DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 10(10), 1565-1585 (1984)

THE PHYSICAL STABILITY OF TABLETS COATED USING AN AQUEOUS DISPERSION OF ETHYLCELLULOSE

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ABSTRACT

Films formed from an aqueous dispersion of ethylcellulose mixed with hydroxypropylmethylcellulose were deposited onto sodium bicarbonate, microcrystalline cellulose, and acetylsalicylic acid (ASA) tablets. Upon storage at elevated temperatures and relative humidity, no changes in disintegration times were observed with the sodium bicarbonate tablets or with tablets containing microcrystalline cellulose. Marked increases were observed in disintegration times with the ASA tablets, these increases being dependent on both temperature and relative humidity. Examination of films by scanning electron microscopy indicated that coalescence of particles within the films had occurred in those samples where increases in disintegration times were observed.

INTRODUCTION

One of the most recent innovations in aqueous film coating of pharmaceutical tablets has been the development of pseudolatex dispersions of water insoluble polymers (1,2). While many pro-

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 0363-9045/85/1010-1565$3.50/0

perties of films formed from pseudolatex dispersions have been described, there have been no reports on the physical stability of such films. Since the dissolution rate of acetylsalicylic acid (ASA) from tablets coated using ethylcellulose (EC):hydroxypropylmethylcellulose (HPMC) films deposited from non-aqueous solvents (3) or HPMC films deposited from water (4), has been reported to decrease upon aging, we have undertaken a study of the effect of aging on tablets coated using EC:HPMC films deposited from water.

EXPERIMENTAL

Tablet Preparation

The compositions of the core tablets used in this study are given in Table 1. In series A, sodium bicarbonate powder was granulated using a 30% w/v solution of polyvinylpyrrolidone in ethanol, passed through a #16 mesh screen, and dried for 16 hours at 45°C. In each series all ingredients, except the magnesium stearate and 50 g of microcrystalline cellulose were blended in a Twin-Shell blender[1]. The remaining microcrystalline cellulose was mixed with the magnesium stearate, passed through a #60 mesh screen, and added to the main granulation. All ingredients were blended prior to compression.

TABLE 1

Core Tablet Composition (Per Tablet)

	A (Sodium Bicarbonate)	B (Placebo)	C (ASA)
Sodium Bicarbonate Powder[2]	325 mg	--	--
Polyvinylpyrrolidone[3]	20 mg	--	--
Microcrystalline Cellulose[4]	128 mg	331.1 mg	100.7 mg
Acetylsalicylic Acid Granular[5]	--	--	325.0 mg
Corn Starch Pharmaceutical[6]	25 mg	17.5 mg	22.5 mg
Magnesium Stearate[7]	2 mg	1.4 mg	1.8 mg

TABLE 2

Core Tablet Properties*

	A	B	C
Average Tablet Weight	528 mg	355 mg	449 mg
Tablet Thickness	4.53 mm	4.58 mm	4.53 mm
Breaking Strength**	9.5 kp	10.8 kp	7.1 kp

* Average of 10 determinations

** Schleuniger

TABLE 3

Coating Composition (Per Litre)

Hydroxypropylmethylcellulose 15 cP[9]	50 g
Ethylcellulose Dispersion (30% solids)[10]	162 mL
Dibutyl Sebacate[11]	15 g
Water to	1000 mL

Tablets were compressed on a Stokes Model 566-S Layer Press[8] using 1.111 cm round, standard-concave tooling. Die fill was at station 1. The upper compression rolls were adjusted to permit one precompression of the tablets. The properties of the core tablets are listed in Table 2.

Coating

The coating formulation was prepared by mixing an aqueous solution of HPMC with a commercially available aqueous ethylcellulose dispersion to which dibutyl sebacate had already been added and mixed for 30 minutes. The composition of the coating mixture is given in Table 3.

TABLE 4

Properties of Coated Tablets

Tablet	Film Weight (mg)	Moisture Content* After Drying (%)
Sodium Bicarbonate	23.1	0.96 (1.54)**
Microcrystalline Cellulose	18.8	3.29 (4.94)
ASA	18.1	1.08 (1.38)

* Expressed as percent weight loss after drying over P_2O_5 at 10mm Hg for 18 hours at room temperature.

** Values in parentheses are the moisture contents of the core tablets prior to coating.

Sixteen hundred tablets were coated in a 4" diameter air suspension column using an external air-atomizing nozzle. Inlet air temperature, application rate, and atomizing air pressure were held constant in all coating experiments. Sufficient coating was applied to obtain a target film weight of 20 mg per tablet. Actual film weights are given in Table 4. All tablets were dried for 24 hours at 45°C prior to packaging. The moisture content of the core tablets and the coated tablets after drying is also given in Table 4.

Storage

Tablets were packaged in high density polyethylene bottles with waxed pulp and vinyl lined metal caps. Tablets occupied approximately 50% of the container volume. An additional series was packaged in identical containers but containing absorbent packets[12]. The containers were stored at 40°C, 30°C and 79% relative humidity, 30°C, and room temperature.

Disintegration Tests

Tablet disintegration times were measured on 6 tablets in the USP XX apparatus with discs. The medium used was distilled water at 37°C. In all cases disintegration times of core tablets, stored under identical conditions as the film-coated tablets, were determined. Values for disintegration are dimensionless (5) representing the ratio of the disintegration time of a particular sample to its initial value.

Scanning Electron Microscopy

Cores and film coated tablets were gold sputter coated[13] and tablet faces and fracture faces examined and photographed in a scanning electron microscope[14]. The initial images were recorded just prior to packaging the samples. Stressed samples were examined after 18 and 36 weeks, concurrent with the measurements of disintegration times, as well as after one year storage.

RESULTS AND DISCUSSION

The dimensionless disintegration values for the three series of tablets, both coated and uncoated, are given in Tables 5 to 7. As seen in Tables 5 and 6, the disintegration behavior of sodium bicarbonate and placebo core tablets, as well as those coated with the EC:HPMC film, is relatively unaffected by elevated temperature or relative humidity. That is, the disintegration time of a particular sample, normalized with respect to that sample's initial disintegration time, is approximately one. In Table 7, for the film coated ASA tablets, a progressive increase is seen in tablet disintegration values upon storage, indicating a marked sensitivity to both temperature and relative humidity. The effect is illustrated in Figures 1a and 1b where the dimensionless disintegration values are plotted vs. time for all storage conditions.

Figure 1a shows the effect of storage temperature on the

TABLE 5

Dimensionless Disintegration Values for Film Coated Sodium Bicarbonate Tablets

Storage Conditions		Coated tablets		Core tablets	
		Without Absorbent Packet	With Absorbent Packet	Without Absorbent Packet	With Absorbent Packet
Initial		1.00	1.00	1.00	1.00
40°C	3 wks	1.33	0.89	1.40	1.20
	6 wks	1.26	1.17	1.13	1.27
	12 wks	1.11	1.06	1.67	1.40
	18 wks	1.00	0.89	1.50	1.37
	36 wks	1.11	1.19	1.57	1.57
30°C 79%	3 wks	1.00	0.85	1.03	1.20
	6 wks	1.00	1.13	1.40	1.03
	12 wks	1.11	0.94	0.80	1.07
	18 wks	0.70	0.89	0.70	1.20
	36 wks	0.89	0.94	0.80	0.40
30°C	3 wks	1.06	0.83	1.10	1.03
	6 wks	0.94	1.06	1.33	0.87
	12 wks	1.11	1.44	0.80	1.00
	18 wks	0.94	0.94	1.40	1.27
	36 wks	0.96	0.85	1.03	1.47
RT	3 wks	1.00	0.94	0.67	1.13
	6 wks	0.94	0.96	1.00	0.87
	12 wks	1.04	1.15	1.30	0.80
	18 wks	0.89	0.93	1.00	1.13
	36 wks	1.00	1.04	0.90	1.30

TABLE 6

Dimensionless Disintegration Values for Film Coated Placebo Tablets

Storage Conditions		Coated tablets		Core tablets	
		Without Absorbent Packet	With Absorbent Packet	Without Absorbent Packet	With Absorbent Packet
Initial		1.00	1.00	1.00	1.00
40°C	3 wks	0.71	0.83	1.40	0.83
	6 wks	1.14	0.83	1.13	0.67
	12 wks	1.07	0.83	1.67	0.83
	18 wks	0.88	0.67	1.50	0.67
	36 wks	0.93	1.00	1.57	1.00
30°C 79%	3 wks	0.95	0.67	1.03	0.83
	6 wks	1.07	0.67	1.40	0.67
	12 wks	0.86	1.00	0.80	0.67
	18 wks	0.71	1.00	0.70	0.83
	36 wks	0.98	1.00	0.80	1.00
30°C	3 wks	0.86	1.00	1.10	0.83
	6 wks	0.86	0.67	1.33	0.67
	12 wks	1.05	0.67	0.80	0.83
	18 wks	0.71	0.67	1.40	0.50
	36 wks	1.00	1.00	1.03	0.67
RT	3 wks	0.90	1.00	0.67	0.83
	6 wks	1.33	0.67	1.00	0.83
	12 wks	0.93	0.83	1.30	0.50
	18 wks	0.79	0.50	1.00	0.50
	36 wks	0.71	0.67	0.90	0.50

TABLE 7

Dimensionless Disintegration Values for Film Coated ASA Tablets

Storage Conditions		Coated tablets		Core tablets	
		Without Absorbent Packet	With Absorbent Packet	Without Absorbent Packet	With Absorbent Packet
Initial		1.00	1.00	1.00	1.00
40°C	3 wks	2.17	1.71	0.50	1.00
	6 wks	2.25	2.46	0.50	1.00
	12 wks	4.04	3.33	0.50	1.00
	18 wks	7.04	5.88	0.33	0.83
	36 wks	> 15 (0.33)*	> 15 (0.33)*	0.50	0.33
30°C 79%	3 wks	1.25	1.46	0.50	0.83
	6 wks	1.83	1.42	0.50	0.83
	12 wks	2.21	1.92	0.33	0.50
	18 wks	4.25	2.42	0.50	0.33
	36 wks	8.50	7.50	0.33	0.33
30°C	3 wks	1.63	1.42	0.50	1.00
	6 wks	1.29	1.63	0.50	1.33
	12 wks	1.75	1.75	0.67	1.33
	18 wks	2.13	2.33	0.33	1.17
	36 wks	3.38	2.00	0.33	0.67
RT	3 wks	1.54	1.29	0.67	0.67
	6 wks	0.83	1.58	0.83	0.83
	12 wks	1.79	1.67	0.50	0.83
	18 wks	1.67	1.58	0.50	1.17
	36 wks	1.71	1.42	0.50	1.00

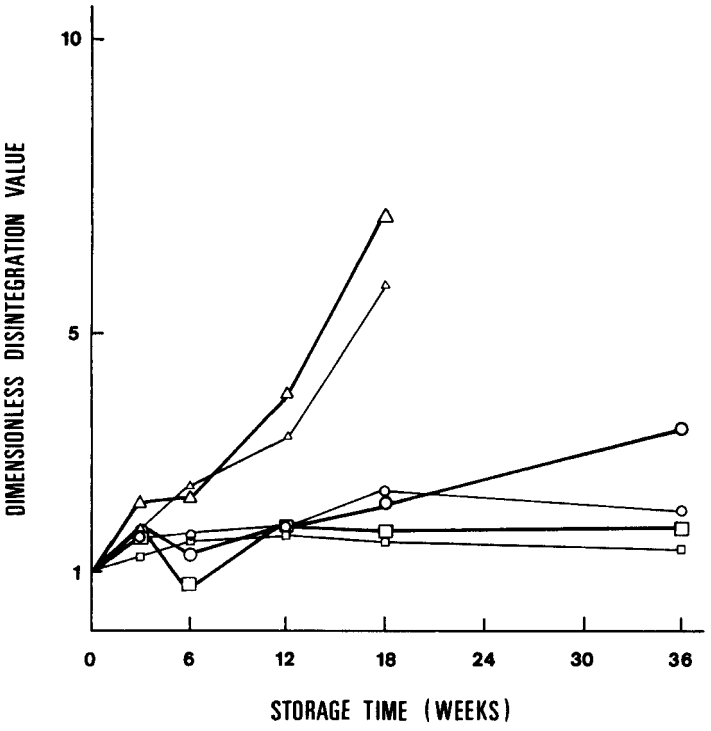

FIGURE 1(a)

Effect of temperature on the dimensionless disintegration values for ASA tablets coated with the aqueous EC:HPMC film.

Legend: ——— stored without absorbent packet
——— stored with absorbent packet
△ 40°C
○ 30°C
□ RT

disintegration values of ASA tablets coated with the aqueous EC:HPMC film. Storage at room temperature results in only slight increases in disintegration values, while storage at 40°C can result in increases from 2 to 15 fold. The effect of relative humidity on disintegration values is illustrated in Figure 1b for tablets which were stored at 30°C and at either ambient or 79% relative humidity. A marked increase is seen in disintegration values for tablets stored at elevated relative humidity. It also is apparent that the addition of an absorbent packet produces a

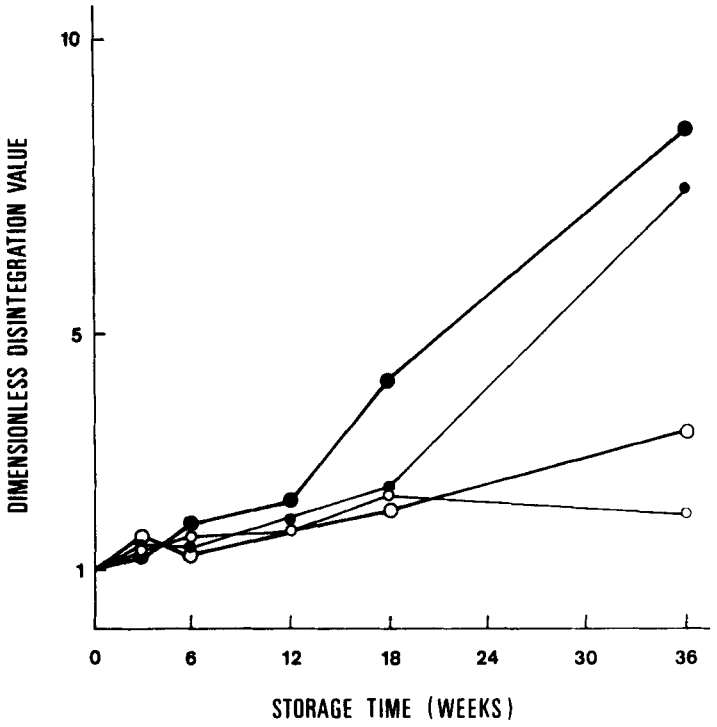

FIGURE 1(b)

Effect of relative humidity on the dimensionless disintegration values for ASA tablets coated with the aqueous EC:HPMC film.

Legend: ——— stored without absorbent packet
——— stored with absorbent packet
● 30°C/79% relative humidity
○ 30°C/ambient humidity

reduction, but not elimination of this effect at all temperatures, further indicating moisture sensitivity.

While the disintegration values of the uncoated ASA tablets do not appear to be affected by accelerated storage conditions, we cannot overlook possible changes in the core upon storage which may have been induced by the coating or the coating process. Therefore, whenever the dimensionless disintegration value exceeded 10, the coating was peeled off the tablets, and the disintegration time of the peeled core tablet was measured. In all

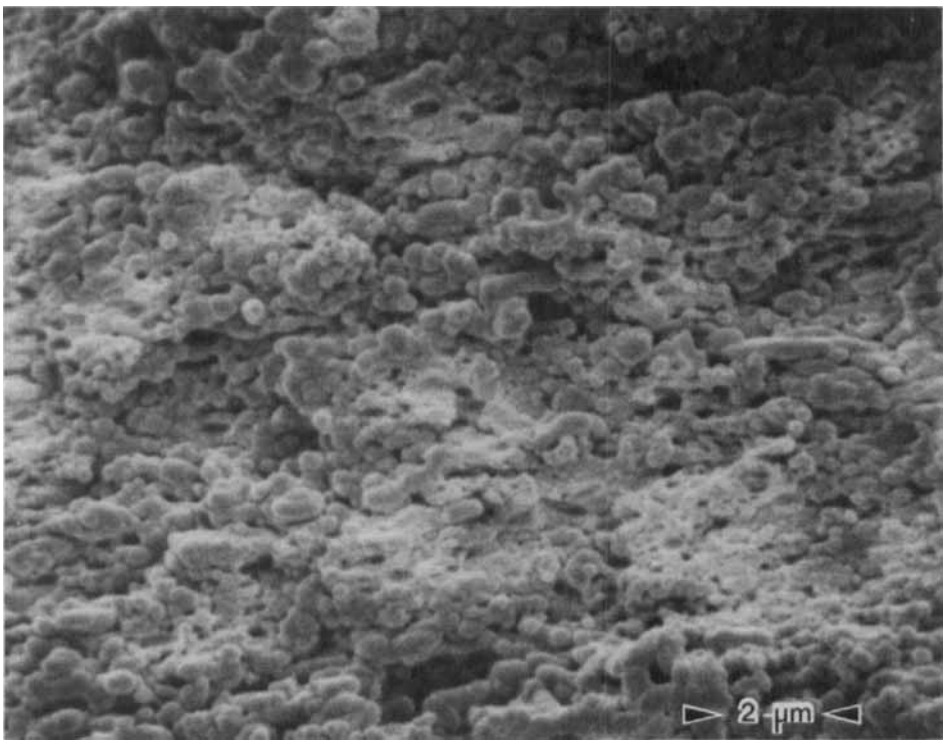

FIGURE 2

Scanning electron micrograph showing in cross section the aqueous EC:HPMC film deposited on the microcrystalline cellulose core. The film was examined just prior to packaging the tablets for stability study.

cases, the disintegration values were equivalent to those of the stressed core tablets. These values also are given in Table 7.

Statistical evaluation of the disintegration values (using the test of equality of means when variances are unknown) indicates that, in the case of ASA tablets, disintegration values for tablets stored at 30°C, 30°C/79% RH, and 40° are significantly greater than disintegration values for tablets stored at RT. Furthermore, the presence of absorbent packets significantly reduces moisture and temperature dependent changes in disintegra-

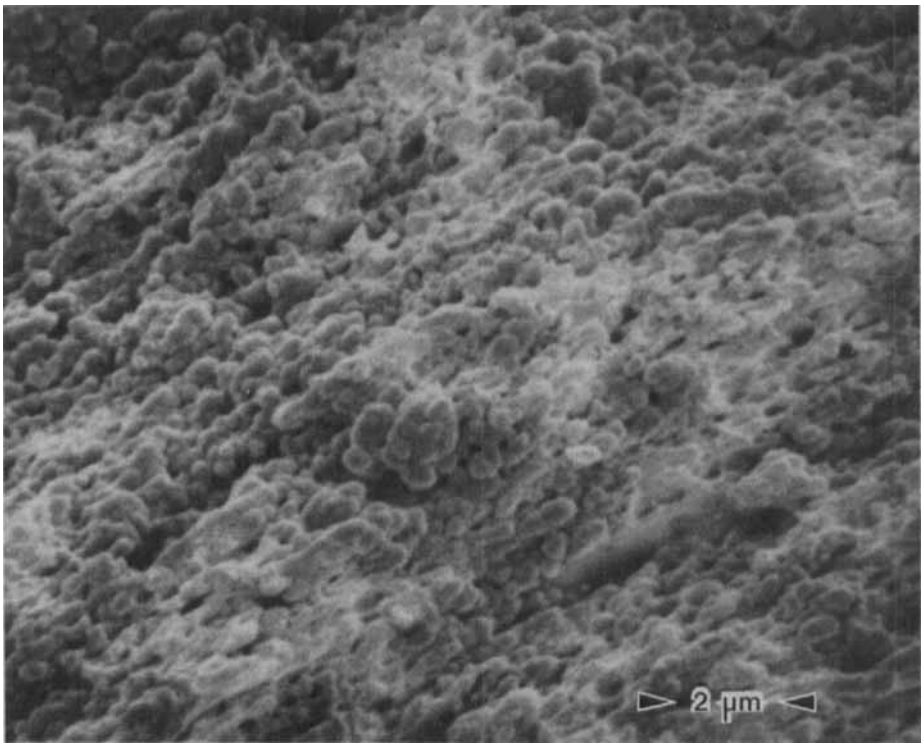

FIGURE 3

Scanning electron micrograph showing in cross section the aqueous EC:HPMC film deposited on the sodium bicarbonate core. The film was examined just prior to packaging the tablets for stability study.

tion values for the same tablets. Changes observed in disintegration values of the microcrystalline cellulose and sodium bicarbonate tablets are not significant. Details of the complete statistical analysis using ANOVA techniques will be published elsewhere.

In order to understand the physical changes taking place in the film coated ASA tablets better, scanning electron microscopy was used to examine and compare the initial and aged samples. Tablet cores did not reveal any changes in the appearance of either tablet faces or fracture faces upon storage; a finding not

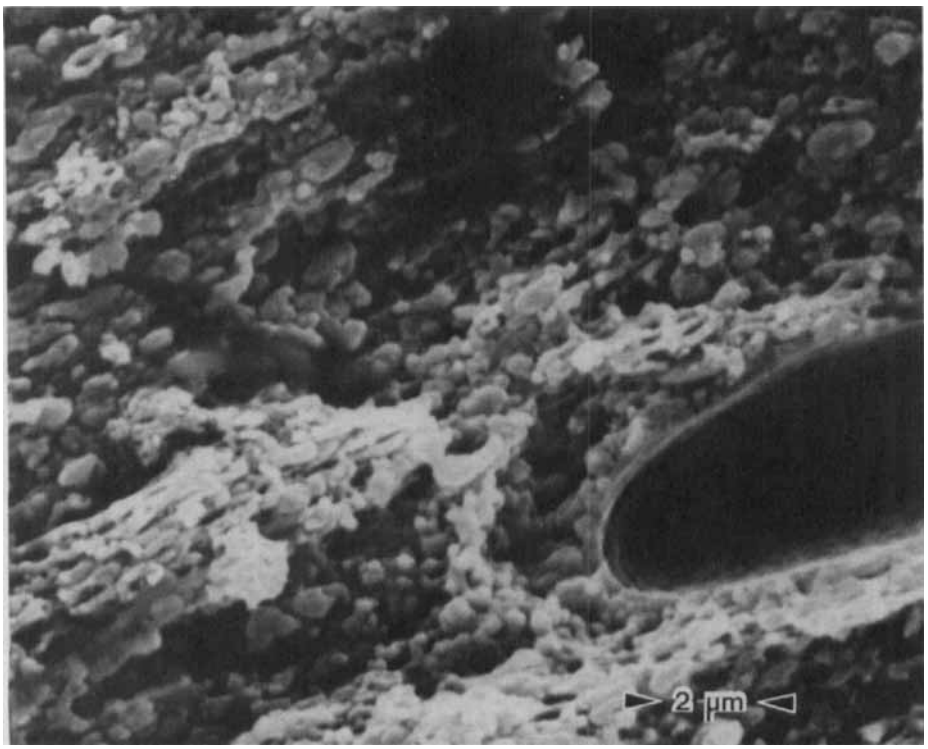

FIGURE 4

Scanning electron micrograph showing in cross section the EC:HPMC film deposited on the ASA core. The film was examined just prior to packaging the tablets for the stability study.

unexpected in view of the disintegration behavior of peeled ASA tablets. Film surfaces of the samples before storage appeared smooth and featureless and remained so with time. Examination of the films in cross section, however, revealed a well defined film structure in the initial samples, i.e., the individual pseudolatex particles were easily discernible in the samples before storage, as shown in Figures 2 (microcrystalline cellulose core), 3 (sodium bicarbonate core), and 4 (ASA core) . Examination of the films deposited on the microcrystalline cellulose and sodium bicarbonate cores revealed little or no change in film structure after 18

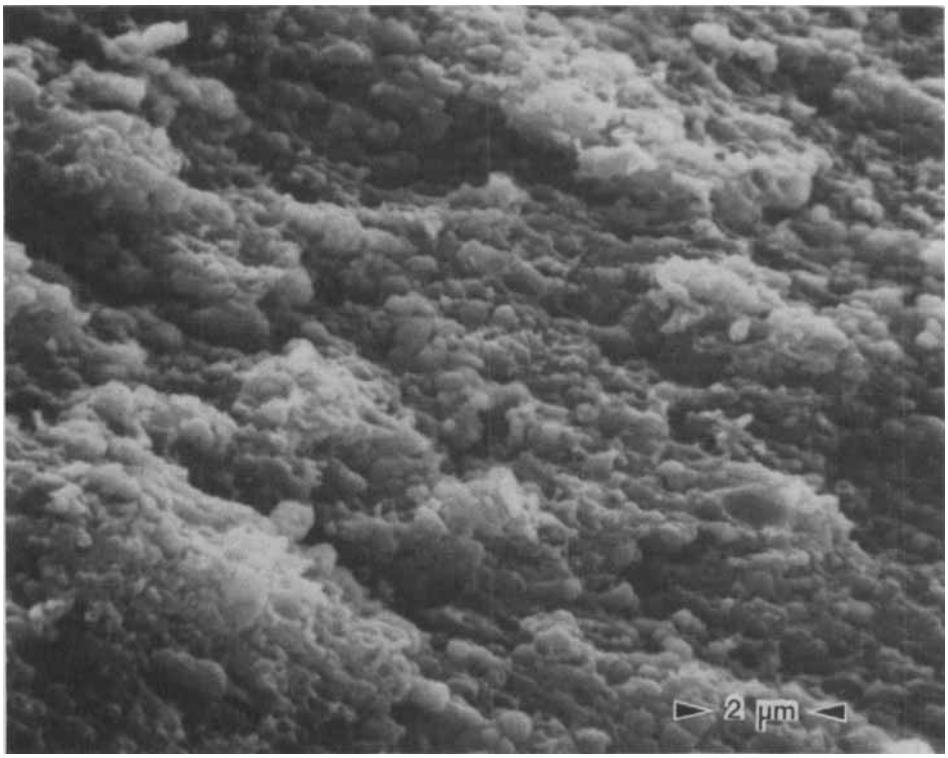

FIGURE 5

Scanning electron micrograph showing in cross section the EC:HPMC film, deposited on the microcrystalline cellulose core, after storage at 40°C for one year.

weeks and 36 weeks of storage at 40°C. Even after 1 year storage at 40°C the film structure appeared to be qualitatively the same as that observed initially,i.e., most particles seemed to retain their identity, as shown in Figures 5 and 6.

In contrast, when examining the cross sectional views of the EC:HPMC film deposited on the ASA cores, the pseudolatex particles which were initially discernible, appeared to undergo coalescence upon storage. Qualitatively, the phenomenon is both time and temperature dependent, as illustrated by Figures 7, 8, 9 and 10.

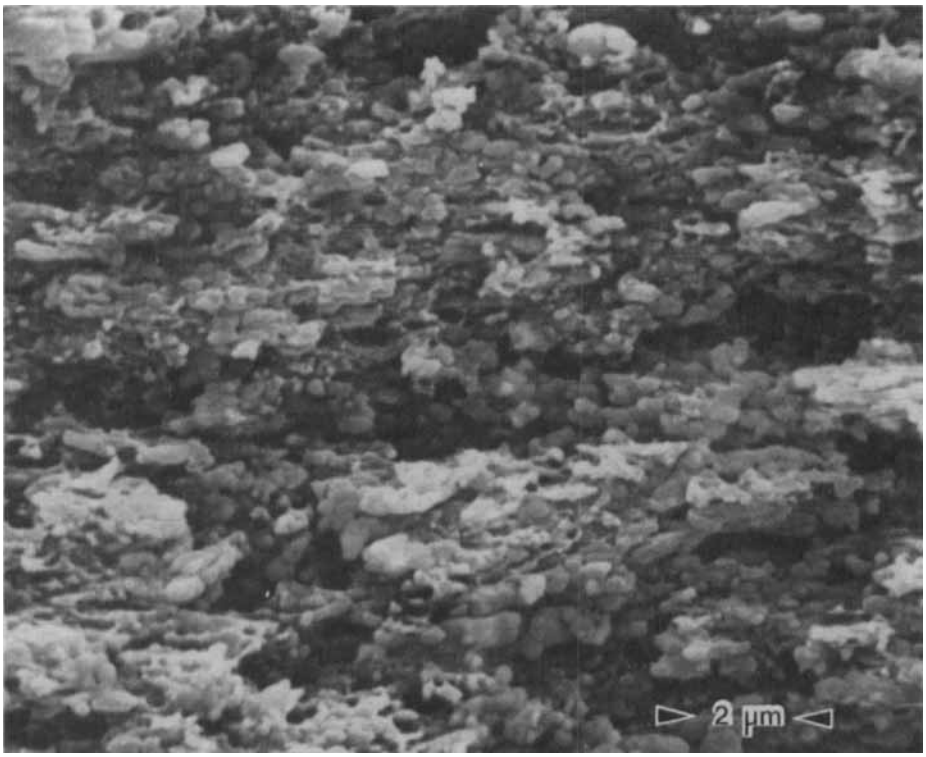

FIGURE 6

Scanning electron micrograph showing in cross section the EC:HPMC film, deposited on the sodium bicarbonate core, after storage at 40°C for one year.

Figures 7, 8 and 9 show cross sectional views of the EC:HPMC film deposited on the ASA cores and stored at 40°C for 18 weeks, 36 weeks and 1 year, respectively. These figures clearly indicate a slow, dynamic change in film structure with time. Figure 10 is a cross sectional view of the film after 36 weeks storage at room temperature. Here, although some coalescence occurred, the individual particles are still easily recognizable, particularly in comparison with the sample stored at 40°C for the same length of time (Fig. 8). The coalescence shown in Figures 7, 8 and 9

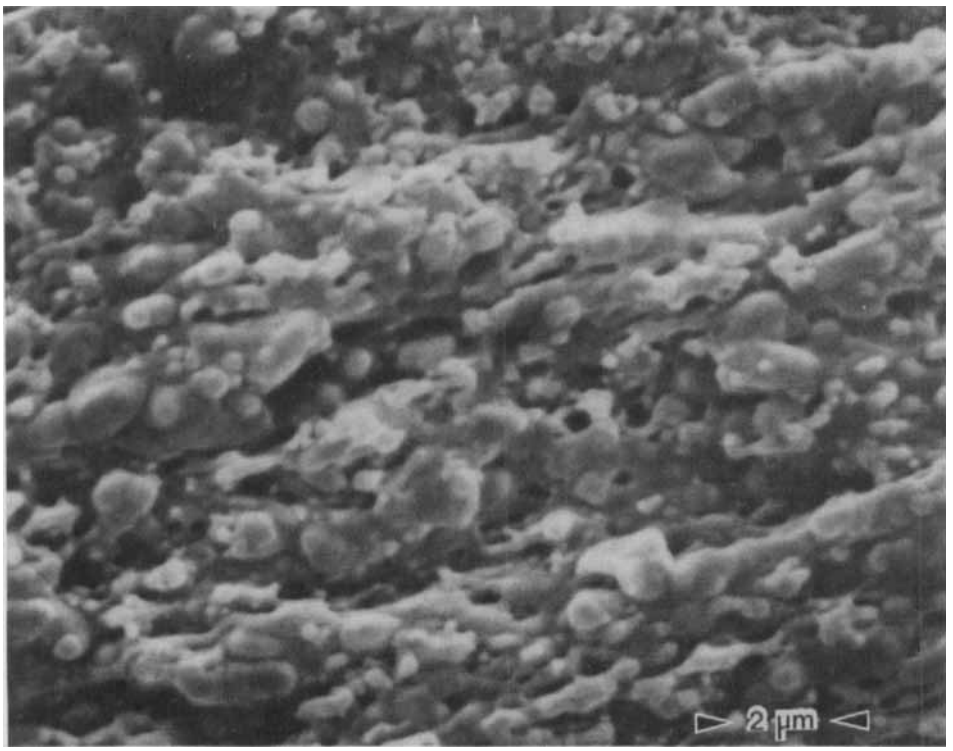

FIGURE 7

Scanning electron micrograph showing in cross section the EC:HPMC film, deposited on the ASA core, after storage at 40°C for 18 weeks.

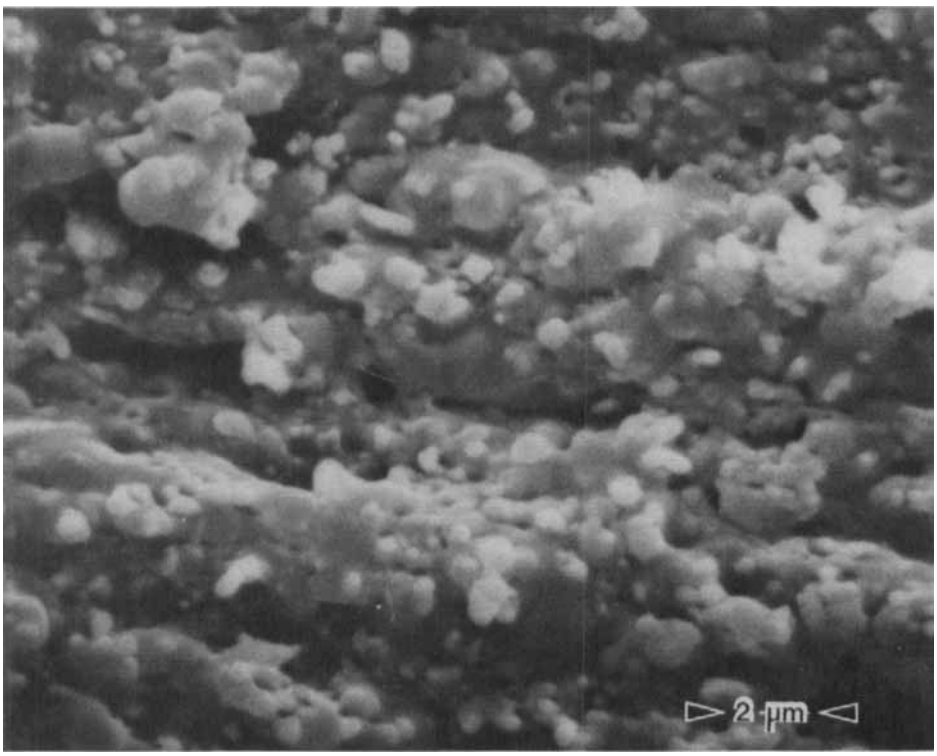

FIGURE 8

Scanning electron micrograph showing in cross section the EC:HPMC film, deposited on the ASA core, after storage at 40°C for 36 weeks.

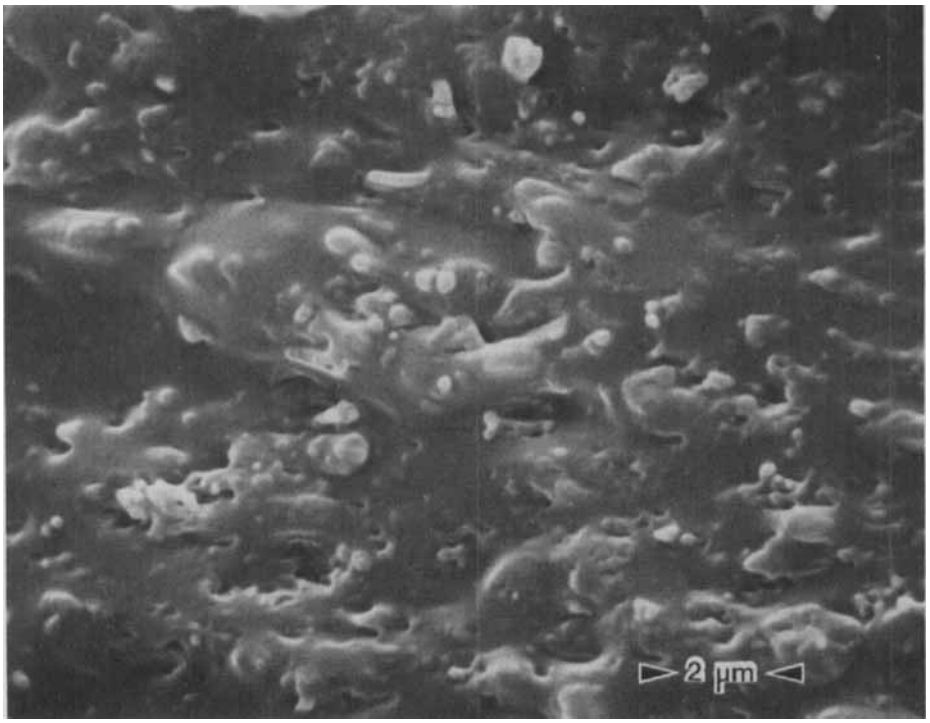

FIGURE 9

Scanning electron micrograph showing in cross section the EC:HPMC film, deposited on the ASA core, after storage at 40°C for one year.

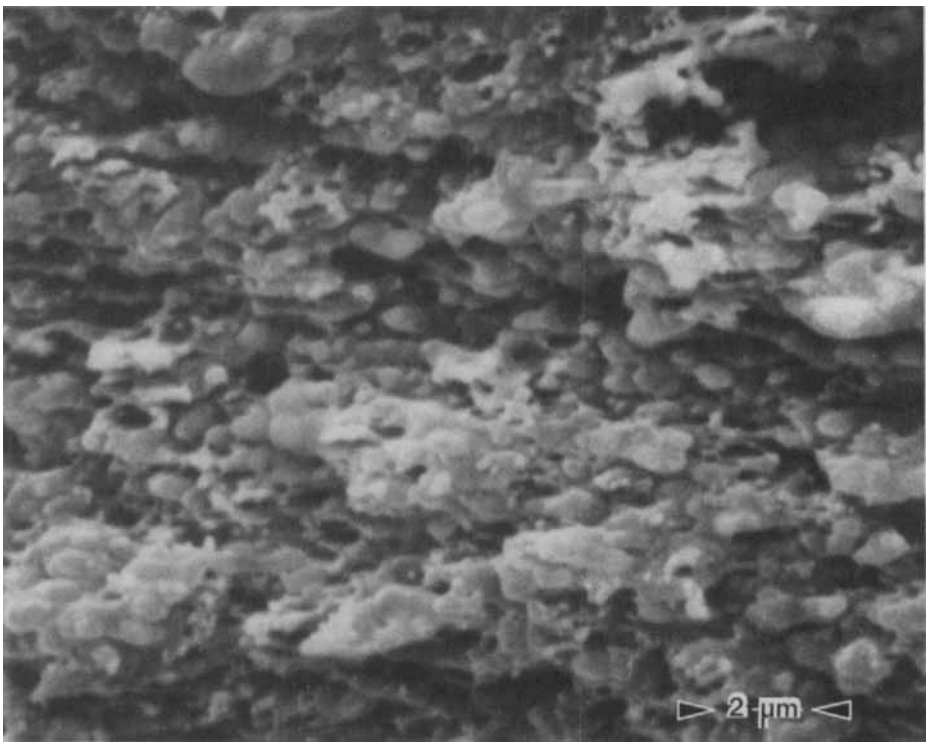

FIGURE 10

Scanning electron micrograph showing in cross section the EC:HPMC film, deposited on the ASA core, after storage at room temperature for 36 weeks.

corresponds with the marked increases observed in disintegration times of these samples relative to their initial values.

The mechanism responsible for the changes in film solubility is presently under investigation. Preliminary results suggest a substrate related change in the disintegration behavior of tablets coated with EC:HPMC films, a phenomenon hitherto unreported in the scientific literature. It must be noted, however, that no direct correlation was observed between increases in disintegration values of the ASA tablets and decomposition of the drug during storage.

ACKNOWLEDGEMENT

The authors thank Dr. M. Vallee for his statistical analysis of the disintegration data and Mr. P. Lamarche for the determination of moisture contents of the tablets.

FOOTNOTES

1. Patterson - Kelley Co. Inc., East Stroudsberg, PA
2. Anachemia Ltd., Lachine, Quebec, Canada
3. Plasdone K 29-32, Domtar Inc.,Montreal, Quebec, Canada
4. Avicel PH-101, FMC Corp., Dorval, Quebec, Canada
5. Monsanto Ltd., Ruabon, U.K.
6. St. Lawrence Starch, Montreal, Quebec, Canada
7. Witco Chemical Co., Montreal, Quebec, Canada
8. Pennwalt Corp., Stokes Div., Warminster, PA
9. Methocel E-15 Premium, Chemroy Ltd., Montreal, Quebec, Canada
10. Aquacoat, FMC Corp., Dorval, Quebec, Canada
11. Union Camp, Chemical Products Division, Jacksonville, FL
12. N.T. Gates "2 in 1" Combination Packets, Ampak Ltd., Dorval, Quebec.
13. Polaron E 5100, J.B. EM Services Inc., Montreal, Quebec,Canada
14. ISI-40, Radionics Ltd., Montreal, Quebec, Canada

REFERENCES

1) G. S. Banker, U.S. Patent 4330338, 1982.

2) G. S. Banker and G. E. Peck, Pharm. Technol., 5, 54 (1981).

3) J. F. Pickard, P. H. Elworthy, and H. Sucker, J. Pharm. Pharmacol., 28, 20P (1976).

4) K. Saarmivaara and P. Kahela, presented at the 4th Pharmaceutical Technology Conference, Edinburgh, Scotland, April 1984.

5) E. B. Vadas, G. R. B. Down, and R. A. Miller, J. Pharm. Sci. In press.