International Journal of Pharmaceutics, 70 (1991) 261–270

ADONIS 037851739100170J

IJP 02375

The effect of various polymeric coating systems on the dissolution and tableting properties of potassium chloride microcapsules

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(Received 20 April 1990)
(Modified version received 19 November 1990)
(Accepted 20 December 1990)

Key words: Latex coating; Pseudolatex coating; Potassium chloride; tableting

Summary

Two solvent-based coating systems and four aqueous film-forming dispersions were evaluated for their ability to encapsulate potassium chloride crystals and to regulate drug release by fluid-bed technology. Coated potassium chloride crystals were compressed into dispersible tablets as an alternative to capsule filling. Solvent-based coatings generated films with high flexibility and mechanical stability, so that very few coated crystals were damaged. The effect of mixed latex coatings on potassium chloride release rate from microcapsules was also studied.

Introduction

Potassium depletion and hypokalemia are encountered frequently in the clinical setting, usually as a result of diuretic use. Potassium chloride (KCl) is the drug of choice for the treatment of most hypokalemic states. However, KCl is known for its gastrointestinal complications such as ulcerations, hemorrhage, obstruction and perforation.

Dispersible sustained release KCl tablets, which disperse individually coated KCl crystals upon rapid tablet disintegration, seem to be the ideal dosage form because of reduced possibility of high local concentration of KCl near gastrointestinal mucosa and an acceptable size for swallowing. Due to high solubility of KCl in water, a relatively thick film is needed to impart the desired sustained release properties to KCl crystals. Consequently, large amounts of solvents are needed. The objectives of this work were to determine the feasibility of latex/pseudolatex coating for KCl crystals with the aim of eliminating solvent use, to study the effect of mixed latex coating on KCl release rate from microcapsules and to compare the resistance to compression damage of films prepared from solvent-based and latex-based coating systems.

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Materials and Methods

Potassium chloride crystals were obtained from Heico Chemicals Division, Whittaker Corp., Delaware Watergap, PA. Ethyl cellulose (Ethocel 10,

Dow Chemical, U.S.A.), Eudragit RS-100 (polyethylacrylate methylmethacrylate trimethylammonio-ethylmethacrylate chloride, Rohm Pharma, Darmstadt, Germany), and four commercially available aqueous coating systems, Aquacoat (ethyl cellulose pseudolatex, FMC, Philadelphia, PA), Eudragit RS-30D (Eudragit RS pseudolatex, Rohm Pharma) and Eudragit NE-30D (polyethylacrylate methylmethacrylate latex, Rohm Pharma) were used in this study. Microcrystalline cellulose (Avicel pH101, FMC), Crospovidone (polyplasdone XL, GAF Corp., Wayne, NJ) and polyethylene glycol 4500 (Dow Chemical, U.S.A.) were used as obtained.

Preparation of coating formulations

All aqueous dispersions were diluted with deionized water to 15% w/w solid content. For Aquacoat and Eudragit RS-30D dispersions, dibutyl sebacate (20% w/w based on the weight of film former) was added to the diluted pseudolatex. Each mixture was stirred for 30 min before coating and throughout the coating process.

Ethylcellulose was dissolved in methylene chloride : methanol (4 : 1) to make a 4% w/v solution. Eudragit RS-100 was dissolved in acetone : isopropyl alcohol (9 : 1) to make a 10% w/v solution. Dibutyl sebacate was mixed into the Eudragit solution at a 20% concentration level.

Coating process

KCl crystals (800 g) prescreened through no. 18 mesh were coated by using a fluidized bed (Uni-Glatt, Glatt Air Techniques, Inc., Ramsey, NJ). The coating conditions are listed in Table 1. After the coating process, the crystals were dried in the coating chamber for another 15 min at the same temperature and air flow. After drying, the coated crystals were passed through a no. 14 mesh sieve to remove oversized particles.

Particle size determination

50 g of the sample were placed on the top screen of a nest of suitable U.S. Standard sieves and agitated for 15 min. The weight of the factions retained on the screens was obtained.

TABLE 1

Fluidized-bed coating conditions for various coating systems

Coating system	Coating level [a] (%)	Inlet temp. (°C)	Spray rate [b] (ml/min)
Ethocel 10	15	30	26
Aquacoat	20	60	15
Surelease	20	60	15
Eudragit RS-100	20	30	28
Eudragit RS-30D	20	30	17
Eudragit NE-30D	20	30	10
Aquacoat: Surelease (50 : 50)	20	60	15
Aquacoat Eudragit NE-30D (50 : 50)	20	30	12
Surelease Eudragit NE-30D (50 : 50)	20	30	12
Opadry [c]	1	60	10

[a] % w/w based on theoretical weight of batch.

[b] A peristatic pump (Masterflex, Model 7562–00, Cole-Parmer Instrument Co., Chicago, IL) was used for aqueous coating. A gear pump (Zenith Products Co., West Newton, MA) was used for polymer solutions.

[c] Opadry (Colorcon, West Point, PA) overcoat was used to prevent sticking problems of the coated crystals during the storage, especially necessary for Eudragit RS-100 coating.

Note: For all coating systems, spray pressure was set at 1.6 bar with a spray nozzle orifice of 0.8 mm. Initial air flap was set at 30% and gradually increased during the coating process to maintain proper fluidization.

Scanning electron microscopy

A thin layer of gold-palladium was applied to the KCl microcapsules to enable electrical conductance by using a sputter coater. A microscope (Jeol, JSM 6400; accelerating voltage, 2 kV; magnification ×1000) was used for the scanning electron microscopy.

Tableting

All ingredients listed in Table 2 were mixed prior to compression. A Carver Laboratory Press (Model C, Fred S. Carver Inc., Denomonee Falls, WI) was used to compress the tablet blend into 10 meq. KCl tablets at 120 MPa for a duration of 5 s. All tablets produced had satisfactory tablet prop-

TABLE 2

Experimental tablet formula

	%
Coated potassium chloride crystals	68.0
Crospovidone	1.0
Microcrystalline cellulose/polyethylene glycol	30.5
Magnesium stearate	0.5
	100.0

erties such as short disintegration time (less than 5 min), desired crushing strength (hardness: 12 kPa) and low friability (less than 0.7%).

Dissolution test

A USP Dissolution Apparatus 1 was used to determine the dissolution rates of samples containing a total of 10 meq. of KCl. The dissolution medium was 900 ml deionized water maintained at 37°C. A basket constantly rotated at 50 rpm. No attempts have been made to prevent the dispersed microcapsules from falling through the basket during the dissolution test. Serial sampling of the fluid at appropriate times, with subsequent atomic absorption analysis (Perkin-Elmer Atomic Absorption Spectophotometer 3030 equipped with a lamp capable of measuring the absorbance of potassium at its secondary wavelength of 769.9 nm) for KCl level, were performed to generate a cumulative percent release-time profile. Each point represents the mean of data from at least six samples.

Results and Discussion

As contrasted to the organic solvent solutions of the polymers, the latices had a high polymer content and low viscosity in spite of dilution of the latex dispersions to facilitate spray coating in the present study. Consequently, comparable batch cycle times were obtained for KCl sustained release coatings by the two methods. Table 3 shows the particle size distributions of original KCl crystals and coated crystals. After coating, particle size enlarged as expected in all cases. However, solvent-based coatings of both ethocel and Eudragit RS-100 produced approx. 5% oversized rejects and a larger particle size distribution of coated crystals due to higher viscosity of the polymer solutions and a tacky phase during the evaporation of solvent.

With formulation and coating conditions used in the present study, desired in vitro release profiles of KCl from microcapsules can be achieved. The dissolution profiles for KCl crystals coated with four different aqueous film forming dispersions were similar to those obtained with solvent-based coating systems (Figs 1 and 2).

Two major factors influencing the release characteristics of sustained release compressed tablets made from microcapsules are disintegration time of the tablets and resistance of the film around the crystals to compression damage. All tablet batches were formulated to disperse and to expose the microcapsules to the dissolution medium. Thus, Figs 1 and 2 clearly demonstrate the ability of

TABLE 3

Size-weight distribution of KCl crystals and KCl microcapsules coated with various coating systems

Sieve no. (pass/retained)	Crystals	Ethocel 10	Aquacoat	Surelease	Eudragit RS-100	Eudragit RS-30D	Eudragit NE-30D
14/20	0.05	5.80	0.50	0.10	17.30	4.05	1.25
20/30	2.71	17.25	15.25	7.00	18.20	24.65	6.50
30/40	36.69	59.10	80.95	88.80	46.50	61.90	61.25
40/50	47.46	17.75	3.25	4.05	17.10	9.30	30.35
50/Pan	13.09	0.10	0.05	0.05	0.90	0.10	0.65
d_{ave} (μm) [a]	399.8	556.5	542.1	521.4	626.4	573.9	485.7

[a] Average diameter = $\frac{\text{summation of weight size}}{100}$. Weight size = percent retained on smaller sieve × arithmetic mean size of openings.

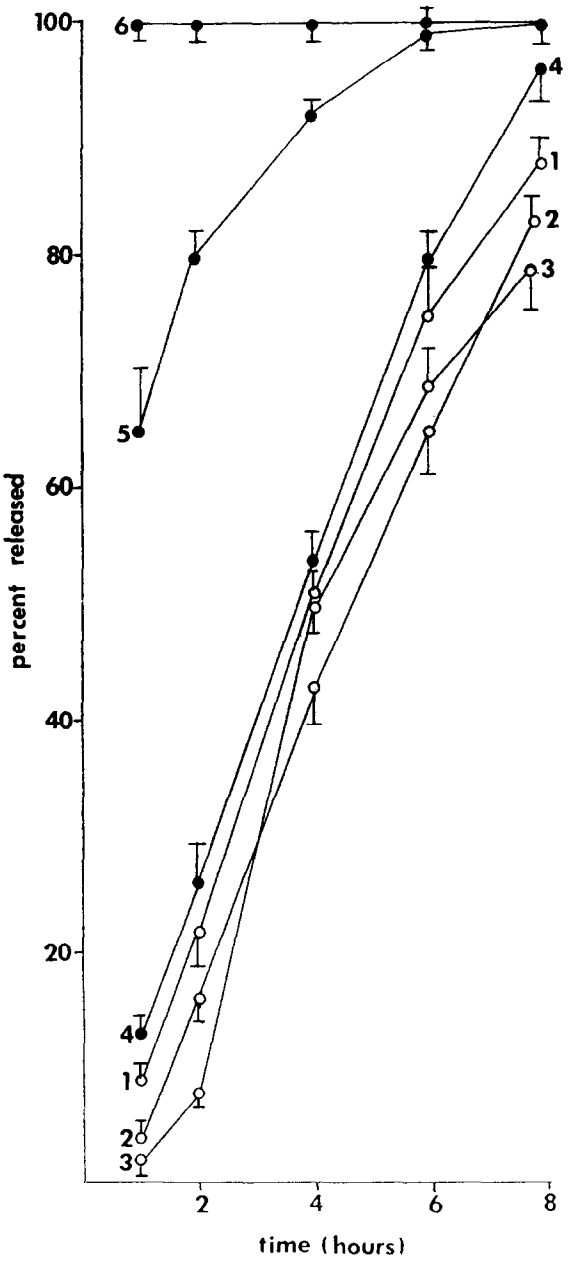


Fig. 1. In vitro dissolution characteristics of potassium chloride microcapsules and tablets. (1) Ethyl cellulose microcapsules, (2) Surelease microcapsules, (3) Aquacoat microcapsules, (4) tablet made from ethyl cellulose microcapsules, (5) tablet made from Surelease microcapsules, (6) tablet made from Aquacoat microcapsules.

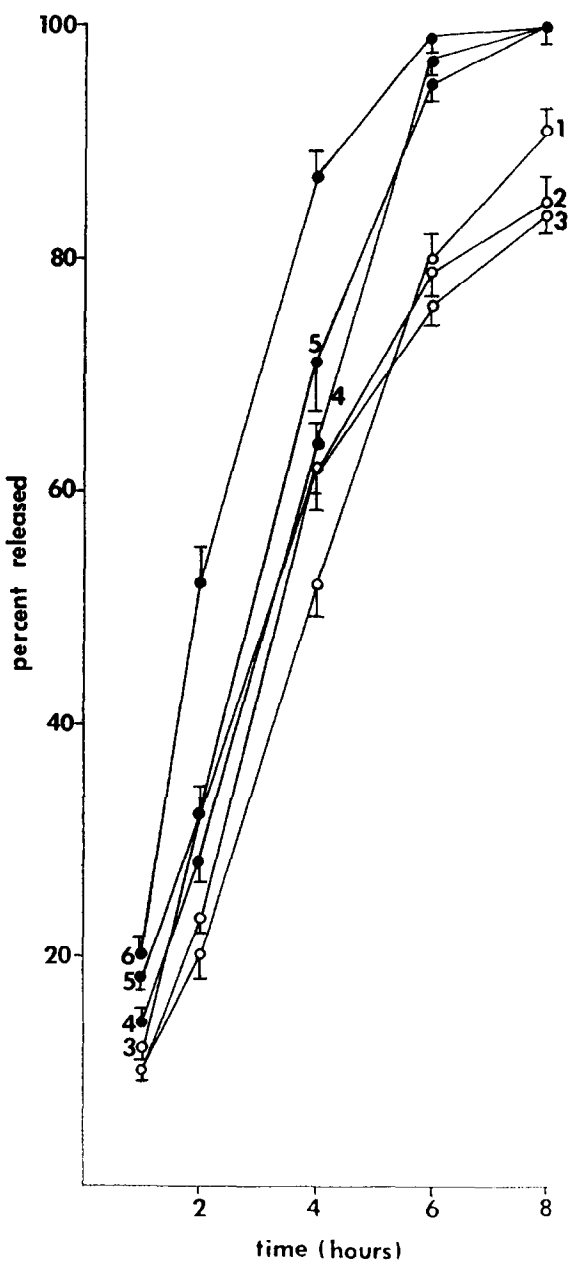


Fig. 2. In vitro dissolution characteristics of potassium chloride microcapsules and tablets. (1) Eudragit RS-100 microcapsules, (2) Eudragit RS-30D microcapsules, (3) Eudragit NE-30D microcapsules, (4) tablet made from Eudragit RS-100 microcapsules, (5) tablet made from Eudragit RS-30D microcapsules, (6) tablet made from Eudragit NE-30D microcapsules.

various films to resist compression damage. Tablet batches made from ethylcellulose solution coated KCl crystals showed an insignificant increase of dissolution rate over uncompressed KCl microcapsules. On the other hand, tablets made from Aquacoat and Surelease coated microcapsules

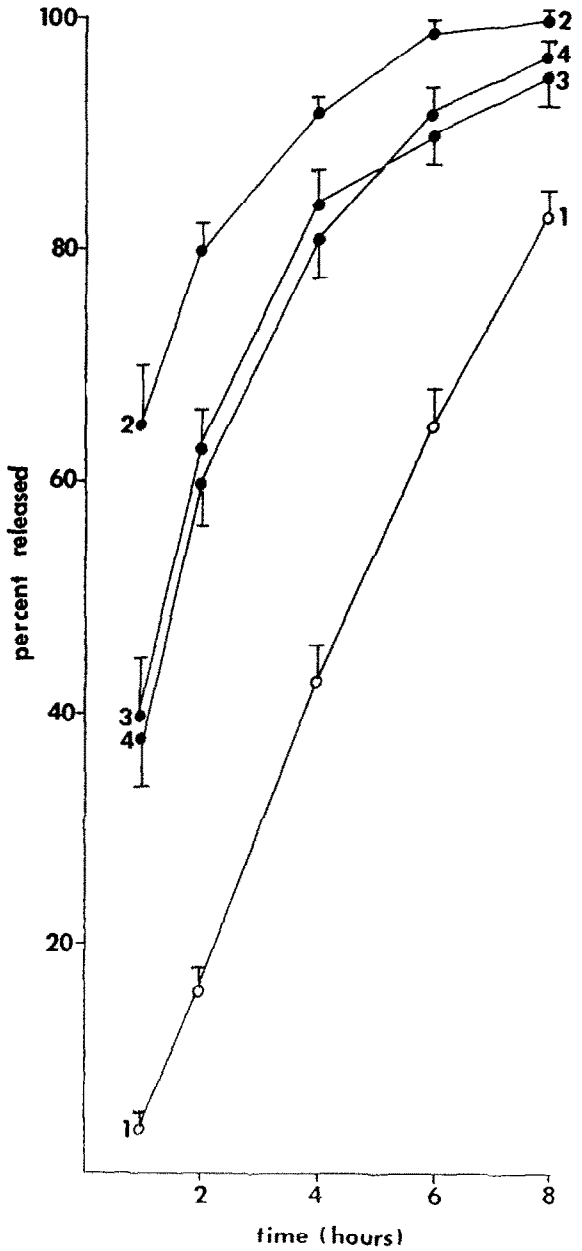


Fig. 3. In vitro dissolution characteristics of potassium chloride microcapsules and tablets. (1) Surelease microcapsules, (2) tablets made from Surelease microcapsules and Avicel, (3) tablets made from Surelease microcapsules and Avicel : polyethylene glycol (65 : 35), (4) tablets made from Surelease microcapsules and Avicel : polyethylene glycol (35 : 65).

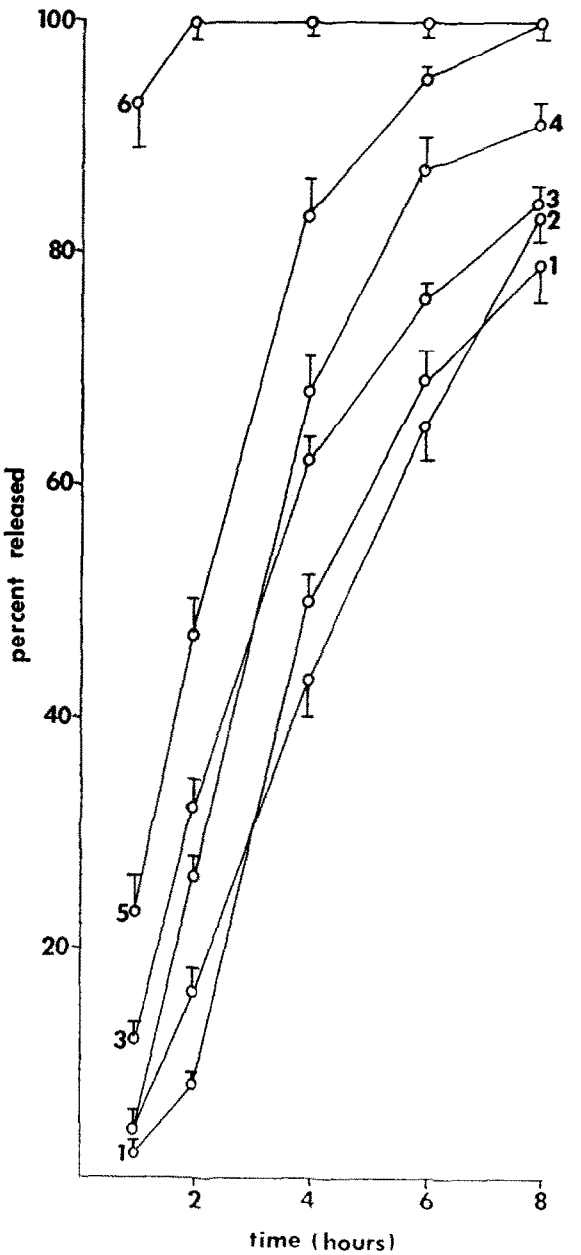


Fig. 4. Effect of mixed latex coatings on the dissolution characteristics of potassium chloride microcapsules. (1) Aquacoat microcapsules, (2) Surelease microcapsules, (3) Eudragit NE-30D microcapsules, (4) Aquacoat: Surelease microcapsules, (5) Surelease: Eudragit NE-30D microcapsules, (6) Aquacoat: Eudragit NE-30D microcapsules.

showed total or almost total loss of sustained release properties (Fig. 1).

Possible reasons for the weak resistance to compression damage are: (1) incomplete fusion of latex spheres, (2) molecular weight changes due to the pseudolatex manufacture process, (3) stabi-

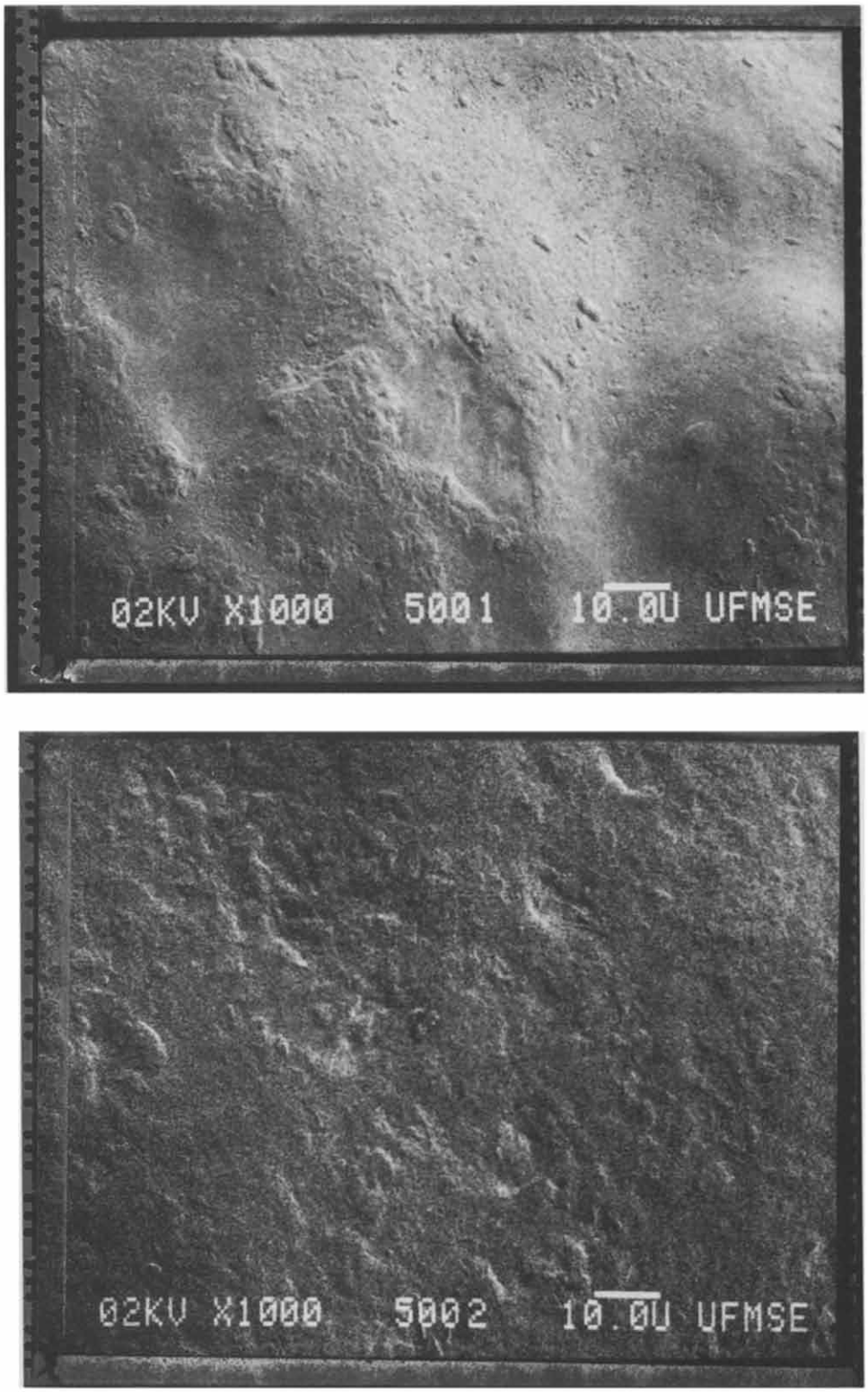
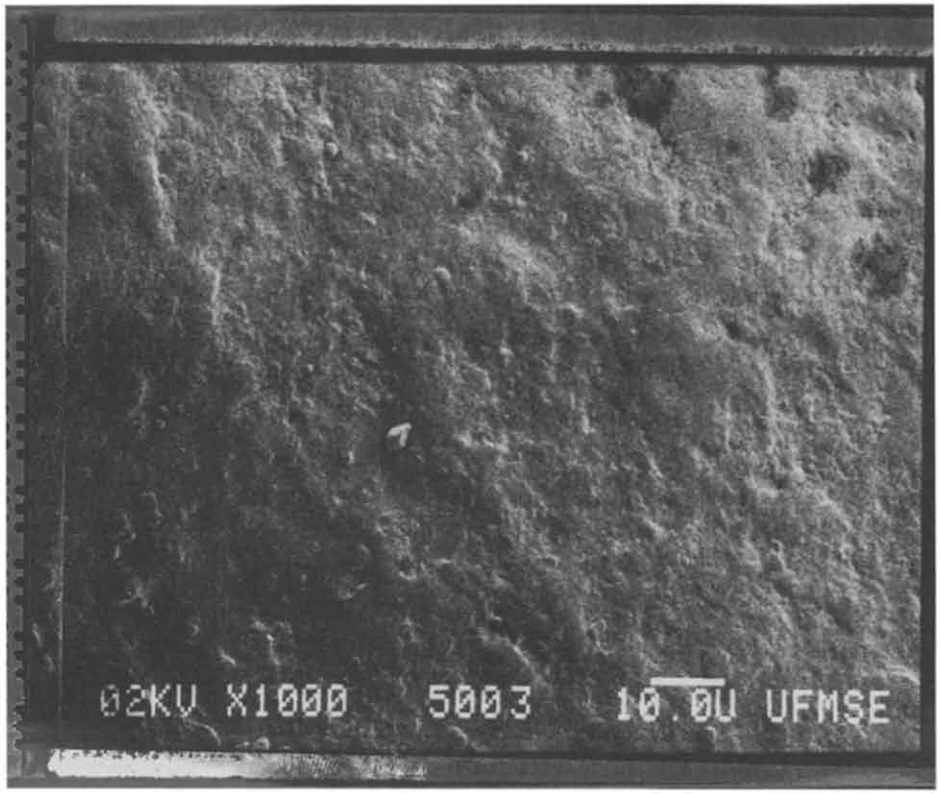


Fig. 5. Scanning electron micrographs of potassium chloride microcapsules prepared with various coating systems. (A) Ethyl cellulose solvent-based coating, (B) Aquacoat coating, (C) Surelease coating, (D) Eudragit RS-100 solvent-based coating, (E) Eudragit RS-30D coating, (F) Eudragit NE-30D coating.



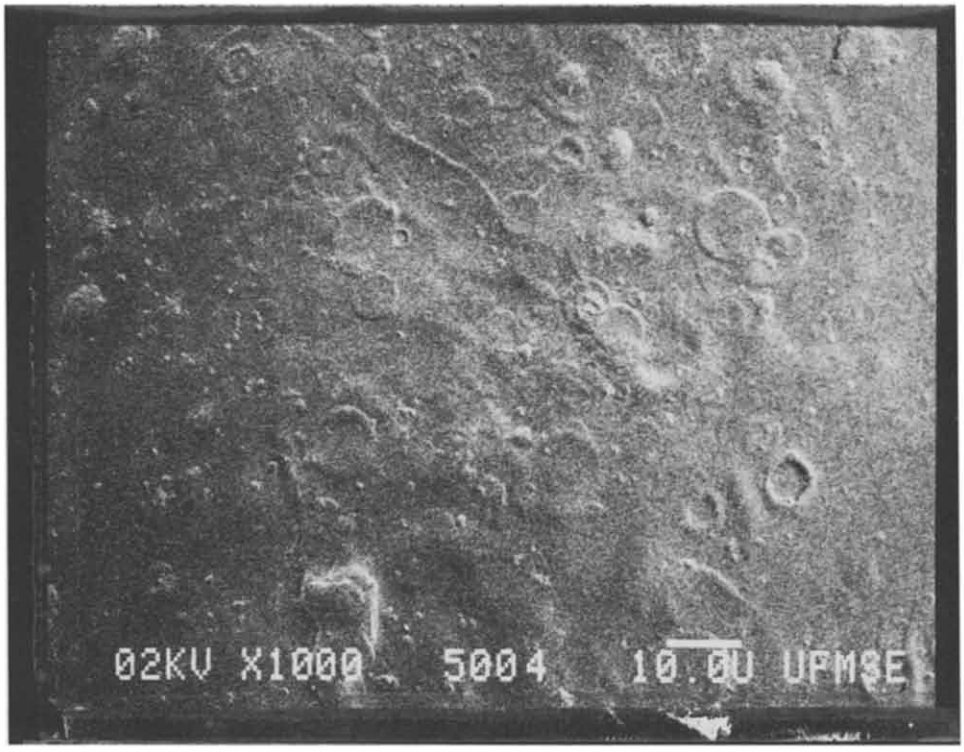


Fig. 5 (continued).

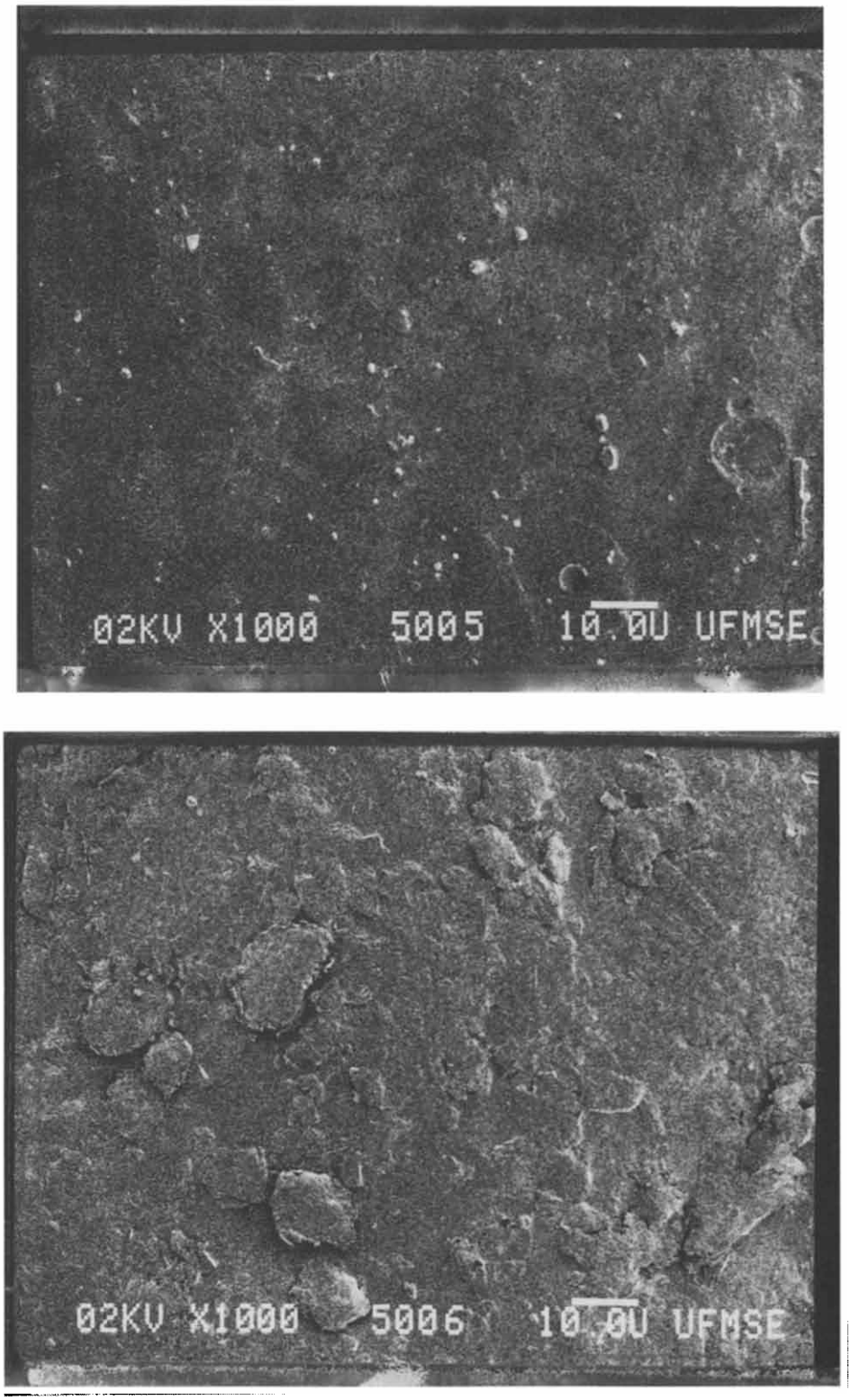


Fig. 5 (continued).

lizer(s) and additive(s) used in the pseudolatex formulation, (4) migration of KCl into latex film during the coating process. Several attempts such as further coalescence at 60°C for 24 h, protective overcoating and lubricating the microcapsules with magnesium stearate to reduce interparticle friction, failed to prevent the cracking and rupture of the Surelease film during compression. Generally, higher molecular weight polyethylene glycols are able to enhance the effectiveness of tablet binders, impart plasticity as well as protective cushion to microcapsules and function as lubricants to reduce interparticle friction. As indicated in Fig. 3, polyethylene glycol 4500 can be used to minimize the compression damage to the microcapsules probably due to its ability of facilitating the packing and reducing friction between microcapsules during compression. This confirms the results of a previous report by Walker et al. (1977). However, considerable sustained release properties were lost, even when Avicel : polyethylene glycol (35 : 65) were used as the excipients for tableting. In the Eudragit examples, sustained release properties were lost to a lesser extent. Minimal loss of the retard effect was obtained with Eudragit RS-100 solvent-based coating (Fig. 2).

Most latices or pseudolatices are stabilized by the high surface potential of deflocculated particles arising either from ionic function groups on the polymer or from adsorbed ionic surfactant/stabilizer. For example, the positive charge on Eudragit RS 30D and RL 30D pseudolatex particles arises from quarternary groups on the polymer; the negative charge on Aquacoat and Surelease pseudolatex particles originates from anionic surfactants such as sodium lauryl sulfate and oleic acid. The size and size distribution of latex spheres are also important factors which affect stability, rheological properties and film properties.

Small, monodispersed latex particles are required to have complete coalescence of latex spheres into films. Although mixed latex coating systems have been successfully used to prevent coated granules sticking together, (Kopf 1982) and to regulate the drug release (Chang et al., 1987, 1989), it is generally not recommended to use mixed latex coating systems because of possible incompatibility of the two latex systems, different glass transition temperatures of the polymers and different sizes of latex spheres. Fig. 4 shows the dissolution profiles of KCl from microcapsules coated with Aquacoat, Surelease, Eudragit NE-30D and 50 : 50 mixtures of any two of these aqueous dispersions. It clearly demonstrated that a single latex coating system which coalesces better and leads to slower dissolution rate, is superior to the mixed coating system.

Scanning electron micrographs of KCl microcapsules are shown in Fig. 5. There are distinct differences in the surface features among microcapsules prepared by different coating systems. In contrast to latex coating, the films generated by solvent-based coating have smoother and more continuous structures (Fig. 5A and D). Fig. 5F shows the surface of KCl microcapsules coated with Eudragit NE-30D. The surface is a rough, porous, discontinuous structure. However, Eudragit NE-30D film effectively retarded KCl release from microcapsules and released only 12% of the drug during a 60 min dissolution test. This indicates that the surface morphology may not be an important criterion for sustained release performance of relatively thick films.

Conclusion

Although any of these coatings can create a suitable membrane for controlling KCl release, the latex/pseudolatex films were not mechanically stable enough to withstand compression stress. On the other hand, solvent-based coatings generated films with sufficient flexibility and mechanical stability, that only an insignificant increase in dissolution rate was observed after compression of coated crystals into tablets. Single latex coating systems were superior to mixed latex coating systems.

Acknowledgements

The authors wish to thank Dr James C. Price for helpful discussions, Mr Samuel Yuk for technical assistance and Mrs Marietta Parrotta for preparing the manuscript.

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