. After being reheated, both aged samples lost their crystalline materials, which is also consistent with the results in our photomicroscopy analysis.

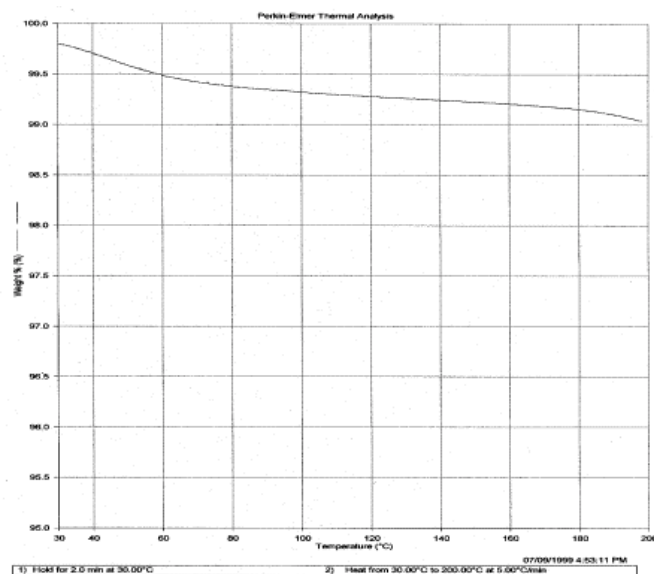


Figure 5. Thermogravimetric analysis profile of Eudragit NE30D free film cured at 45°C for 3 hours and stored at room temperature for 8 months

Table 2. Summary of weight loss of uncured, cured, and aged films in the temperature range from 25°C to 120°C based on thermogravimetric analysis data, n = 3.

	Fresh free film weight change (%)	Fresh free film curing at 60°C, 3 hours weight change (%)	Free film 4 months at ambient conditions weight change (%)
Sample 1	0.435	0.461	0.619
Sample 2	0.599	0.358	0.509
Sample 3	0.533	0.348	0.46
Average	0.522	0.389	0.529
Standard Deviation	0.0825	0.0626	0.0814

In Figure 5, the TGA profile of Eudragit NE30D-free film, cured at 45°C for 3 hours and stored at room temperature for 8 months, showed no evidence of volatile molecules, such as water molecules or ethanol, combined with polymer molecules. Based on TGA data, Table 2 summarized the percentages of weight loss of fresh films, fresh films after curing at 60°C for 3 hours and 4-month-old films at ambient conditions. This weight loss is mainly the result of moisture loss. By comparison, there is no moisture gain for the film stored at ambient conditions for 4 months compared to the fresh film. Therefore, the moisture did not play a role here.

FTIR analysis was also conducted on the fresh and aged free film to study the effects of crystallization on the chemical compositions of Eudragit NE30D. Figure 6, which is the FTIR curve of Eudragit NE30D cured at 60°C for 3 hours and stored at room temperature for 8 months, showed very similar absorption curve to Figure 7, which is the FTIR curve of Eudragit NE30D newly dried film at a room temperature. Particularly, both curves have the same characteristic bands of the C = O ester vibration at 1730 cm^{-1} , ester vibrations at 1158 cm^{-1} to 1160 cm^{-1} , and 1236 cm^{-1} as well as CH_x vibrations at 1382, 1448, and 2982 cm^{-1} . These results indicate that the Eudragit NE30D-free film has the same chemical composition before and after aging. These also suggest that it is very unlikely that the crystallization is caused by impurities from contamination. Because the crystals are not likely to be formed by polymer molecules and impurities, it is reasonable for us to believe that the crystalline materials must be formed by the endogenous surfactant, nonoxynol 100.

From Figure 8 and Table 3, it is important to note that the endothermic peak increases with prolonged storage time in DSC curve of free films stored at a room temperature. The fresh free film did not exhibit an endothermic peak in DSC curve. The endothermic peak appeared after 2-week storage at room temperature and kept increasing in an 8-week period. After 8 months' storage, the delta H is 6.0 J/g compared to 4.8 J/g of the 8-week sample. Such data suggest that most of the crystallization happened within the first 8 weeks.

DSC analysis in Figure 9 shows that 2-month-old free films of Eudragit NE30D with 5% and 10% extra nonoxynol 100 exhibit the endothermic peaks occurring around the same place as the endothermic peak of 2-month old Eudragit NE30D-free film without additional nonoxynol 100. In addition, the delta H of the peak increases as the level of nonoxynol 100 increases showed in Figure 9 and Table 4. This information reconfirms that the crystals are formed by nonoxynol 100.

The DSC curve of pure nonoxynol 100 in our analysis has delta H equal to 168 J/g and the endothermic peak appeared at 58°C, matching the literature melting range of 58°C to 59°C. Based on

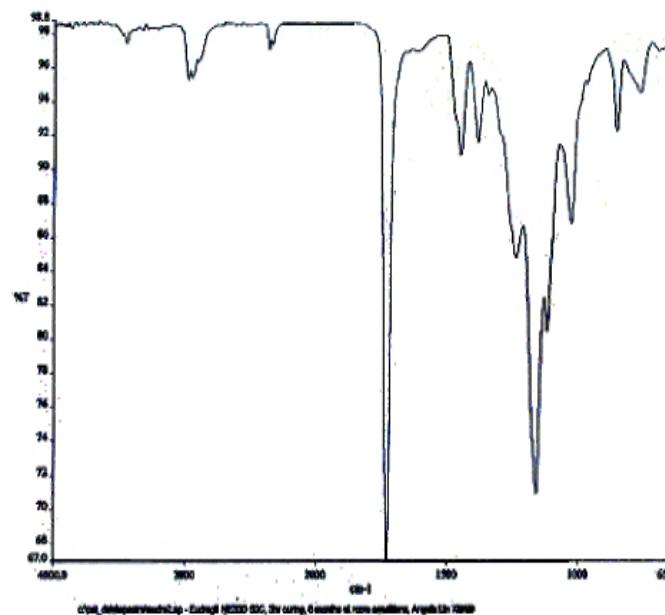


Figure 6. Eudragit NE30D film cured at 60°C for 3 hours and stored at room temperature for 8 months.

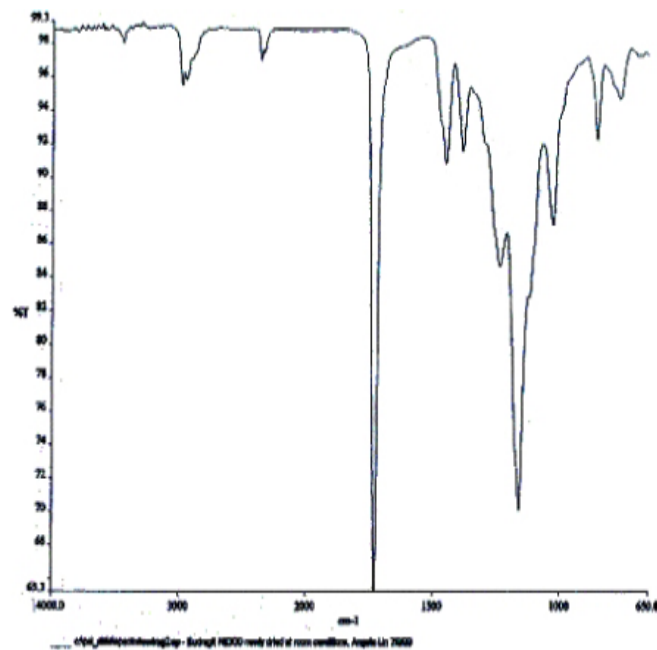


Figure 7. Newly dried film at room temperature

the delta H of pure nonoxynol 100 and aged Eudragit NE30D film measured by DSC, a 3.6% of nonoxynol 100 was calculated to exist in the commercially available Eudragit NE30D dispersion.

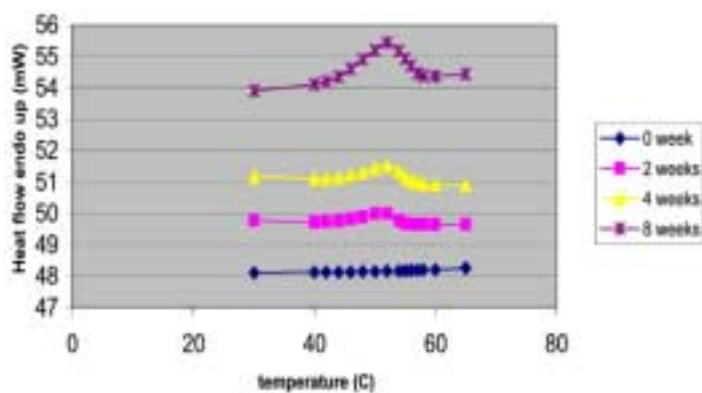


Figure 8. Differential scanning calorimeter profiles of Eudragit NE30D free films after storage at room temperature, n=5

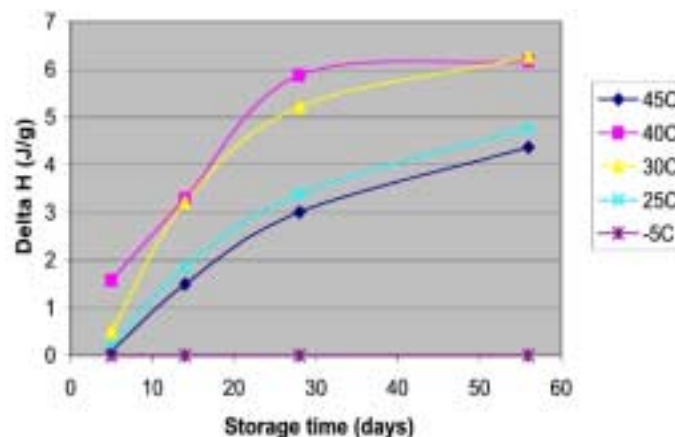


Figure 10. The crystallization rates of the endogenous surfactant in Eudragit NE30D free films under different storage temperatures, n = 5.

The existence of 1.5% of nonoxynol 100 is listed in the manufacturer's information sheet. Such discrepancy may be allowable because calculation based on delta H is only qualitative. Shown in Figure 9 and Table 4, about 2.9%, 7.6%, and 12.2% nonoxynol 100 crystallized out from the free films of original Eudragit NE30D, 5% addition, and 10% addition of nonoxynol 100 in the Eudragit NE30D after 8 weeks. The total calculated amounts of nonoxynol 100 are 3.6%, 8.6% (5.0% + 3.6%), and 13.6% (10.0% + 3.6%) in these 3 free films, respectively.

The crystallization rates of nonoxynol 100 from the free film under different storage temperatures are derived in Figure 10. The films stored at 30°C and 40°C have the fastest crystallization rates, whereas the film stored under 25°C and 45°C have much slower crystallization rates. Notably, the crystallization rate was close to zero when stored at -5°C.

In Figure 11, a film of Eudragit NE30D cured at 45°C for 3 hours followed by storage at -5°C freezer for 20 days displayed far fewer crystals than other films, which indicates that the polymer crystallization could be fully impeded when storage temperature is maintained low enough

Based on the above studies, it is obvious that the crystallization rate is highly dependent on temperature. We hypothesized that as the temperature increases from -5°C toward the melting point of this surfactant, the crystallization rate increases and eventually passes through the maximum point. As the temperature continues to increase, the crystallization rate would

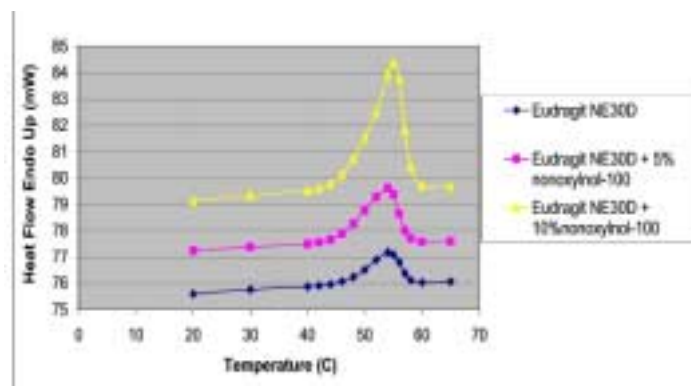


Figure 9. DSC profiles of Eudragit NE30D free films stored at room temperature for 2 months, n = 3

Table 3. The Increase of the Endothermic Peaks of Eudragit NE30D Stored at Ambient Conditions, n = 5

Storage time (weeks)	Delta H (J/g)	Peak (°C)
0	0 (RSD = 0%, n = 5)	0 (RSD = 0%, n = 5)
2	1.9 (RSD = 10.5%, n = 5)	51.8 (RSD = 1.5%, n = 5)
4	3.4 (RSD = 8.3%, n = 5)	51.5 (RSD = 0.9%, n = 5)
8	4.8 (RSD = 2.3%, n = 5)	53.0 (RSD = 0.7%, n = 5)
32	6.0 (RSD = 7.1%, n = 2)	51.9 (RSD = 1.0%, n = 2)

RSD indicates relative standard deviation

Table 4. The Increase of the Endothermic Peaks with Extra Surfactant, n = 3

	Delta H (J/g)	Peak (°C)
Eudragit NE30D free film	4.8 (RSD = 1.9%, n = 3)	53.2 (RSD = 0.1%, n = 3)
Eudragit NE30D + 5% nonoxynol-100	12.8 (RSD = 1.0%, n = 3)	53.9 (RSD = 1.2%, n = 3)
Eudragit NE30D + 10% nonoxynol-100	20.5 (RSD = 0.4%, n = 3)	54.6 (RSD = 0.8%, n = 3)

RSD indicates relative standard deviation.

decrease and become low again. At temperatures much lower than the melting temperature, the molecules have a large driving force to settle down to form crystals and therefore in a thermodynamic favor state. However, the low temperatures make the molecules have low kinetic energy to reach each other to form crystals and therefore in a kinetic disfavor state in the same time. The constitution and properties of crystallization that are achieved are the results of the competition between the kinetic factors involved in the transformation and the requirements of thermodynamic equilibrium. This generalization is not unique to this system but applies for a vast majority of substances that undergo state transformation.

After studying the dissolution profile for Eudragit NE30D-coated diphenhydramine HCl pellets with nonoxynol 100 or HPMC addition, it appeared that nonoxynol 100 is a dissolution enhancer. As shown in Figure 12, at the 6-hour time point, dissolution was 14% and 23% higher, respectively, for the coating formulas having 5% and 10% extra nonoxynol 100 compared to the commercial coating composition. In Figure 13, however, the dissolution rates were 6%, 17%, and 20% higher, respectively, for the coating formula having 4%, 8%, and 12% HPMC (dry basis). Nonoxynol 100 thus appears to be an even better water-soluble additive than HPMC. With the help of a small portion of nonoxynol 100 in the commercially available Eudragit NE30D, the dissolution rate of diphenhydramine HCl pellets coated with the commercially available Eudragit NE30D should be higher than diphenhydramine HCl pellets coated with the extracted Eudragit NE30D (without or very small amount of nonoxynol 100).



Figure 11. Polarizing-light microscope analysis of cured Eudragit NE30D free film.*

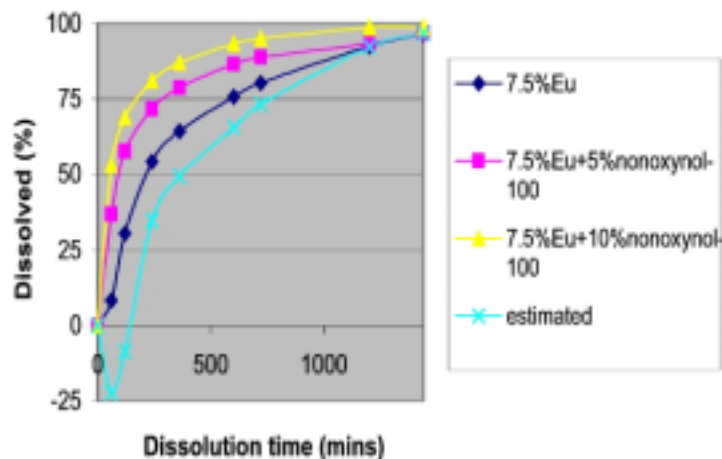


Figure 12. The effect of fresh nonoxynol 100 on dissolution rates of controlled release diphenhydramine hydrochloric acid pellets, n = 6.*
*Eu indicates original Eudragit NE30D. and fresh and

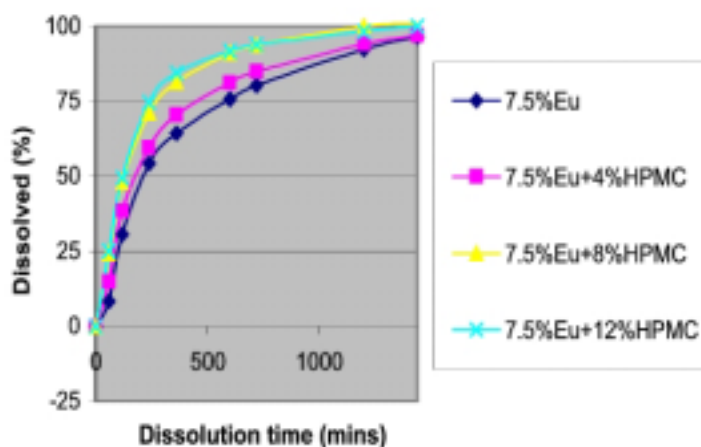


Figure 13. The effect of HPMC on dissolution rates of controlled release diphenhydramine HCl pellets, n = 6.* (*Eu indicates original Eudragit NE30D.)

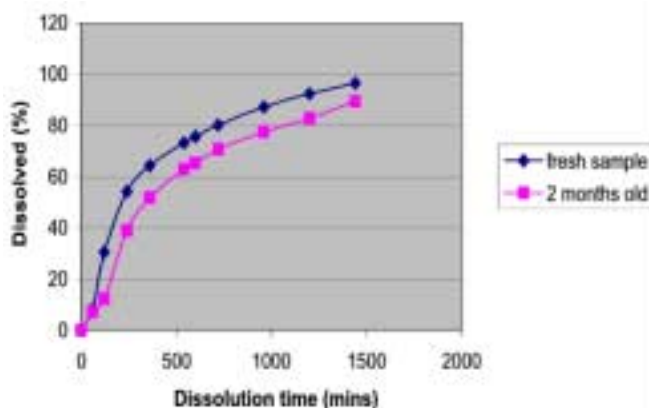


Figure 14. The effect of aging on controlled release diphenhydramine HCl pellets coated with 7.5% Eudragit NE30D, n = 6.

The dissolution profiles of the fresh and 2-month-old diphenhydramine HCl pellets coated with 7.5% Eudragit NE30D, fresh and 2-month old diphenhydramine HCl pellets coated with 7.5% Eudragit NE30D with 5% additional nonoxynol 100, 2-month old diphenhydramine HCl pellets coated with 7.5% Eudragit NE30D with 10% additional nonoxynol 100 are shown in Figures 14, 15, and 16, respectively. After 2 months' storage at room temperature, there was about a 10% decrease of dissolution with the plain Eudragit NE30D, 5% decrease with 5% additional nonoxynol 100, and a slight increase of dissolution with 10% additional nonoxynol 100. In the coating process, the inlet and outlet temperatures were 25°C and 20°C, respectively. Because of the low glass transition temperature (T_g) of this polymer, any higher temperature cannot be used. However, this is not very much above the film formation temperature. Storage at room temperature for 2 months can assist the film further gradual coalescence. This is why the dissolution results decreased in Figures 14 and 15. On the contrary, nonoxynol 100 is water soluble and a dissolution enhancer and it would gradually crystallize out in the polymer phase during storage at room temperature and the crystallization helped dissolution rates increase. From a comparison of Figures 14, 15, and 16, at higher levels of surfactant, the phase separation of the surfactant during aging tends to stabilize or slightly increase the dissolution rates. An explanation for such phenomena might be that when the polymer swells in water, there are numerous small holes that will be formed in the coating film. If the surfactant is fresh and in its amorphous state, it will make the film more easily wetted and quicker to swell. However, if the surfactant has already formed crystals in the polymer film, they aggregate to form larger masses. When the polymer swells, these larger masses will dissolve and form larger holes in the polymer films compared to the small holes made just by swelling; therefore, these larger holes in the polymer film will make the dissolution rates faster. There are two factors in this phenomenon and they play contrary roles. One is the film further gradual coalescence, which decreases the dissolution rates and the other is the crystallization of surfactant in the films, which increases the dissolution rates. In Figure 16, further gradual

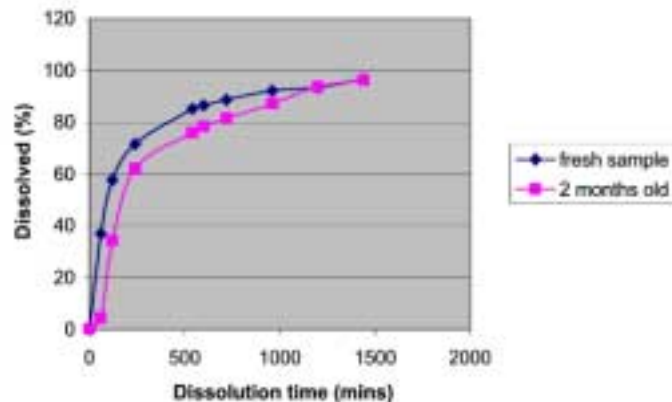


Figure 15. The effect of aging on controlled release diphenhydramine HCl pellets coated with 7.5% Eudragit NE30D + 5% nonoxynol 100 on the dry coating film basis, $n = 6$.

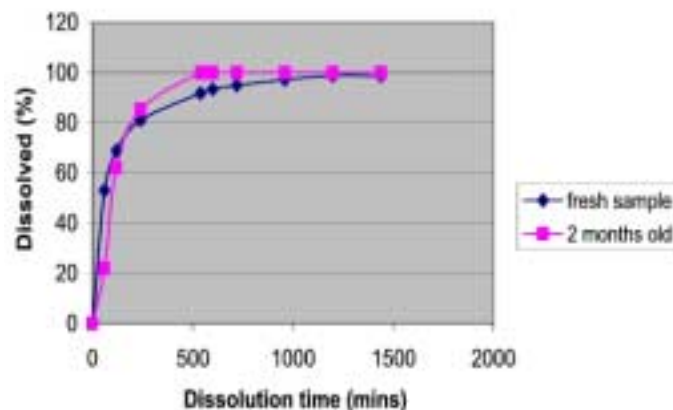


Figure 16. The effect of aging on controlled release diphenhydramine HCl pellets coated with 7.5% Eudragit NE30D + 10% nonoxynol 100 on the dry coating film basis, $n = 6$.

coalescence still decreased the dissolution rate, but because of the contrary influence of the higher amount of surfactant on dissolution, the combined result is that the dissolution rate of the 2-month-old sample is slightly higher than the fresh sample but not lower.

CONCLUSION

The endogenous surfactant of Eudragit NE30D, nonoxynol 100, was observed to crystallize out significantly from the polymer phase when stored under ambient conditions. The endogenous surfactant, nonoxynol 100, in Eudragit NE30D dispersion can crystallize out at room temperature and at 30 °C, 40°C,

and 45°C on aging. After 2 weeks' storage, crystals were already observable. However, most of the surfactant crystallizes out after 2 months or longer, but in less than 8 months. The rate of crystallization of surfactant was seen to be a temperature-dependent process. The rates of crystallization were faster when the crystallization temperature was in the middle rather than at the 2 ends of the temperature range of 25 °C to 45°C. When the samples were stored at 0°C, the surfactant did not crystallize out.

Nonoxynol 100 is a dissolution enhancer to the pellets and the dissolution enhancement ability of nonoxynol 100 is similar to that of HPMC. The phase separation of nonoxynol 100 from the polymer contributes the dissolution enhancement to diphenhydramine HCl pellets. After the crystallization of nonoxynol 100 with aging in the coating film, its dissolution enhancement ability is increased even further. Without the compensation because of the crystallization of nonoxynol 100 from the polymer, the dissolution rates of the pellets would exhibit a greater decrease on aging.

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REFERENCES

1. Sinko CM, Yee AF, Amidon GL. Prediction of physical aging controlled-release coatings: the application of the relaxation coupling model to glassy cellulose acetate. *Pharm Res.* 1991;8(6):698-705.
2. Guo JH, Robertson RE, Amidon GL. Influence of physical aging on mechanical properties of polymer free films: the prediction of long-term aging effects on the water permeability and dissolution rate of polymer film-coated tablets. *Pharm Res.* 1991;8(12):1500-1504.
3. Herman J, Visavarungroj N, Remon JP. Instability of drug release from anhydrous theophylline-microcrystalline cellulose formulations. *Int J Pharm.* 1989;55:143-146.
4. Gutierrez-Rocca JC, McGinity JW. Influence of ageing on the physical-mechanical properties of acrylic resin films cast from aqueous dispersions and organic solutions. *Drug Dev Ind Pharm.* 1993;19:315-332.
5. Amighi K, Moes AJ. Influence of curing conditions on the drug release rate from Eudragit NE30D film coated sustained-release theophylline pellets. *S.T.P. PHARMA SCIENCES* 1997;7(2):141-147.
6. Ghebre-Sellassie I, Gordon RH, Nesbitt RU, Fawzi MB. Evaluation of acrylic-based modified-release film coatings. *Int J Pharm.* 1987;37:211-218.
7. Robertson RE. Effect of free-volume fluctuations on polymer relaxation in the glassy state. *J Polym Sci Polym Symp.* 1978;63:173-183.
8. Bodmeier R, Paeratakul O. Propranolol HCl release from acrylic films prepared from aqueous latexes. *Int J Pharm.* 1990;59:197-203.

9. Gopferich A, Lee G. The influence of endogenous surfactant on the structure and drug-release properties of Eudragit NE30D-matrices. *J Control Rel.* 1992;18:133-144.