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RESEARCH PAPER

Studies Comparing Kollicoat MAE 30 D with Commercial Cellulose Derivatives for Enteric Coating on Caffeine Cores

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ABSTRACT

The products that are processed in aqueous form, such as Aqoat MF (suspension), Aquateric (pseudolatex), HP 55 (ammonia-based solution), and Kollicoat MAE 30 D (latex), were compared (in the form of spray dispersions, isolated films prepared from the dispersions, and caffeine–film-coated tablets with 5.5, 8.0, and 11.0 mg film/cm^2) with one another and with ethanolic HP 55 S solution. The addition of pigments to all of the liquid preparations, with the exception of the ammoniacal solution of HP 55, led to a slight increase in pH. In each case, the viscosity of both solutions was well above that of the other formulations. The minimum film-forming temperature was decidedly reduced by the addition of pigment. Kollicoat MAE was the undissolved film-former that had the smallest particle size and particle size distribution. The next smallest were those of Aqoat MF. The latex and the suspension were the only products that were sensitive to shear and heat. The isolated films did not display any tack. The strongest films and the films most impermeable to water vapor were obtained from solutions, and this can be ascribed to the fine distribution of the film-former. None of the isolated films showed signs of dissolving at pH 4.5. At pH 5.5, only the HP 55 was dissolved. This was because HP 55 was processed in ammonia-based solution; as a result of which, films that were not very resistant to gastric juice were obtained. The other formulations did not dissolve until the pH reached 6.0. As the pH rose, the rate of dissolution increased for all of the films. The permeability to protons was similar to that of caffeine–film-coated tablets to gastric juice. The resistance increased in the following sequence: HP 55 (ammonia-based) < Aquateric < Aqoat MF < HP 55 S (organic) and Kollicoat MAE.

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As a result of the temperature treatment and the rate of spraying, the production time on a 5-kg scale was twice as long for 5.5 mg Aqoat MF/cm² as it was for Kollicoat MAE. This amount of film sufficed for Kollicoat MAE and HP 55 S solution to achieve adequate resistance to gastric juice. Aqoat MF did not attain the same resistance until a thickness of 11 mg film/cm² was reached. Film tablets with Aquateric and ammonia-based HP 55 solution absorbed more than 20% of gastric juice at this film thickness.

INTRODUCTION

In the production of enteric film coatings, efforts have been made to replace organic solvents by water for ecological reasons (1). The film dispersions that are offered for processing in water can be divided into two categories. (*a*) Formulations of film-formers that were originally intended for processing in organic media and are now used as pseudolatices (2) or as ammonium salts (3). (*b*) Formulations whose film-formers have been specially developed for use in aqueous media. They are supplied as latices (4) or suspensions (5).

Kollicoat MAE 30 D (6) is a copolymer produced from a 1:1 ratio of methacrylic acid and ethyl acrylate and has recently appeared as a latex on the market.

In the present study, Kollicoat MAE 30 D was compared in each case with a known product of the other processing variants including an organic film solution. The individual film dispersions and isolated films, and film-coated tablets produced from them, were investigated. The following products were selected for comparison. Aqoat MF (7), hydroxypropylmethylcellulose acetate succinate, was chosen as an aqueous suspension. Aquateric (8) is a cellulose acetate phthalate processed to a pseudolatex. Hydroxypropylmethylcellulose phthalate, first dissolved as an ammonium salt (9) and then processed as an alcohol solution, was also used.

EXPERIMENTAL

Materials

The following materials were used: hydroxypropylmethylcellulose acetate succinate, Aqoat MF (Shin-Etsu Chemical Ltd., Tokyo, Japan); hydroxypropylmethylcellulose phthalate, HP 55 or HP-55 S (Eastman Chemical, Kingsport, TN or Shin-Etsu Chemical Ltd.); cellulose acetate phthalate in Aquateric aqueous enteric coating (FMC Corp., Philadelphia, PA); ethyl acrylate/methacrylic acid copolymer 1:1, Kollicoat MAE 30 D (BASF AG, Ludwigshafen, Germany); Kollidon 30 and Kollidon CL (BASF AG); sodium lauryl sulfate (Riedel de Haen, Seelze, Germany); Sicovit Red 30 (BASF AG); talc (Riedel de Haen); titanium dioxide RN 56 (Kronos Titan GmbH, Leverkusen, Germany); triacetin (Fluka Chemie AG, Buchs, Switzerland); triethyl citrate (Merck-Schuchardt, Hohenbrunn, Germany); Tween 80 (ICI Specialty Chemicals, Essen, Germany); anhydrous caffeine (Knoll AG, Ludwigshafen, Germany); Ludipress (BASF AG); Avicel PH 101 (FMC Corp.); and magnesium stearate DAB 10 (Chem. Werke Otto Bärlocher, Munich, Germany). All other substances and solvents were of analytical purity.

Apparatus

The following apparatus were used: Accela Cota 24 in. tablet coater (Manesty Machines Ltd., Liverpool, UK); Diosna Mixer V 50 (Dierks & Söhne Maschinenfabrik, Osnabrück, Germany); MDG 24 pressure vessel with electric stirrer (Richard C. Walther GmbH & Co. KG., Wuppertal-Vohwinkel, Germany); Hygroscope M1 (Rotronic AG, Basserdorf, Switzerland); model 509/3 film applicator with temperature controller (Erichsen GmbH & Co. KG, Hemer, Sundwig, Germany); PTWS dissolution tester (Pharmatest Apparatebau GmbH, Hainburg, Germany); HC 2020 air-conditioned cupboard (Heraeus-Vötsch GmbH, Balingen, Germany); O112 MS corundum disk mill (Fryma, Rheinfelden, Germany); falling-sphere viscometer (Haake, Karlsruhe, Germany); MR 2002 magnetic stirrer (Heidolph Elektro GmbH & Co. KG, Kehlheim, Germany); MSX 14 Series 237 particle sizer (Malvern Instruments Ltd., Worcestershire, UK); Permatran W 600 (Mocon, Minneapolis, MI); N 6180 pH electrode (Schott, Mainz, Germany); Series 7XX pH meter (Knick Elektronische Messgeräte GmbH & Co., Berlin, Germany); 8452 A spectrophotometer (Hewlett Packard, Waldbronn, Germany); Accela Cota model Pilot WAXV spray gun (Richard C. Walther GmbH & Co.); manual model Pilot XIII spray gun (Richard C. Walther GmbH & Co.); Type TAR-20 tablet wear and friability tester (Erweka, Heusenstamm, Germany); RL 15 tablet press (Kilian & Co. GmbH, Cologne, Germany); HT-TMB-CI-12 F tablet tester (Kraemer Elektronik GmbH, Darmstadt, Germany); Transsonic 780/H Elma ultrasonic bath (Labotec,

Table 1

Composition of the Spray Dispersions (% wt)

Ingredients	Aquateric (8)	Kollicoat (6)	HP 55 (9)	HP-55 S	Aqoat (7)
Ammonia (30%)			1.80		
Ethanol				79.19	
Kollidon 30		0.50			
Sodium lauryl sulfate					0.21
Sicovit	0.26	0.50	0.33	0.17	0.24
Talc		2.00	2.50	1.50	2.10
Titanium dioxide	0.26	0.50	0.33	0.17	0.24
Triacetin	3.35		1.00		
Triethyl citrate		1.50			1.96
Tween 80	0.10				
Water	84.99	80.00	84.34	13.97	88.25
Film-former	11.04[a]	15.00	9.70	5.00	7.00
Solids content	15.00	20.00	13.86	6.84	11.75

[a]Aquateric contains 70% cellulose acetate phthalate (CAP).

Wiesbaden, Germany); and DES-4AS disintegration tester (Kraemer Elektronik GmbH).

Composition of formulations is described in Tables 1 and 2.

Production of the Spray Dispersions

The components of the pigment suspension (titanium dioxide, Sicovit, and when applicable, talc) were stirred into part of the water, and homogenized in the corundum disk mill.

Aqoat MF Dispersion (7)

Triethyl citrate was dissolved in water at 10–15°C, and sodium lauryl sulfate and Aqoat MF were incorporated with intensive stirring. Subsequently, the pigment suspension was included in the mixture.

Table 2

Composition of Caffeine Cores

Ingredients	mg	% wt
Caffeine, anhydrous	50	15.15
Ludipress	229	69.40
Avicel PH 101	40	12.12
Kollidon CL	10	3.03
Magnesium stearate	1	0.30
Total	330	100

Aquateric Dispersion (8)

Triacetin and Tween 80 were dispersed in part of the water, and the film-former was subsequently incorporated. The mixture was stirred for 60–90 min at room temperature, then the pigment suspension was added, stirred, and diluted with water to a solids content of 15%.

Ammonia-Based HP 55 Solution (9)

Triacetin was dissolved in water. Afterward, the HP 55 was stirred in, and ammonia added. The pigment suspension was added to the clear solution.

Alcohol HP 55 S Solution

HP 55 S was suspended in ethanol and water was added. After the film-former had dissolved, the pigment suspension was stirred in.

Kollicoat MAE 30 D Dispersion (6)

Triethyl citrate was dissolved in water, and the dispersion was stirred in. The pigment suspension was incorporated with the lacquer suspension.

The prepared spray dispersion was passed through a screen of 80-μm mesh.

Apart from the formulations for the individual films, some formulations without pigments were prepared to investigate the spray dispersions.

Preparation of Isolated Films

Isolated films were prepared by spraying the spray suspensions containing pigment onto the heated plate of the film applicator. The films were subjected to a heat treatment in an oven at the corresponding temperature.

Preparation of the Caffeine Cores

Three lots of 30 kg each were prepared. To this purpose, the ingredients of the formulation were mixed for 3 min in Stage 1 of the Diosna mixer without the chopper and compressed with a force of 10 kN at a rate of 40,000 tablets/hr into cores of the following description: 9-mm diameter, 12-mm radius of curvature, 330-mg weight, and with the engraving "BASF" on the one side.

Preparation of Enteric Film-Coated Tablets

In each case, the spray dispersions were continuously applied by the spray gun from the pressure tank onto 5 kg of prewarmed cores in the Accela Cota tablet coater (Table 3). All of the samples, including those taken after given periods of time, were subsequently dried for 5 min each. The following process parameters were continuously measured and documented: the inlet air, outlet air, and tablet-bed temperatures; inlet and outlet air humidities; the inlet and outlet air flow rates; the dispersion consumption; and the pressure difference between the inlet and the outlet air.

Examination of the Spray Dispersions

pH values were measured with a pH meter. Viscosity was measured with the falling-sphere viscometer at 25°C. Minimum film-forming temperature was determined according to DIN 53787.

Glass Transition Temperature

The dispersion was cast in a 10 × 10 cm Teflon dish and subsequently dried for 24 hr at 80°C. The glass transition temperature was determined by differential thermal analysis.

Particle Size Distribution

The sample was fed into the particle size analyzer by hand or through the on-line feed line for the wet dispersion, which was kept homogeneous by stirring and ultrasonic devices. The following equation was used for particle size distribution calculations:

$$\text{span} = \frac{\alpha(0.9) - \alpha(0.1)}{\alpha(0.5)}$$

Coagulation Under Shear and Heat

An amount of 800 g of dispersion was brought to a temperature of 45°C in the release device and stirred with the paddle for 1 hr at 250 rpm. The residue on a sieve of 80-μm mesh was dried for 24 hr at 80°C and expressed as a percentage of the dispersion.

Wetting Angle

Wetting angle was determined on specially prepared biplanar caffeine tablets of two different hardnesses by a method described by André and Zosel (10). The average of three measurements was taken in each case.

Examination of the Isolated Films

Tack (11) was determined in the following manner. The isolated film was secured by adhesive tape to the edges of a 6.5 × 20 cm prepared glass panel, which was then allowed to stand overnight in an air-conditioned chamber at 20°C and 80% relative humidity (RH). After-

Table 3

Process Parameters in Coating and Subsequent Treatment

Process Parameter	Aquateric (8)	Kollicoat (6)	HP 55 (9)	HP-55 S	Aqoat (7)
Air inlet temperature (°C)	78	50	70	60	70
Product temperature (°C)	32–33	35–38	>32	36	33–35
Rate of spraying (g/min)	60	30	30	60	40
Drying schedule			5 min at 50°C		
Heat treatment (min/°C)	60/60		No heat treatment		30/60

ward, the glass panel was positioned about 5 mm below a plastic–carbon tape that, for the purposes of the test, was then pressed with a round rubber punch (400 mm diameter) onto the polymer film. The force of 250 N was applied for 10 sec. The printing ink on the carbon tape adhered to the polymer film to an extent related to the tack of the surface (which was assessed on a scale of five ratings ranging from no tack to very tacky).

Elongation at break, tensile strength, and tensile strength at break were determined according to DIN 53504.

Rate of film dissolution at pH 6.8 was determined in 500 ml of a buffer solution (USP 23) by stirring with the paddle in the release device at 37°C. Speed of stirring was 75 rpm and size of specimen was 2 × 2 cm. The average of three measurements was taken in each case. Rate of film dissolution = weight of film/(area of film × time required for dissolving).

Rate of film dissolution and pH were determined with DAB 1996 buffer solution at pH 4.5, 5.5, 6.0, and 6.6 and with demineralized water.

Permeability to water vapor (12) studies were performed with Permatran using a saturated lithium chloride solution and an aluminium mask at 23°C/12% RH.

Permeability to acids was determined using an apparatus that consisted of two glass angle pieces, each of which had an opening at the top to accommodate the electrodes. The circular openings at the side were jointly closed by a piece of film that was first swollen for 1 hr in 0.1 N hydrochloric acid (3), and then rinsed in water.

Examination of the Cores

Weight, height, diameter, and hardness were determined on 20 cores in the tablet tester. Friability was determined according to DAB 1996. Content was determined in each case at 273 nm by spectrophotometer on 10 individual cores. Disintegration time was determined in 0.1 N hydrochloric acid or buffer solution with a pH of 6.8 in accordance with USP 23.

Dissolution rate was determined according to USP 23, with Apparatus II, Method B in 0.1 N hydrochloric acid and in buffer solution with a pH of 6.8. Samples were taken after 2, 4, 6, 8, 10, and 12 min. Caffeine was determined by spectrophotometer at 273 nm.

Examination of Film-Coated Tablets

Weight, height, diameter, and hardness were determined as described for examination of cores. Increase in weight during the resistance test was determined in each case with six film tablets after 1 or 2 hr in 0.1 N hydrochloric acid. Resistance to gastric juice and disintegration time was determined according to USP 23.

Dissolution rate was determined according to USP 23. During the test for resistance, samples were taken after 30, 60, 90, and 120 min; after rebuffering, samples are taken at 5-min intervals. The samples were subjected to spectrophotometric determination at 273 nm.

RESULTS AND DISCUSSION

Composition and Production of the Spray Dispersions

To effect a comparison under conditions that closely simulate those in practice, the individual formulations and their process parameters were taken from the manufacturers' leaflets. If more than one variation of a formulation existed, the one that was the most similar to the Kollicoat MAE 30 D formulation was selected. The mixture of pigments and its fraction, expressed in terms of the film-former, was the same in all of the spray dispersions, and the fraction was comparatively low. Thus, any likely effect of the pigment phase on the permeability of the film (13) was kept to a minimum. No problems were encountered in incorporating the individual ingredients in all of the formulations. Conversely, the times required for production of the ingredients differed. Thus, Aquateric had to be stirred for 60–90 min after the film-former was dispersed. Another 15 min of stirring was prescribed after the pigment dispersion was added (8).

After the ammonia was added, HP 55 required 30–60 min for complete solution of the polymer. The same applied to HP 55 S after the water was added.

The only dispersions that were ready for use immediately after the film-former was dispersed and the pigment suspension was incorporated were those of Aqoat MF and Kollicoat MAE 30 D.

Caffeine Cores

Caffeine was selected as the active substance, because no pH-dependent interactions with the film-former were expected from it (14). In addition, its ready solubility in water allowed a pronounced escape of active substance to be anticipated if the film leaked during the test for resistance to gastric juice.

The results of the investigations on the caffeine cores are summarized in Table 4. Very good agreement was reached between the parameters measured in all three batches of cores. This is an important prerequisite for the

Table 4

Results of the Caffeine Core Examination

Batch		Weight (mg)	Height (mm)	Hardness (N)	Content (%)	Disintegration Time (sec) 0.1 N HCl/Buffer
1	n	20	20	20	10	6
	Φ	330	4.79	131	103	102/105
	S_{rel}	0.9	0.7	8.8	1.84	3.04/17.85
2	n	20	20	20	10	6
	Φ	327	4.76	128	97.81	103/82
	S_{rel}	0.6	0.8	8.1	2.63	15.17/32.05
3	n	20	20	20	10	6
	Φ	329.5	4.70	171	99.26	105/110
	S_{rel}	1.4	0.6	6.5	3.14	2.69/4.08

Φ: Mean value; S_{rel}: relative standard deviation.

subsequent comparison of the various film tablets. In view of the great hardness and the immeasurable friability, core isolation could be dispensed with.

The indifference of caffeine toward pH was revealed by the disintegration time and the dissolution rate. There was no significant difference between 0.1 N hydrochloric acid and the buffer solution of pH 6.8.

Production and Appearance of Enteric Film-Coated Tablets

The different process times in production are notable. As is summarized in Table 5, they can be ascribed to differences in the time required for spraying or to the difference in heat treatment in some cases. Accordingly, Aquateric required the longest production time (85 min) and Kollicoat required the shortest production time (35 min).

If, in addition, allowance was made for the difference in coat weights required until the maximum resistance to gastric juice was reached (11.0 mg/cm^2 for HP 55, Aquateric, and Aqoat MF, and 5.5 mg/cm^2 each for Kollicoat MAE 30 D and HP 55 S), the difference in preparation times was even more pronounced (see Table 5a). The difference in preparation times extended from 35 min for Kollicoat MAE 30 D to 123 min for Aquateric. No allowance was made for the difference in production times for the spray dispersions. In general, powders, such as HP 55 S, HP 55, Aquateric, and Aqoat MF, exact greater time and labor than do aqueous dispersions, such as Kollicoat MAE 30 D. All of the formulations, with the exception of those based on Aquateric, yielded uniformly smooth coatings. Decided irregularities were recognized in the films obtained from Aquateric. Reproduction of the engraving was poor or hardly recognizable if the film thickness was increased.

Examination of the Spray Dispersions

The pH values of the spray dispersions with and without pigments are listed in Table 6. The addition of pigments lead to an increase in pH in all cases except for

Table 5

Times Required for the Production of the Enteric-Coated Film Tablets Made by 5-kg Cores with a Coat Weight of 5.5 mg/cm^2 According to Tables 1–3

	Spraying Time (min)	Drying Time (min)	Heat Treatment Time (min)	Production Time (min)
Kollicoat MAE	30	5	–	35
HP 55	43	5	–	48
HP 55 S	44	5	–	49
Aqoat MF	39	5	30	74
Aquateric	20	5	60	85

Table 5a

Times Required to Produce the Film Tablets Up to the Point of Maximum Resistance to Gastric Juice or to a Coat Weight of 11.0 mg/cm² According to Tables 1–3

	Spraying Time (min)	Drying Time (min)	Heat Treatment Time (min)	Production Time (min)
Kollicoat MAE	30	5	–	35
HP 55	86	5	–	91
HP 55 S	44	5	–	49
Aqoat MF	78	5	30	113
Aquateric	40	5	60	123

Table 6

pH Values of the Pigmented and Unpigmented Spray Dispersions

	Unpigmented	Pigmented
Aqoat MF (7)	3.76	4.44
Aquateric (8)	2.53	2.72
HP 55 (9)	9.09	8.52
HP 55 S	3.62	4.01
Kollicoat MAE (6)	2.64	3.51

that of HP 55. The well known, large differences in the viscosity of pigment-free and pigmented spray dispersions that exist between dissolved and undissolved film-formers (15,16) are shown in Table 7. These differences cannot be explained by their solids content.

The fact that the viscosity of HP 55 was somewhat higher than that of HP 55 S, although the solids content was inversely related, is explained by the dissociation of the ammonium salt and the associated interaction between the film-former molecules (16). Because all of the preparations can be readily sprayed, the higher values of viscosity shown by the solutions do not constitute a technical barrier. In fact, according to Stokes's law, high viscosity slows the pigment sedimentation.

The minimum film-forming temperature (MFT) and the plasticizer content of pigmented and unpigmented spray dispersions, with the exception of the lacquer solutions, are listed in Table 8. In all three formulations, the addition of pigment lead to a decided decrease in MFT. As a result, lower product temperatures combined with higher application rates were feasible during coating. The glass transition temperatures, T_g (Table 9), in the individual formulations reacted differently to the addition of pigment: the T_g of the Aquateric and HP-55 S formulations increased and the T_g of the other formulations decreased. The maximum particle size distribution, which was determined from the unpigmented film dispersions (Table 10), increased quite definitely in the direction from Kollicoat MAE 30 D through Aqoat MF to Aquateric. This allowed differences in the uniformity of the films and thus their resistance was to be expected. In the test for coagulation under shear and heat, only the pigmented spray dispersions of Aqoat MF and Kollicoat MAE 30 D displayed decided coagulation of 14.7 and 19.3%, respectively. The

Table 7

Viscosity and Solids Content of the Pigmented and Unpigmented Spray Dispersions

	Viscosity (mPa·sec)/Solids Content (% wt)	
	Unpigmented	Pigmented
Aqoat MF (7)	2.01/8.96	2.50/11.75
Aquateric (8)	2.69/14.39	3.43/15.00
HP 55 (9)	45.58/10.70	67.03/13.86
HP 55 S	40.00/5.00	51.37/6.84
Kollicoat MAE (6)	1.51/15.00	2.07/20.00

Table 8

Minimum Film-Forming Temperatures (MFT) and Plasticizer Contents (PC) of Pigmented and Unpigmented Spray Dispersions

	MFT (°C)/PC (% solids)	
	Unpigmented	Pigmented
Aqoat MF (7)	35/28.0	7/28.0
Aquateric (8)	>52/43.3	36/43.3
Kollicoat MAE (6)	27/10.0	12/10.0

Table 9

Glass Transition Temperatures of the Pigmented and Unpigmented Spray Dispersions

	Glass Transition Temperature (°C)	
	Unpigmented	Pigmented
Aqoat MF (7)	117	55
Aquateric (8)	48	56
HP 55 (9)	68	57
HP 55 S	102	115
Kollicoat MAE (6)	116	96

Table 10

Particle Size Distribution of the Unpigmented Spray Dispersions

	Particle Size (μm)	
	Span	Mean Diameter D[4/3]
Aqoat MF (7)	1.69	7.07
Aquateric (8)	1.58	20.33
Kollicoat MAE (6)	1.20	0.32

necessity of limiting the upper stirring intensity and processing temperature of these two dispersions follows from this.

When caffeine cores of different hardness were used or pigment suspensions were added, no trend in the wetting angle was recognized (Table 11). However, a relationship can be assumed between the wetting angle and the viscosity of HP 55 and HP 55 S.

Examination of the Free Films

Owing to the method of preparation, the films had a smooth and a not smooth side. The test for tack was performed on both sides in each case. Tack was not observed in any of the films.

The tests for the mechanical strength comprised that for the elongation at break, the tensile strength at break, and the tensile strength (Table 12). In this case, the tensile strength at break was identical to the tear strength according to DIN 53504. The films with the highest tensile strength were those obtained from the solutions of HP 55 and HP 55 S.

This can be explained by the high degree of dispersion of these two dispersions, so that the best possible condi-

Table 11

Wetting Angle of Pigmented and Unpigmented Spray Dispersions on Caffeine Cores of Two Different Hardnesses Measured After 0.1 sec

	Unpigmented Hard/Soft Caffeine Cores	Pigmented Hard/Soft Caffeine Cores
Aqoat MF (7)	28.8/37.0	28.0/26.4
Aquateric (8)	38.1/43.4	39.0/39.7
HP 55 (9)	54.7/63.3	65.0/66.3
HP 55 S	47.2/40.7	53.2/37.5
Kollicoat MAE (6)	39.5/25.3	26.2/53.7

tions exist for the formation of bonds between the individual molecules of the polymer. The values for the ultimate elongation of the nonsolutions increased in the direction from Kollicoat MAE 30 D through Aqoat MF to Aquateric. This can also be ascribed to the fact that the plasticizer content of these formulations increased (cf. Table 8) in the same direction (17,18).

In the determination of the film dissolution rate none of the films showed signs of dissolving when the pH was 4.5. In the pH 5.5 buffer, HP 55 dissolved after 12 min. The other films displayed no signs of dissolving even after 3 hr. The rates of solution of the individual films at pH values of 6.0, 6.6, and 6.8 are shown in Fig. 1. In all of the determinations, rate of solution of HP 55 was well ahead of the others. It was followed by Aqoat MF, Aquateric, Kollicoat MAE 30 D, and finally, HP 55 S. As the pH increased, the rate of film dissolution increased. This

Table 12

Tensile Strength and Elongation at Break of Pigmented Free Films

		Tensile Strength (N/mm^2)	Elongation at Break (%)
Aqoat MF	Φ	8.97	2.00
	S_{rel}	13.78	19.74
Aquateric	Φ	11.28	5.31
	S_{rel}	7.23	8.53
HP 55	Φ	48.15	2.98
	S_{rel}	10.71	9.57
HP 55 S	Φ	24.50	2.81
	S_{rel}	26.31	10.79
Kollicoat MAE	Φ	11.77	1.28
	S_{rel}	75.75	57.56

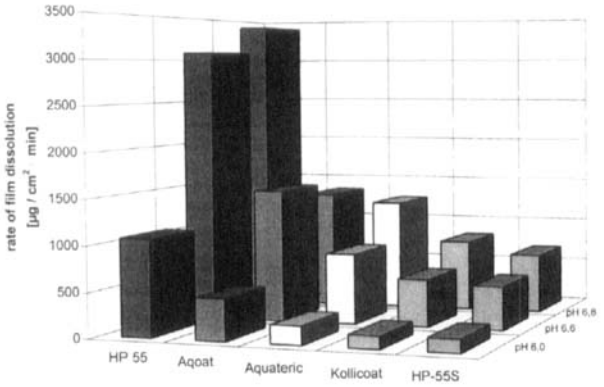

Figure 1. Isothermal rate of solution of the isolated films at pH 6.0, 6.6, and 6.8.

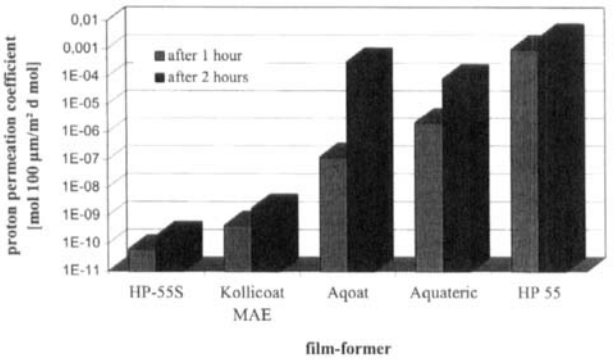

Figure 2. Proton permeabilty through isolated films.

is explained by the increasing speed of proton transfer, which leads to dissociation and dissolving of the polymers, and obeys Brönstedt's law of catalysis (12). The high rate at which HP 55 dissolved can probably be ascribed to the ammonium ions present in the film (3). In unbuffered water, all films were resistant for more than 3 hr.

The results of the tests for permeability to water vapor are shown in Table 13. The lowest permeability was displayed by the two film solutions, probably for the same reason as that given for the tear strength. The fact that the permeability to water vapor of Kollicoat MAE 30 D was lower than that of Aqoat MF and Aquateric can be ascribed to the low particle size and narrow particle size distribution of Kollicoat MAE 30 D (cf. Table 10). In Fig. 2, there are decided differences in proton permeability between the individual films. This increased from HP 55 S through Kollicoat MAE 30 D, Aqoat MF, and Aquateric to HP 55, at which point it reached its highest value. The results of this model experiment are parallel to the increase in weight of enteric-coated film tablets during the resistance tests [cf. Figs. 3(a)–(c)]. However, because free films are swollen on both sides, they can be expected to have a somewhat higher proton permeability than that of film-coated tablets (19).

Table 13

Water Vapor Permeability of the Free Films

	Permeation Coefficient to Water Vapor [g 100 µm/m² d]
Aqoat MF	279
Aquateric	239
HP 55	54
HP 55 S	79
Kollicoat MAE	126

Examination of the Film-Coated Tablets

The relatively low standard deviations in the weight, height, and diameter of the various film-coated tablets permit the conclusion that the individual spray dispersions were well distributed on the caffeine cores. The individual film coatings proved to be of very different resistance during the tests for resistance to gastric juice. This is evident from the increase in weight of the film tablets treated with gastric juice [cf. Figs. 3(a)–(c)] and from the amounts of active substance given off to the gastric juice (cf. Figs. 4 and 5).

The latter must be added to the weight increases in Figs. 3(a)–(c). As the film thickness increased, the permeability in all of the formulations decreased. When the film thickness was 8.0 mg of film/cm², all of the samples were resistant to gastric juice in conformance with USP 23. Depending on the sensitivity of a core formulation toward gastric juice, a high permeability of a film causes degradation of the drug and may alter the bioavailability (20).

Kollicoat MAE 30 D was the aqueous film-former with by far the most impermeable coatings. This agrees with the results of other studies (21) and can be explained by the fact that cellulose derivatives are more permeable than ethyl acrylate methacrylate polymers because they are much more hydrophilic and their molecular arrangement is less dense (22). Kollicoat MAE 30 D has a smaller particle size and narrower particle size distribution than do Aquateric and Aqoat MF, the other two undissolved film-formers, and this probably also contributes

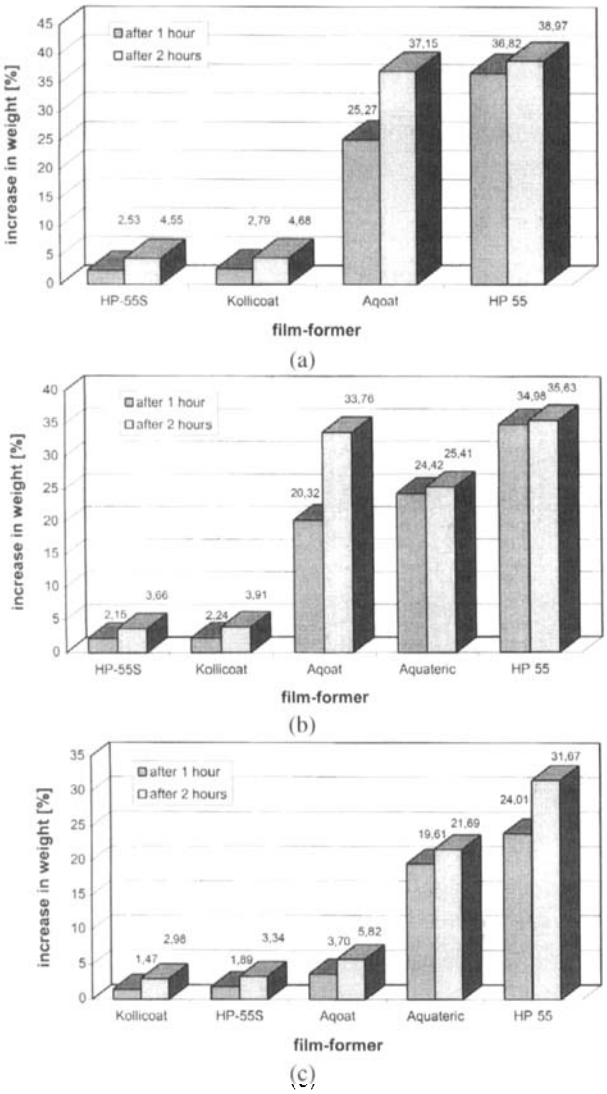

Figure 3. (a) Increase in weight of the film tablets with a coat weight of 5.5 mg/cm^2 after 1 or 2 hr, respectively, in artificial gastric juice. (b) Increase in weight of the film tablets with a coat weight of 8.0 mg/cm^2 after 1 or 2 hr, respectively, in artificial gastric juice. (c) Increase in weight of the film tablets with a coat weight of 11.0 mg/cm^2 after 1 or 2 hr, respectively, in artificial gastric juice.

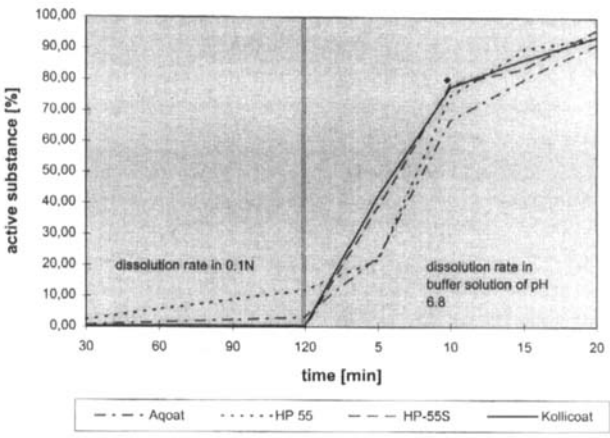

Figure 4. Dissolution rate of the film tablets with a coat weight of 5.5 mg/cm^2 in 0.1 N hydrochloric acid and buffer solution of pH 6.8.

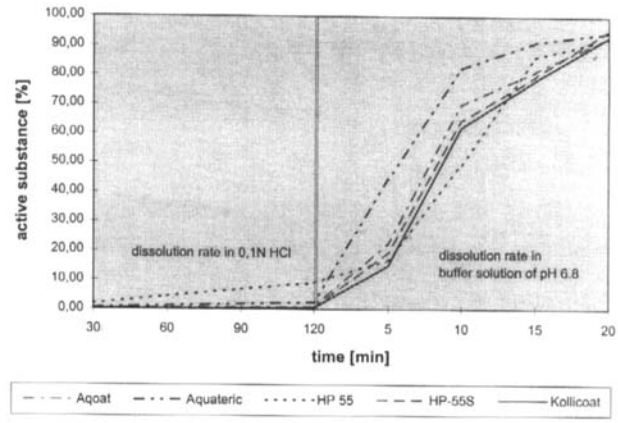

Figure 5. Dissolution rate of the film tablets with a coat weight of 8.0 mg/cm^2 in 0.1 N hydrochloric acid and buffer solution of pH 6.8.

to the lower permeability of the films derived from it. The most permeable film is that of HP 55. In the present study, the thickness of the film was built up to 11.0 mg of film/cm^2 before the USP 23 demands on the diffusion of active substance could be fulfilled. Because the HP 55 S film has the same good impermeability as that of the Kollicoat MAE 30 D film, the fact that HP 55 exhibits such high permeability must be ascribed primarily to the presence of ammonium ions. Aquateric's resistance to gastric juice, as determined by the release of caffeine to the gastric juice, does not commence until the thickness reaches 8.0 mg of film/cm^2.

No doubt, the irregular coating on the engraving, as well as the low proportion of film-former (cf. Table 1), was responsible for the comparatively large amount of film required in this case (23). Analogous differences in permeability were detected in studies involving a comparison between Eudragit L 30 D and Aquateric (17,21,24,25).

Tablets coated with film of the same thickness (Fig. 6) disintegrated in the same sequence as the rates of dissolu-

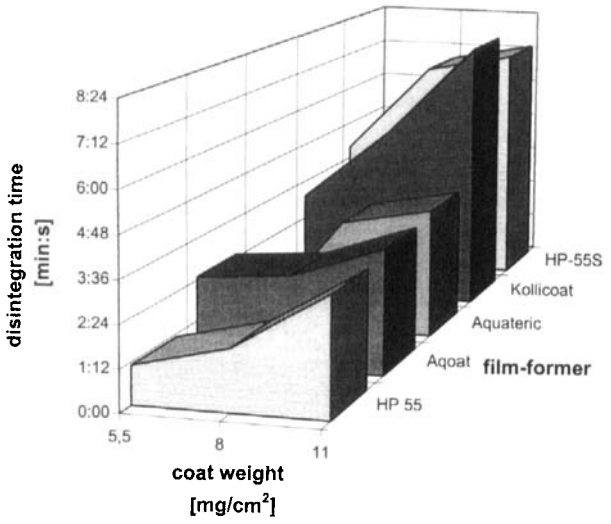

Figure 6. Comparison of the disintegration times, according to USP 23, of the film tablets with different coat weights.

tion of the corresponding free films (Fig. 1). Thus specific interactions between the coating and the core were of no significance. Film-coated tablets with HP 55 disintegrated the most rapidly; those with Kollicoat MAE 30 D or HP 55 S disintegrated the most slowly. However, if allowance is made for the film thickness required to achieve maximum resistance to gastric juice in the individual formulations (cf. Table 5), the difference in disintegration time becomes insignificant. All of the film-coated tablets released more than 90% of active substance after 20 min in a buffer solution of pH 6.8 (cf. Figs. 4 and 5) and thus conformed to USP 23. If resistance to gastric juice in the sense of the pharmacopeia is already achieved with 5.5 mg of film/cm^2, any further application of film slows the rate of release. This agrees with other studies (25).

CONCLUSION

Decided differences exist between Aqoat MF, Aquateric, HP 55, and Kollicoat MAE 30 D in the formulations recommended by the manufacturers of water-based enteric film coatings. Whereas Aquateric must be stirred for about 100 min in dispersion preparation, Aqoat MF and Kollicoat MAE are ready for spraying after they have been briefly mixed.

Kollicoat MAE 30 D requires only 5.5 mg of film/cm^2 to ensure adequate resistance to gastric juice; i.e., just as little as an HP 55 S film applied in organic media. The coat weight of Aqoat MF must be built up to 11.0 mg of film/cm^2 before the film attains the same resistance. Even at this coating weight, film-coated tablets with Aquateric and ammonia-based HP 55 still absorb more than 20% of gastric juice.

As a result of the heat treatment and the rate of spraying, the time required for the production on a 5-kg scale of 5.5 mg of Aqoat MF/cm^2 is twice as high as that for Kollicoat MAE 30 D. The production of film-coated tablets with Aqoat MF and Aquateric is three times longer than that with Kollicoat MAE 30 D, if the maximum resistance to gastric juice has to be attained.

REFERENCES

1. F. Gumowski, E. Doelker, and R. Gurny, Pharm. Technol., February 26 (1987).
2. G. S. Banker and G. E. Peck, Pharm. Technol., April, 54–61 (1981).
3. J. T. Heinämäki, A. Iraizoz Colarte, A. J. Nordström, and I. K. Yliruusi, Int. J. Pharm., 109, 9–16 (1994).
4. K. O. R. Lehmann, in *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms* (J. W. McGinity, ed.), Marcel Dekker, New York and Basel, 1989, pp. 153–245.
5. T. Nagai, F. Sekigawa, and N. Hoshi, in *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms* (J. W. McGinity, ed.), Marcel Dekker, New York and Basel, 1989, pp. 112–113.
6. Kollicoat MAE 30 D, Provisional Technical Information (MPM), File 9, Fine Chemicals, BASF, Ludwigshafen, Germany.
7. H. Kokubo, General Information on Shin-Etsu Aqoat, Aqoat Seminar, Darmstadt, Germany, 1995.
8. Aquateric Case History 2, FMC Corp., Philadelphia, PA, 1986.
9. Pharmaceutical Ingredients, Cellulosic Enteric Polymers, July 10–11, Eastman Fine Chemicals, Kingsport, TN, 1993.
10. V. André and A. Zosel, Ber. Bunsen-Ges. Phys. Chem., 98, 429–434 (1994).
11. P. Hössel, W. Schrepp, and R. Sander, International Federation Societies of Cosmetic Chemists, Between-Congress Conference, Montreux, Switzerland, 1995.
12. J. Spitael, R. Kinget, and K. Naessens, Pharm. Ind., 42(8), 846–849 (1980).
13. P. C. Schmidt and K. Teuber, Pharm. Unserer Zeit, 20(4), 171–172 (1991).
14. A. G. Eshra, Ph.D. Dissertation, Albert-Ludwigs University, Freiburg i. Breisgav, Germany, 1982.
15. H. P. Osterwald and K. H. Bauer, Acta Pharm. Technol. 26(3), 207 (1980).
16. R.-K. Chang, Pharm. Technol., October, 62–70 (1990).

17. K. H. Bauer, K. Lehmann, H. P. Osterwald, and G. Rothgang, *Überzogene Arzneiformen*, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1988, pp. 114–116.
18. M. E. Aulton, M. H. Abdul Razzak, and J. E. Hogan, Drug Dev. Ind. Pharm., 7(6), 649–668 (1981).
19. K. Thoma and R. Oschmann, Pharm., 46(4), 281, (1991).
20. G. Schepky, Acta Pharm. Technol., 26(3), 196–200 (1980).
21. M. Tardieu, J.-P. Dechesne, L. Halfkan, A. Gayot, and L. Delattre, Pharm. Acta Helv., 67(1), 29–33 (1992).
22. P. H. List and G. Kassis, Acta Pharm. Technol., 28(11), 21–33 (1982).
23. G. R. B. Down, S. Booth, W. Pfendner, and S. Ghodbane, Drug Dev. Ind. Pharm., 19(20), 2743–2749 (1993).
24. K. S. Murthy, N. A. Enders, M. Mahjour, and M. B. Fawzy, Pharm. Technol., October, 36–46 (1986).
25. M. Baudoux, J.-P. Dechesne, and L. Delattre, Pharm. Technol. Int., December, 24–26 (1990).