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RESEARCH PAPER

Evaluation of the Film-Coating Properties of a Hydroxyethyl Cellulose/ Hydroxypropyl Methylcellulose Polymer System

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ABSTRACT

The effect of different grades of hydroxyethyl cellulose (HEC) and hydroxypropyl methylcellulose (HPMC) on the film-formation and taste-masking ability for ibuprofen granules was evaluated. Three batches of coated ibuprofen granules were prepared using a roto-granulator, each with a different coating composition. Two grades of HEC [MW 300,000 (H) and MW 90,000 (L)] were combined with three different grades of HPMC [MW 11,000 (L), MW 25,000 (M) and MW 35,000 (H)] to prepare the coating solutions. Mechanical strength and physical properties of the polymer films were evaluated. Films made from HPMC (L)/HEC (H), HPMC (M)/HEC (H), and HPMC (H)/HEC (H) were stronger and more flexible than the HPMC (L)/HEC (L) films. The assay, dissolution, particle size distribution, and environmental scanning electron microscopy (ESEM) data of the three batches of the coated ibuprofen granules were similar.

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These data indicated that the two grades of HEC had equivalent film-coating properties. However, the HPMC (L)/HEC (L) film-coated granules showed better taste-masking characteristics (no burning after-taste) than the HPMC (L)/HEC (H) and HPMC (M)/HEC (H) film-coated granules. The ESEM data of the polymer films indicated that both HPMC (L)/HEC (H) and HPMC (M)/HEC (H) films exhibited more roughness and contained larger particles than the HPMC (L)/HEC (L) films. A hydration/dehydration study of the films revealed that HPMC (L)/HEC (H) and HPMC (M)/HEC (H) films were more susceptible to moisture effects, which subsequently led to a faster hydration rate of the polymer films. These data suggest that the molecular weight of the HEC affects the taste-masking ability of the resultant polymer film. The HEC (L) mixed well with the HPMC (L) to yield a uniform film that was more resistant to moisture effects. Hence, for optimum coating applications, particular attention should be paid to the molecular weight of the coating polymers to ensure that they are comparable to each other.

Key Words: *Hydration rate; Ibuprofen; Molecular weight of polymer; Taste masking*

INTRODUCTION

Film coatings of water-soluble cellulose ethers are widely used, since they give an improved esthetic appearance, can mask color and unpleasant taste, and can act as protective coatings for tablet cores (1–4). As a film-coating material, hydroxypropyl methylcellulose (HPMC) has a few unique characteristics. A tough, flexible, and non-tacky film can be formed from an aqueous solution of low viscosity grades of HPMC. In taste-masking applications, the good water-solubility of HPMC may lead to excessively rapid dissolution and a relatively large amount of coating material may be required to effectively mask a bitter taste. Furthermore, it has been suggested (2) that the higher viscosity grade of HPMC (such as 15 cP) had a better masking effect than 3-cP and 6-cP types of HPMC. Hydroxyethyl cellulose (HEC) films have moderate strength and excellent flexibility (5). However, HEC solutions have been shown to have a higher degree of tackiness than HPMC solutions (6). Another report indicated that the combination of HPMC and HEC might give a good polymeric film for taste-masking functions, since the HEC polymer has a good mechanical flexibility which is advantageous in products where the coating must withstand the forces of tablet compression and chewing in the mouth (7). The HPMC reduces the tackiness of the coating and toughens the film coating when blended with HEC (8). A blend of HEC/HPMC, since both polymers are water-soluble, would disintegrate rapidly to provide rapid release of the drug once it enters the stomach and maintain good bioavailability.

The goal for our work was to investigate a polymeric coating system that can be used to coat ibuprofen granules to yield coated particles for chewable formulations. The ideal polymeric coating system should be an aqueous formulation that can taste-mask the bitter taste of ibuprofen without retarding the dissolution rate. In addition, the system should also have a good mechanical flexibility where the coating must withstand the forces of tablet compression and chewing in the mouth. A HPMC/HEC polymeric mixture film seems ideal to meet the critical criteria for a taste-masking coating. In the present study, a HEC/HPMC film was utilized to coat an ibuprofen granulation using a roto-granulator process. The effect of different grades of HEC and HPMC on the film-coating properties, as well as the impact on the taste sensory of the coated product, was examined.

EXPERIMENTAL

Materials

Ibuprofen granulation was obtained from McNeil CHC, Round Rock, TX. Hydroxyethyl cellulose (NF grades) was obtained either from Clariant, Germany or from Aqualon Company, Wilmington,

DE. Hydroxypropyl methylcellulose (MW 11,000, MW 25,000, and MW 35,000) was obtained from Dow Chemical Company, Midland, MI.

Methods

Preparation of the Coating Solution

Aqueous solutions (6% w/w) of HEC and HPMC were prepared. A combination of various grades of HEC (3%) and HPMC (3%) was mixed to yield polymeric mixture solutions for the coating trials. Nine polymeric solutions were prepared (Table 1).

Preparation of the Polymeric Films

Films of HPMC and HEC were prepared by casting an aqueous polymer solution (6% w/w in water) onto $20 \times 20\,cm^2$ glass plates. Barriers were fitted onto the edges of the plates to prevent overflow. The amount of solution poured was such that 3 g of polymer would remain on the plate after the water was evaporated. Dried films were removed from the glass plates and 1×1 inch^2 films for tensile tests were cut with scissors.

Test Procedures for Polymeric Films

All tests were conducted at room temperature. For tensile tests, film specimens were clamped with 2.54-cm pneumatic grips. The rate of strain was 3 inch/min. The stress–strain tester used for all studies was an Instron Model 1000, fitted with a 5- or 50-kg load-detecting transducer (Instron Corp., Canton, MA). Loads vs. strain data were collected and converted to stress vs. strain data using modified proprietary computer software.

Preparation of Coated Ibuprofen Granules

One batch of ibuprofen granulation was used for all coating trials: 1 kg of granules was coated with three formulations of coating solution (Formulas 1, 2, and 3) using a Glatt roto-granulator (Model GPCG 1-3, Ramsey, NJ). Each granulation sample was coated with an average weight gain of 18%. The same processing conditions were used for all three coating trials.

Assay and Dissolution

Coated granulations were assayed using USP method (USP 24/NF 19) and dissolution tests were conducted using USP Type II apparatus with 900 mL phosphate buffer (pH 5.6) at an agitation speed of 50 rpm.

Hydration Rate Study of Polymers

The hydration rates of two grades of HEC polymers were evaluated using a Brabender Viscoamylograph. This instrument measures viscosity vs. time. A sample (20 g) was added to 40 mL of *n*-propanol to form a slurry in the metal bowl of the Brabender unit; 400 mL of water was then added and the viscosity was measured and recorded

Table 1

Formula of Polymeric Solutions for Film Studies and Coating Trials

	Composition (% w/w)[a]				
Formula No.	HPMC (L)	HPMC (M)	HPMC (H)	HEC (L)	HEC (H)
1	3%	—	—	3%	—
2	3%	—	—	—	3%
3	—	3%	—	—	3%
4	—	—	3%	—	3%
5	6%	—	—	—	—
6	—	6%	—	—	—
7	—	—	6%	—	—
8	—	—	—	6%	—
9	—	—	—	—	6%

[a]HPMC (L): MW 11,000; HPMC (M): MW 25,000; HPMC (H): MW 35,000; HEC (L): MW 90,000; HEC (H): MW 300,000.

onto the viscogram at ambient temperature. The Brabender unit was operated at 150 rpm.

Hydration/Dehydration Studies

In order to simulate the behavior of a film in the mouth, an in vitro hydration/dehydration method was developed where a film could be microscopically examined before and after exposure to moisture. Towards this end, aqueous polymeric solutions (100 μL) were poured onto the thermogravimetric pan. Water was evaporated in a 60°C isotherm using a thermogravimetry analyzer (Hi-Res TGA 2950, TA Instruments Inc., New Castle, DE) to yield films for hydration/dehydration studies directly on the pan. The films were transferred to the DVS (Model DVS-2000, WTB Binder, Tuttlingen, Germany). Films were hydrated for 400 min at 40°C/75% relative humidity (RH) and dehydrated for 200 min at 40°C/0% RH. Environmental scanning electron microscopy images were taken before and after hydration/dehydration studies.

Microscopy

Polymeric films that were cast either at room temperature or by the thermogravimetric analysis (TGA) method and coated granules were viewed using an environmental scanning electron microscope (Model XL30 ESEM LaB6, Philips Electronic Instruments Company, Mahwah, NJ). Image analysis software (AnalySiS, Soft Imaging System Corp., Lakewood, CO) was used to provide digital image-processing of samples. The technique is non-destructive and allows the visualization of wet, oily, or non-conductive samples in their natural state. Since sample preparation is not required, it avoids the potential for artifact formation during the extensive specimen preparation involving freezing, drying, and fracturing of the sample that is required by conventional scanning electron microscopy. This approach allows the films to be observed in their natural state and thus can provide more in-depth morphological information (9).

Taste Evaluation

The coated granules were chewed in the mouth cavity for 2 min. An ideal taste-masking polymeric film for ibuprofen granules should be void of any burning after-taste after 2 min of chewing.

RESULTS AND DISCUSSION

Interpretation of Tensile Data

In general, HPMC films showed high tensile strength and average percentage of elongation, whereas HEC films exhibited low tensile strength and high percentage of elongation. This tensile data agreed with data reported in the literature (3). Formula 8 [HEC (L)] showed the lowest tensile strength, which indicated that the film was rather weak to be used as a single polymeric film (Table 2). Among the mixed polymeric films, data indicated that the molecular weight of the individual polymer had a direct effect on the film properties. Films made from Formula 4 [HPMC (H)/HEC (H)] showed the highest tensile strength and the highest percentage elongation, which indicated that this mixture of polymers yielded a hard and strong film. Formula 1 [HPMC (L)/HEC (L)] exhibited the lowest tensile strength and percentage elongation values, which indicated that this polymeric mixture yielded a soft and weak film. Hence, the HPMC (L)/HEC (H) film (Formula 2) was 60% stronger and 63% more flexible than the HPMC (L)/HEC (L) film (Formula 1). The tensile data implies that Formula 1 should be the least desirable polymeric mixture to yield an acceptable film for taste-masking functions compared to the other three combinations of polymers (Table 2; Fig. 1).

Evaluation of Polymeric Films Using ESEM

Environmental scanning electron microscopy images of the nine polymer films cast at ambient

Table 2

The Mechanical Properties of Polymer Films Containing Different Levels of HPMC and/or HEC (N = 5)

Formula No.	Tensile Strength (kN/m) (mean ± SD)	Elongation (%) (mean ± SD)
1	1.43 (0.55)	3.3 (1.20)
2	2.28 (0.92)	5.4 (0.47)
3	2.52 (0.81)	5.8 (1.37)
4	3.55 (0.39)	13.9 (5.55)
5	4.99 (0.58)	10.6 (2.68)
6	3.02 (0.22)	14.9 (3.19)
7	4.61 (1.20)	18.4 (12.36)
8	0.97 (0.10)	17.5 (2.80)
9	3.50 (0.49)	16.5 (6.64)

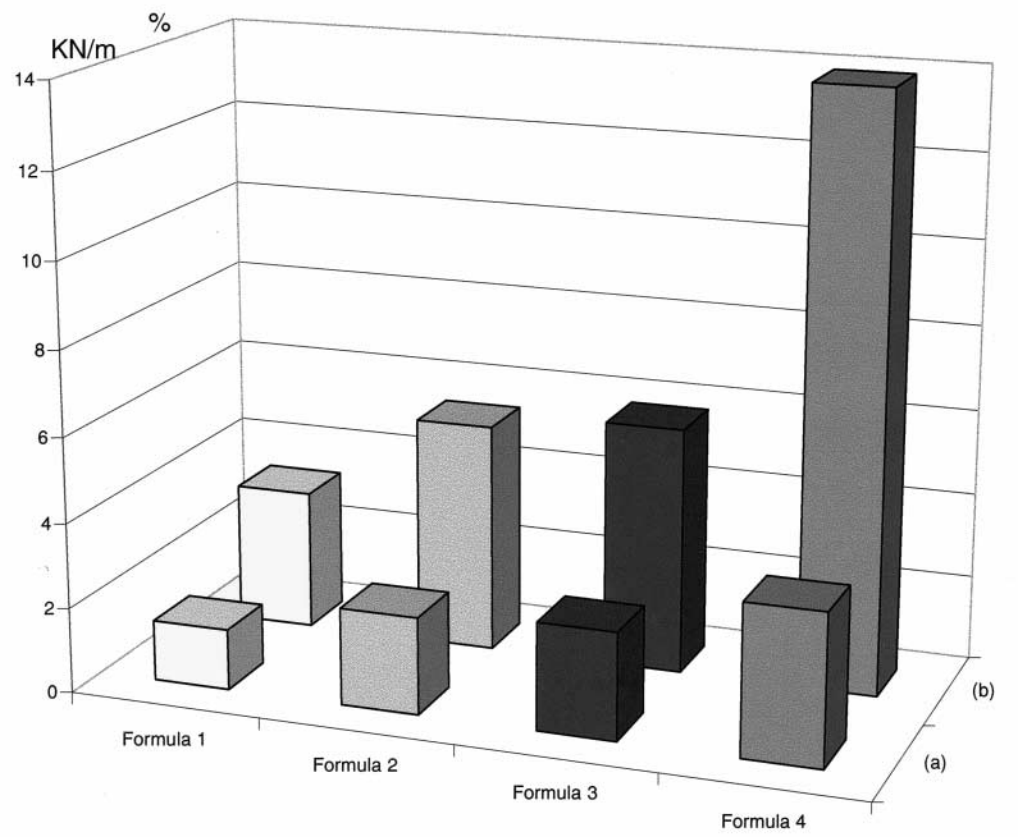

Figure 1. (a) Tensile strength for cast mixed polymeric films. (b) Percentage elongation for the cast mixed polymeric films.

temperature indicated that the films from Formulas 2, 3, and 4 exhibited more roughness and contained larger particles than the Formula 1 [HPMC (L)/ HEC (L)] film (Figs. 2 and 3). The images implied that the HPMC and HEC did not mix well to yield uniform coating films compared to the individual polymeric films. Furthermore, the molecular weight of these two types of polymers seemed to play a critical role in producing an acceptable polymeric film. It was also observed that HPMC (L) polymer (MW 11,000) mixed better with lower molecular weight HEC (L) (MW 90,000) than the higher molecular weight HEC (H) (MW 300,000) to yield a relatively smooth and uniform film.

Evaluation of Hydrated/Dehydrated Films Using ESEM

Environmental scanning electron microscopy images of polymeric films that were subjected to the hydration/dehydration studies revealed that films made from Formulas 2, 3, and 4 were more susceptible to moisture effects compared to film of Formula 1. All three films showed that HEC particles swelled to form spherical balls that were detached from the polymer surface, whereas Formula 1 film showed minimal change in surface morphology (Figs. 4 and 5). Conversely, the five individual polymeric films showed minimal moisture effects (Fig. 6), where the surface morphology of the polymeric films remained intact compared to the films before the hydration/dehydration study.

Digital ESEM images can be processed further with the aid of image analysis software to generate three-dimensional (3-D) perspectives of the polymeric film surface. This in turn would enable a specimen to be viewed topographically and allows us to gain a more detailed measure of the impact of moisture on the polymeric film. Figure 7 shows 3-D images of the polymeric films before and after the hydration/dehydration studies.

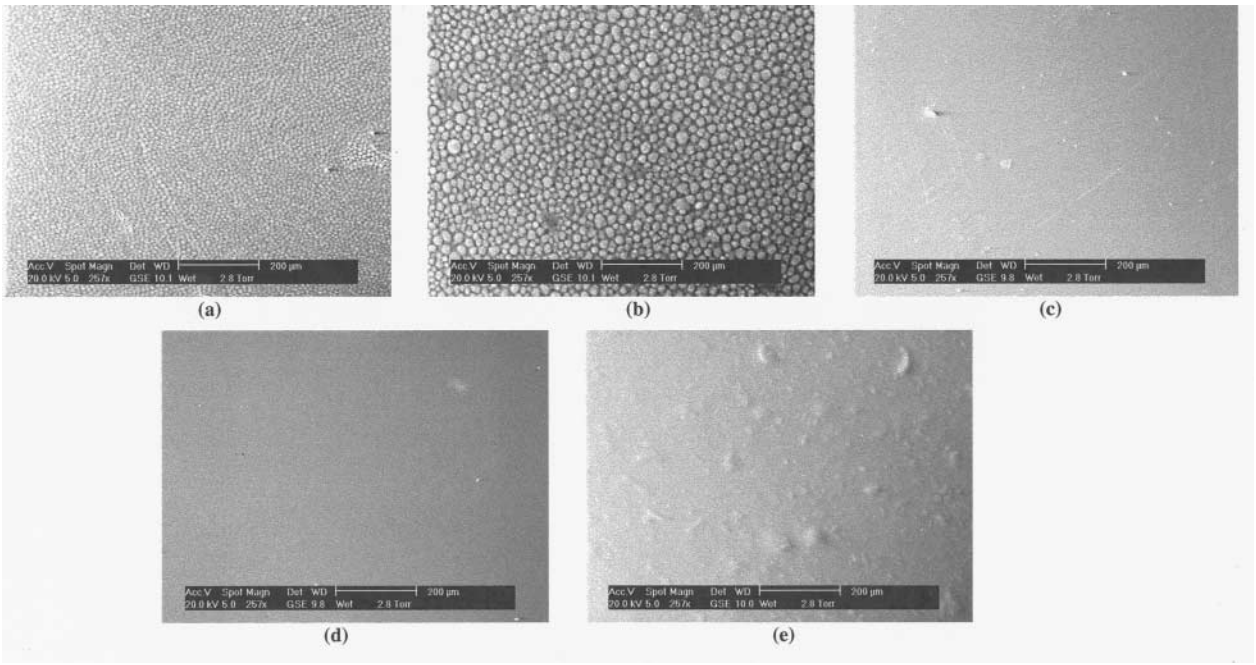

Figure 2. Environmental scanning electron microscopy images of polymeric films cast on glass slides under ambient room temperature at 257× magnification. (a) Formula 1 [3% HPMC (L)+3% HEC (L)]; (b) Formula 2 [3% HPMC (L)+3% HEC (H)]; (c) Formula 5 [6% HPMC (L)]; (d) Formula 8 [6% HEC (L)]; (e) Formula 9 [6% HEC (H)].

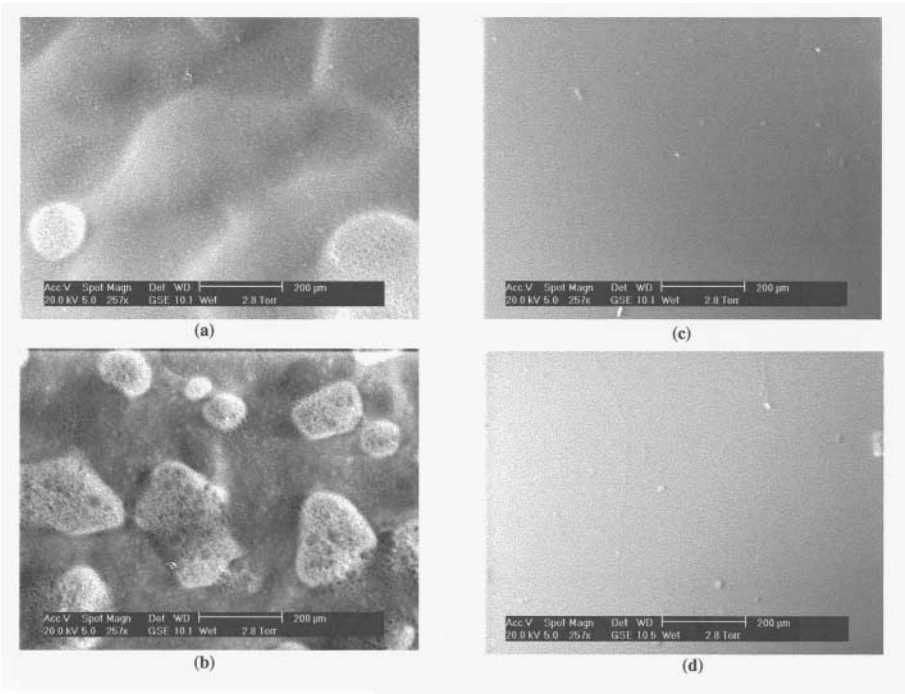

Figure 3. Environmental scanning electron microscopy images of polymeric films cast on glass slides under ambient room temperature at 257× magnification. (a) Formula 3 [3% HPMC (M)+3% HEC (H)]; (b) Formula 4 [3% HPMC (H)+3% HEC (H)]; (c) Formula 6 [6% HPMC (M)]; (d) Formula 7 [6% HPMC (H)].

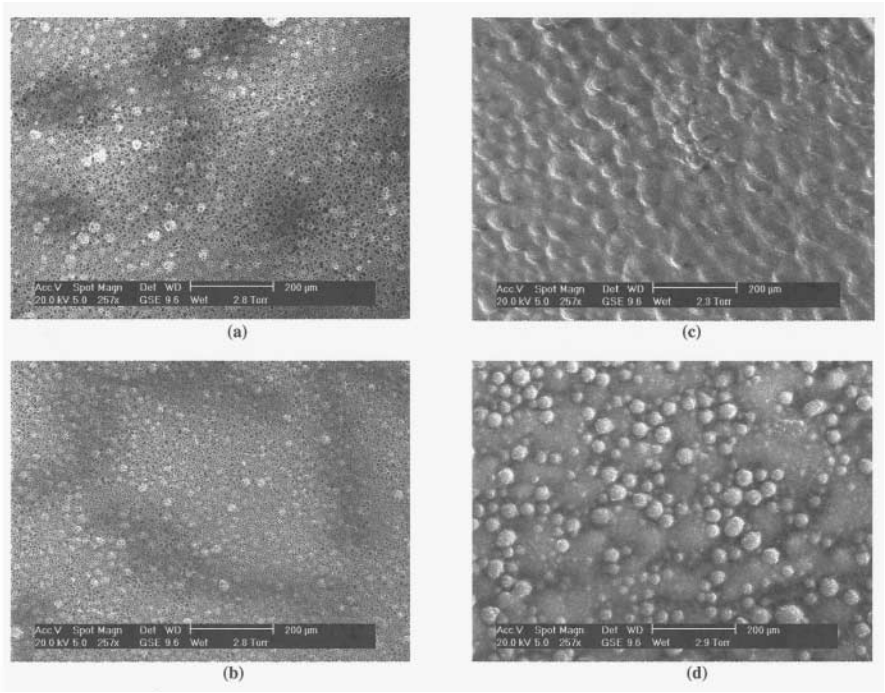

Figure 4. Environmental scanning electron microscopy images of polymeric films cast on TGA pan taken before and after the hydration/dehydration study at 257× magnification. (a) Formula 1 [3% HPMC (L)+3% HEC (L)] before; (b) Formula 1 after; (c) Formula 2 [3% HPMC (L)+3% HEC (H)] before; (d) Formula 2 after.

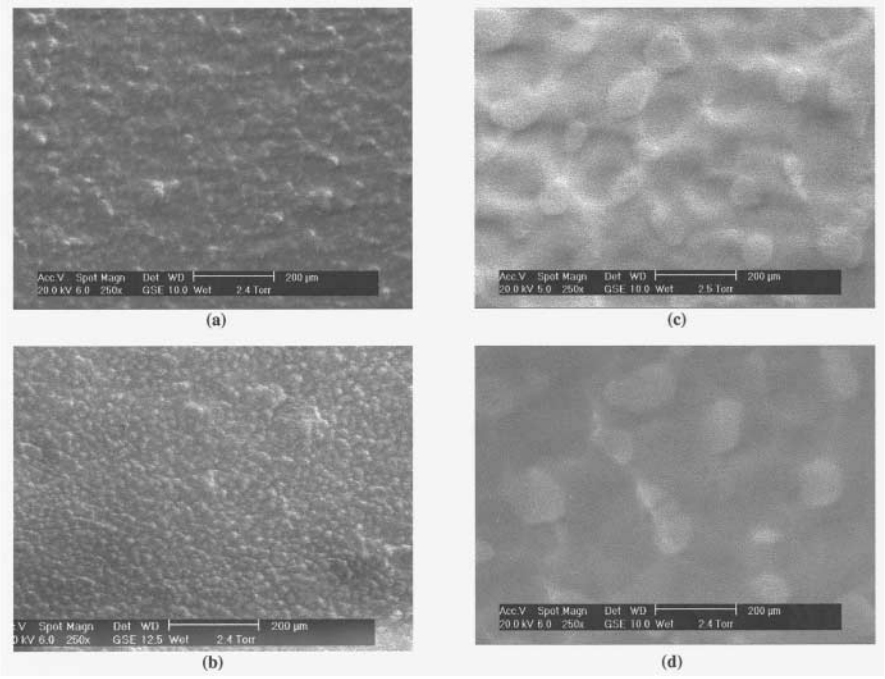

Figure 5. Environmental scanning electron microscopy images of polymeric films cast on TGA pan taken before and after the hydration/dehydration study at 257× magnification. (a) Formula 3 [3% HPMC (M)+3% HEC (H)] before; (b) Formula 3 after; (c) Formula 4 [3% HPMC (H)+3% HEC (H)] before; (d) Formula 4 after.

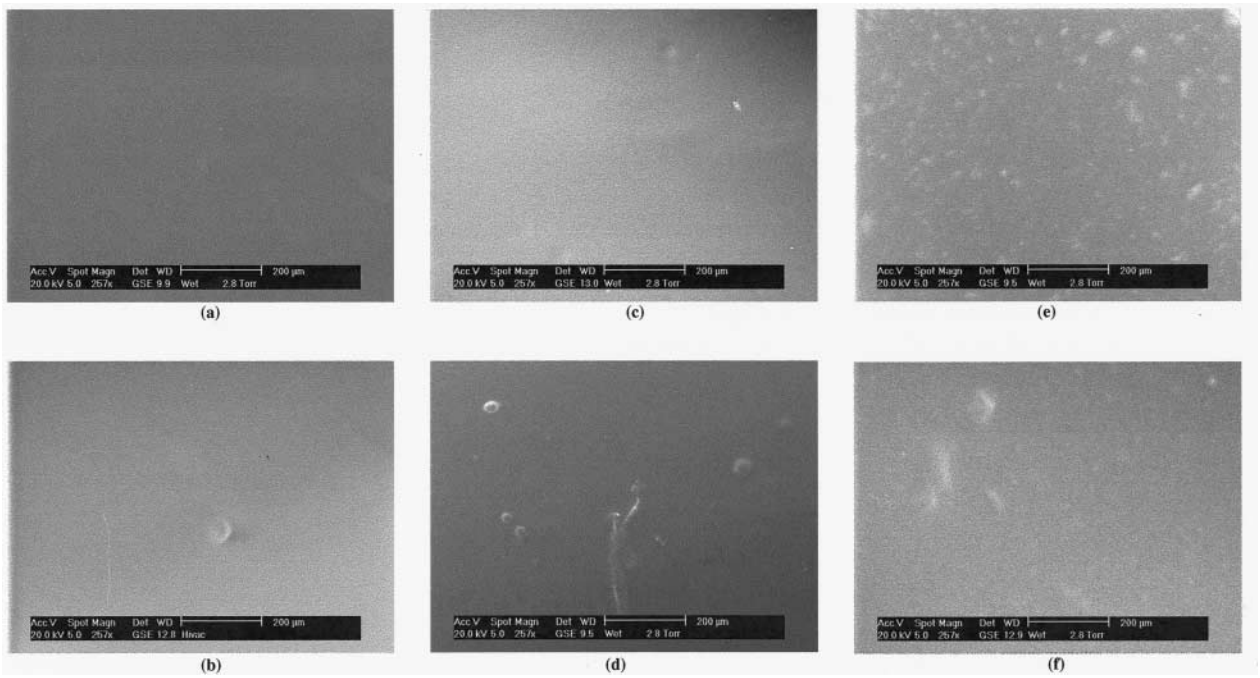

Figure 6. Environmental scanning electron microscopy images of polymeric films cast on TGA pan taken before and after the hydration/dehydration study at 257× magnification. (a) Formula 5 [6% HPMC (L)] before; (b) Formula 5 after; (c) Formula 8 [6% HEC (L)] before; (d) Formula 8 after; (e) Formula 9 [6% HEC (H)] before; (f) Formula 9 after.

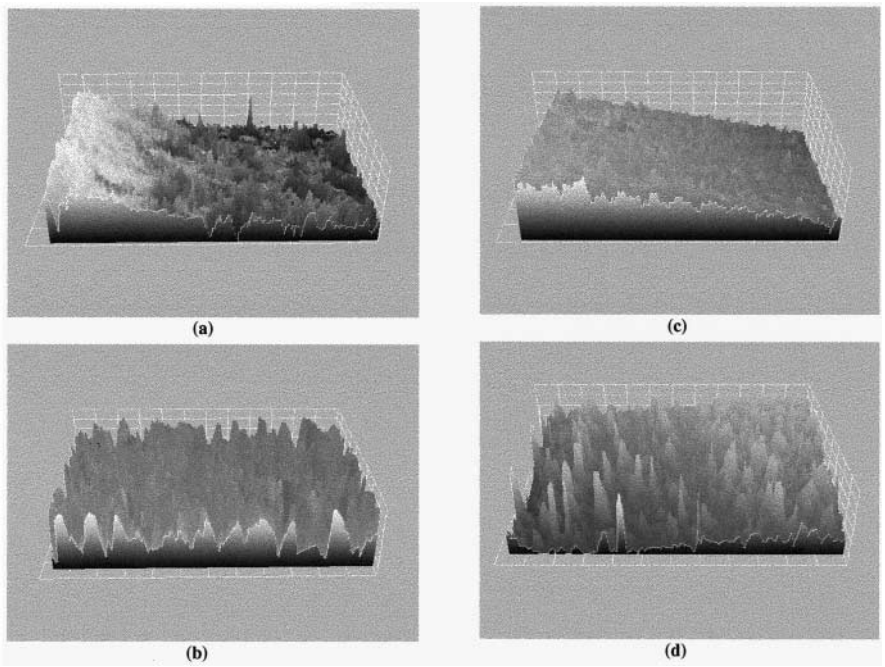

Figure 7. Three-dimensional ESEM images at 60° surface profile of polymeric films cast on TGA pan taken before and after the hydration/dehydration study. (a) Formula 1 [3% HPMC (L)+3% HEC (L)] before; (b) Formula 1 after; (c) Formula 2 [3% HPMC (L)+3% HEC (H)] before; (d) Formula 2 after.

Evaluation of the Coated Ibuprofen Granules

Due to the high viscosity of Formula 4 (944 cP) compared to Formulas 1, 2, and 3 (96, 152, and 329 cP, respectively), it was decided that Formula 4 would not be used for the coating trials since modifications in the coating process parameters would be required. Therefore, only three coating trials were conducted.

The assays (Formula 1: 74.6%; Formula 2: 74.8%; Formula 3: 74.9%) of the three batches of the coated ibuprofen granules were similar. The dissolution profiles (Fig. 8) and particle size distribution data (Fig. 9) of Formulas 1 and 2 were similar. Formula 3 showed a slightly slower dissolution profile and a more coarse particle size distribution compared to the other two batches of coated granules.

Environmental scanning electron microscopy images of three batches of coated granules showed smooth coatings were deposited onto the ibuprofen granules, indicating that these three polymer systems yielded acceptable coated products (Figs. 10 and 11).

Dissolution data indicated that the two different grades of HEC were equivalent and could be combined with two different grades of HPMC to yield acceptable polymeric films that could be used to coat ibuprofen granules. However, even though all three coating formulations yielded coated products with similar dissolution profiles and assay value, it was found that the ibuprofen granules coated with Formula 1 showed much better taste-masking characteristics (reduced burning after-taste) than the granules coated with either Formula 2 or Formula 3. It appeared that granules coated with polymeric films of Formulas 2 and 3 dissolved in the mouth more rapidly than those granules coated with Formula 1. Hence, these two coating formulas did not provide an adequate barrier coating for taste-masking of the ibuprofen granules. Since all three batches of the coated products were prepared using the same processing parameters with one single batch of uncoated cores, data indicated that the unacceptable taste evaluation of coated products might be attributed to the grade of HEC used in the coating formulation. In addition, two batches of coated products with unacceptable taste-masking

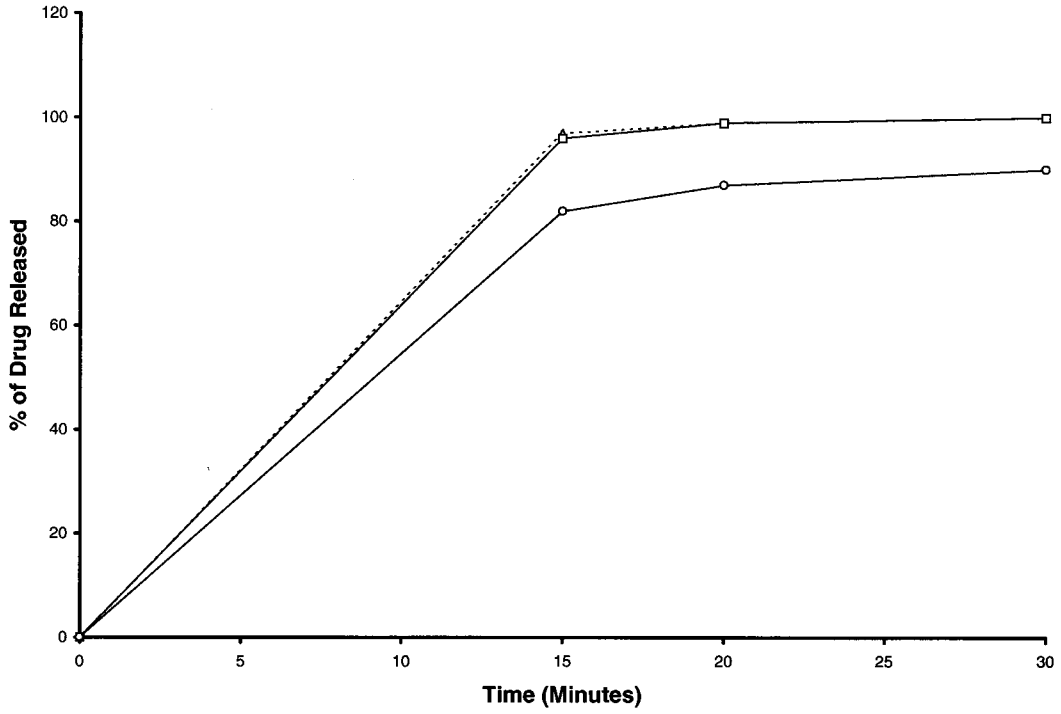

Figure 8. Dissolution profiles of three batches of film-coated ibuprofen granules. (a) Formula 1 (□); (b) Formula 2 (△); (3) Formula 3 (○).

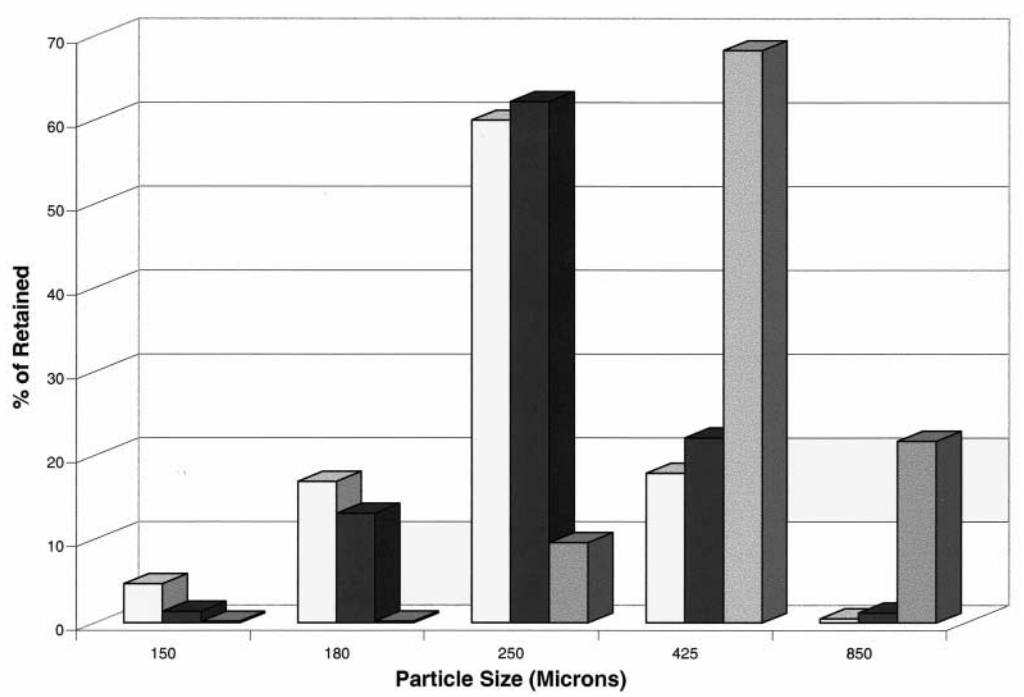

Figure 9. Particle size distribution of three batches of film-coated ibuprofen granules. (a) Formula 1 (□); (b) Formula 2 (■); (3) Formula 3 (▣).

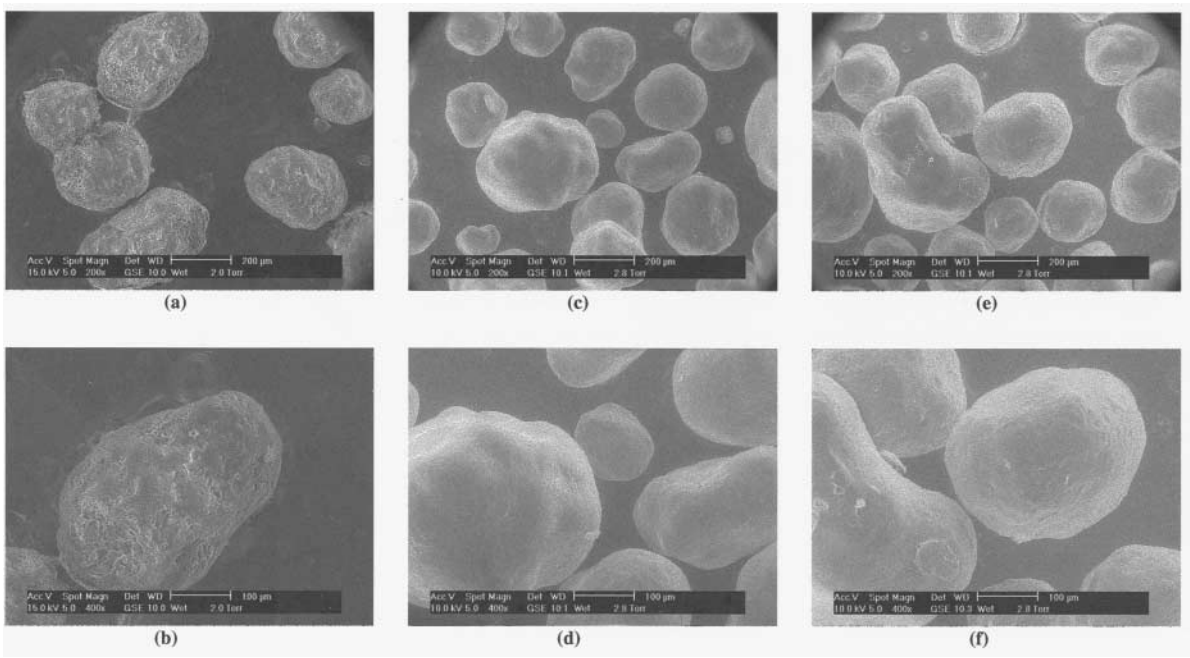

Figure 10. Environmental scanning electron microscopy images of core granules and film-coated ibuprofen granules at 200× magnification and at 400× magnification. (a) Core granules (200×); (b) core granules (400×); (c) Formula 1 [3% HPMC (L)+3% HEC (L)] (200×); (d) Formula 1 (400×); (e) Formula 2 [3% HPMC (L)+3% HEC (H)] (200×); (f) Formula 2 (400×).

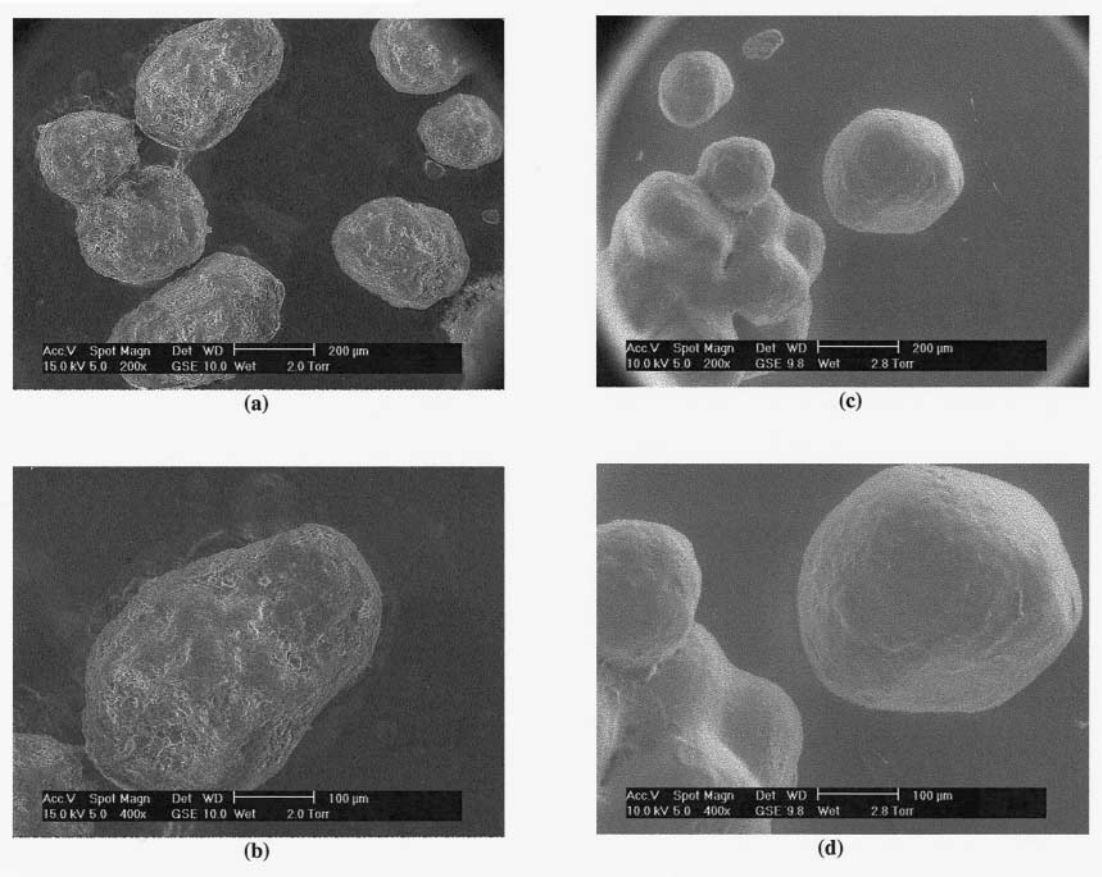

Figure 11. Environmental scanning electron microscopy images of core granules and film-coated ibuprofen granules at 200× magnification and at 400× magnification. (a) Core granules (200×); (b) Core granules (400×); (c) Formula 3 [3% HPMC (M)+3% HEC (H)] (200×); (d) Formula 3 (400×).

characteristics were prepared with two different grades of HPMC (L or M) and HEC (H). These data further supported the supposition that the grades of HEC probably caused the difference in taste-masking ability of the resultant film coating.

Explanation for the Failure of the Polymeric Films as Taste-Masking Barrier Coatings

All three coated products exhibited similar dissolution profiles and similar surface morphology, which indicated that all three formulas were equivalent in providing an effective film coating. However, taste evaluation revealed that all three coating formulations showed different taste-masking capabilities. The above observations indicated that the failure of Formulas 2 and 3 might be related to the hydration rate of the polymeric films. As the coated granules were exposed to the mouth cavity, saliva contacted the outer layer coating. Since the Formula 2 and 3 films contained larger spherical particles (probably HEC particles), these larger particles made contact with saliva and started to swell. The fact that the HEC (H) polymer had a faster hydration rate (2 min) compared to the HEC (L) (7 min based on the Viscoamylograph test) provided further evidence to support the polymer hydration effect. The larger particle size of HEC (H) in the mixed polymeric films (Figs. 2 and 3) plus the faster hydration rate led to rupture of the polymer film as the HEC particle left the polymeric network, creating larger holes in the polymeric film. Consequently, the core ibuprofen granules were exposed to saliva,

which led to a burning sensation. Environmental scanning electron microscopy images of polymeric films exposed to moisture effects further supported the above speculation. Film Formulas 2 and 3 showed that HEC particles swelled to form spherical balls and were detached from the polymer surface, whereas film Formula 1 showed minimal change in surface morphology (Figs. 4 and 5). On the other hand, the smaller HEC spheres in film Formula 1 (with a much slower hydration rate of HEC) allowed the film coating to resist the swelling from saliva in the mouth. The polymeric film remained intact in the mouth cavity for a relatively long time and prevented ibuprofen granules from contacting the saliva. Consequently, this formula yielded an acceptable taste-masking barrier for the ibuprofen granules. Hence, the low molecular weight grade of HEC, which had a slower hydration rate, was much more compatible to HPMC, which made this coating system more suitable for the taste-masking of ibuprofen granules.

In addition, the grade of HPMC (L or M) apparently did not affect the moisture barrier characteristics in the resultant film. Even though Formula 3 (containing a higher molecular weight of HPMC) yielded a coated product with a much slower dissolution rate (Fig. 8), it still did not provide an adequate barrier coating to taste-mask the ibuprofen granules. The data further supports the observation that the grade of HEC used in the polymeric mixture film had the dominant effect on the taste-masking capability of the resultant film.

CONCLUSION

The data suggest that the grade of HEC in the HPMC/HEC blend affected the taste-masking ability of the resultant polymeric film. Hence, for optimum coating applications, particular attention should be paid to the molecular weight of the polymers to ensure they are comparable to each other. It was interesting to observe that the dissolution profiles of the coated granules did not reflect the actual taste-masking performance. This shows that one should be cautious in relying on in vitro dissolution data in predicting taste-masking coating performance. In addition, one should be cautious in relying on information generated from the mechanical properties of polymeric films (from cast films) as a sole means to screen coating formulas for taste-masking functions. Many researchers have questioned the value of data generated from free films since their method of manufacture differs greatly from films which coat a tablet (10). Indeed, in this case the coating formula that exhibited the worst mechanical properties in film studies turned out to be the best formula to provide an acceptable taste-masking polymeric film.

Finally, the approach of using ESEM images taken before and after hydration/dehydration studies is an effective in vitro means to evaluate the performance of mixed polymeric films for taste-masking applications.

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REFERENCES

1. Lehmann, K.; Brogmann, B. Tablet Coating. In *Encyclopedia of Pharmaceutical Technology;* Swarbrick, J., Boylan, J.C., Eds.; Marcel Dekker: New York, 1996; Vol. 14, 355–384.
2. Nagai, T.; Sekigawa, F.; Hoshi, N. Applications of HPMC and HPMCAS Aqueous Film Coating of Pharmaceutical Dosage Forms. In *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*; McGinity, J.W., Ed.; Marcel Dekker: New York, 1989; 81–152.
3. Porter, S.C.; Bruno, C.H. Coating of Pharmaceutical Solid-Dosage Forms. In *Pharmaceutical Dosage Forms: Tablets*, 2nd Ed.; Lieberman, H.A., Lachman, L., Schwartz, J.B., Eds.; Marcel Dekker: New York, 1990; Vol. 3, 77–160.
4. Wallace, J. Cellulose Derivatives and Natural Products Utilized in Pharmaceutics. In *Encyclopedia of Pharmaceutical Technology*; Swarbrick, J., Boylan, J.C., Eds.; Marcel Dekker: New York, 1990; Vol. 2, 319–337.
5. Aqualon, Technical Literature: Natrosol, Hydroxyethyl Cellulose (HEC), 2001.
6. Kovacs, B.; Merenyi, G. Evaluation of Tack Behavior of Coating Solution. Drug Dev. Ind. Pharm. **1990**, *16* (15), 2303–2323.
7. Roche, E.; Reo, J. U.S. Patent 5,215,755, 1993.
8. Radebaugh, G.; Murtha, J.; Julian, T.; Bondi, J. Methods to Evaluate the Puncture and Shear Properties of Pharmaceutical Polymeric Films. Int. J. Pharm. **1988**, *45*, 39–46.

9. Prack, E. An Introduction to Process Visualization Capabilities and Considerations in the Environmental Scanning Electron Microscope (ESEM). Microsc. Res. Tech. **1993**, *25,* 487–492.

10. Radebaugh, G. Film Coatings and Film-Forming Materials: Evaluation. In *Encyclopedia of Pharmaceutical Technology*; Swarbrick, J., Boylan, J.C., Eds.; Marcel Dekker: New York, 199; Vol. 5, 1–28.