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RESEARCH PAPER

Study of Drug Release from Pellets Coated with Surelease Containing Hydroxypropylmethylcellulose

Fatemeh Sadeghi,* James L. Ford, Michael H. Rubinstein, and Ali R. Rajabi-Siahboomi†

School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool, L3 3AF, UK

ABSTRACT

The release of metoclopramide hydrochloride (a very water soluble cationic drug) and diclofenac sodium (a sparingly soluble anionic drug) from pellets coated with Surelease containing hydroxypropylmethylcellulose (HPMC) at different coating loads was investigated. The release rates of either drug at each coating composition decreased as the coating load increased. Inclusion of HPMC E15 increased the release rates of both drugs compared to pellets coated only with Surelease. This was thought to be due to the leakage of the soluble part of the film (HPMC E15) during dissolution, which left pores for drug release. The Surelease:HPMC E15 ratio had a major role in the release rates of drugs. Addition of HPMC E15 into Surelease did not change the release mechanism for metoclopramide hydrochloride (the mean value of $n \approx 0.57$*) from that of Surelease alone, and diffusion remained the main mechanism controlling the release. However, the release exponent (≈1.28) increased for diclofenac sodium on addition of HPMC E15, indicating a dissolution-controlled mechanism. Despite its lower water solubility, diclofenac sodium was released slightly faster than metoclopramide hydrochloride from pellets coated with Surelease containing HPMC E15 at equivalent coating loads.*

Key Words: *Coated pellets; HPMC; Hydroxypropylmethylcellulose; Surelease; Sustained release.*

* Current address: School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.
† Corresponding author. Colorcon Limited, Flagship House, Victory Way, Crossways, Dartford, Kent, DA2 6QD, UK. Fax: +44 (0) 1322 627200; E-mail: asiahboomi@colorcon.co.uk

INTRODUCTION

Drug release from slow-release dosage forms coated with insoluble polymers may be modified by additives that dissolve on exposure to biological fluids and thus make the coating porous (1). It has been reported that addition of suitable hydrophilic polymers such as methylcellulose (2–4), hydroxypropylmethylcellulose (HPMC) (5–7), hydroxypropylcellulose (HPC) (8), and polyethylene glycol (9) to insoluble hydrophobic coatings would increase the permeability characteristics of that coating.

Hydrophilic additives can increase the permeability of hydrophobic films by several mechanisms. Some additives make the film more porous, such as polyethylene glycol (9) or form a hydrated network inside the film, such as HPC (10). Others may act as carriers for drugs such as Span 20 for salicylic acid through ethylcellulose films (1) or form complexes, which increases the solubility of the drug in the membrane or increases the diffusion coefficient, such as the complex of tetrabutylammonium bromide with salicylic acid (11). The ability of HPMC to modify the release of drugs from systems coated with water-insoluble polymers has been demonstrated previously for ethylcellulose films (5,12,13) and Eudragit films (7).

We have recently reported that low-viscosity hydroxypropylmethylcellulose (HPMC E15) coating had no control on the release of metoclopramide hydrochloride or diclofenac sodium from pellets (14). The majority of both drugs was released in less than 1 h, even at the high coating load (20% w/w). Drug release from Surelease-coated pellets was rapid at low coating loads, while it was sustained over 12 h at high coating loads. However, the release of either drug was incomplete at high coating loads. In addition, the duration of the lag time before establishing the continuous-release profile increased at high coating loads of Surelease. Therefore, the addition of a water-soluble hydrophilic HPMC polymer to Surelease film may allow faster onset of drug release (shorter lag time) and facilitate all of the drug to be released at the end of the dissolution test.

In this study, the permeability of Surelease films was modified by the addition of low-viscosity HPMC E15. The influence of the addition of different amounts of HPMC E15 to Surelease on the rate and mechanism of drug release from coated pellets was investigated.

MATERIALS AND METHODS

Materials

Metoclopramide hydrochloride was obtained from Wilfrid Smith Limited (Edgware, Middlesex, UK). Diclofenac sodium was obtained from Industria Chimica Profarmaco (Milan, Italy). Nonpareil (sugar spheres composed of sucrose and starch), 20–25 mesh size (0.710–0.840 mm) were obtained from Forum Chemicals Limited (Redhill, Surrey, UK). HPMC E15 (Methocel E15) and Surelease E-7-7050 (ethylcellulose aqueous dispersion) were supplied by Colorcon (Dartford, Kent, UK).

Table 1

Process Conditions Used in Surelease Film-Coating Operations

Conditions	Values
Inlet air temperature (°C)	60–62
Outlet air temperature (°C)	51–53
Atomizing air temperature (psi)	40
Spray rate (g/min)	16

Preparation of Drug-Loaded Pellets

Metoclopramide hydrochloride or diclofenac sodium were applied to batches of 4500 g of nonpareil seeds using an Accela-Cota 10 (Manesty, Liverpool, UK) as described previously (14). The drug-layering process produced pellets with a metoclopramide hydrochloride load of 3.95 ± 0.08% w/w and diclofenac sodium load of 3.93% ± 0.01% w/w.

Coating of Drug-Loaded Pellets with Surelease Containing Hydroxypropylmethylcellulose E15

For coating, 4500 g quantities of drug-loaded pellets were used. The drug-loaded pellets were coated with Surelease containing 5%, 7.5%, or 10% HPMC E15 to different coating loads. Solutions of HPMC E15 (5% w/w) were prepared and kept overnight. The Surelease was diluted with water to 15% w/w. Then, 5% HPMC solution was added to the diluted Surelease to produce the required HPMC contents and stirred throughout the coating processes. Drug-loaded pellets were coated using an Accela Cota 10 with Surelease/HPMC under the conditions shown in Table 1. Samples of 50 g of coated pellets were removed from the coating pan when the coating loads had reached 4%, 8%, 12%, 16%, and 20% w/w. The drug contents of the coated beads were determined as described previously (14).

Dissolution Studies

The dissolution behavior of the pellets was measured using a Pharmatest tester (GMbH, Germany) (USP apparatus I) in line with a Hewlett Packard HP8452A diode array spectrophotometer. The release profiles of beads containing 15 mg of drug in 900 ml of distilled water at a rotating speed of 50 ± 0.5 rpm and 37°C ± 0.5°C were determined. The means of six determinations were used to calculate the drug release for each formulation.

Release Kinetics for Coated Pellets

To determine drug release rates, the results of dissolution tests were fitted to the following equations using statistical software (SPSS for Windows, release 6.0.1).

In Eqs. 1, 2, and 3, Q is the percentage of drug released at time t, and K_1, K_2, and K_3 are zero-order, root-time, and first-order release rates constants, respectively.

$$Q = 100K_1t \quad (1)$$

$$Q = K_2t^{1/2} + C \quad (2)$$

$$Q = 100e^{K_3t} \quad (3)$$

Regression analyses were used to obtain the release constants K and correlation coefficients r for each model. The correlation coefficients for the best statistical fit were used as the main criterion to evaluate the models. The equation with the highest correlation coefficient was judged to be the most appropriate model for each system. The lag time t_{lag} for pellets coated with Surelease/HPMC E15 was also calculated from X-axis intercept when the amount of drug released was zero.

To evaluate the mechanism of drug release, the dissolution data were also analyzed using Eq. 4, proposed by Ford et al. (15), in which K_4 is the release rate constant, t_{lag} is the lag time, and n is the release exponent indicating the mechanism of drug release. Equations 1 and 2 above may be considered special cases of Eq. 4 where $n = 1$ and $n = 0.5$, respectively.

$$Q = [K_4(t - t_{lag})^n] \quad (4)$$

The release mechanism is determined by fitting the release data to this equation and comparing the value of n to the semiempirical values for various geometries reported by Ritger and Peppas (16). For comparative purposes, release data between 15% and 60% were used for modeling drug release. This range also corresponded to the limits of applicability of Eqs. 1 and 2.

Determination of Hydroxypropylmethylcellulose Release from Free Films of Surelease Containing Hydroxypropylmethylcellulose E15

To examine the effect of HPMC E15 on the Surelease films, free films of Surelease and Surelease containing 7.5% w/w HPMC E15 were prepared by intermittently spraying each coating suspension onto the flat surface of a Teflon-coated pan using the Accela-Cota spray unit. The films were dried at about 70°C. The dried films were carefully removed and stored over silica gel in a desiccator and used within 24 h of preparation. Films of 64 ± 10 μm thickness were cut into strips 5 cm by 5 cm and weighed precisely. The films were immersed in 50 ml of distilled water in a flask at 37°C and shaken for 30 min. Then, the content of the flask was passed through Whatman no. 1 filter papers with washing, and all the undissolved particles and films were removed. The aqueous extracts of the films were collected and dried at 60°C to calculate the amount of HPMC E15 released from the films. The same procedure was performed, as a reference,

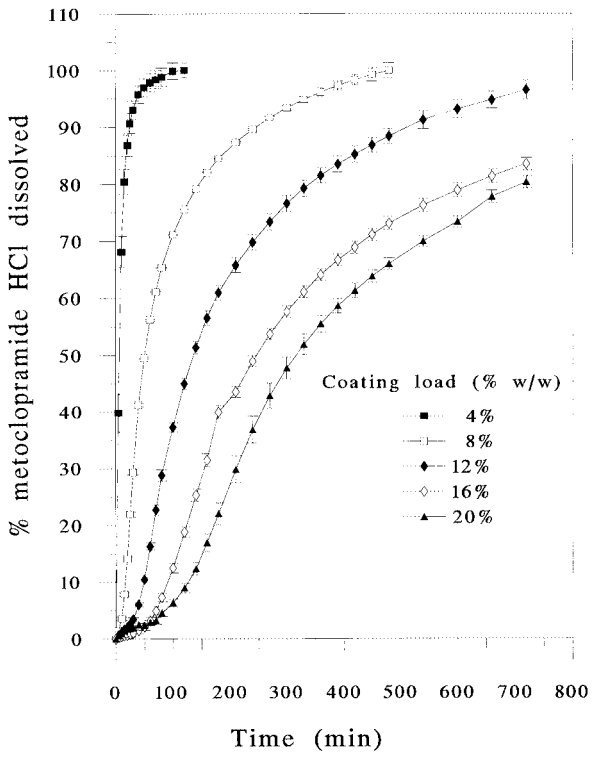

Figure 1. Effect of coating load on the release of metoclopramide HCl from pellets coated with Surelease containing 5% HPMC E15.

for Surelease films without HPMC. The procedure was repeated three times for each type of film.

RESULTS AND DISCUSSION

Metoclopramide Hydrochloride Release from Pellets Coated with Surelease Containing Hydroxypropylmethylcellulose E15

Figures 1–3 show the plots of release of metoclopramide hydrochloride from pellets coated with Surelease containing 5%, 7.5%, and 10% HPMC E15, respectively. As the coating loads increased, the amount of metoclopramide hydrochloride released decreased at each coating composition. The amount of drug released increased with the increase in the HPMC content of the coats.

The release rates K and lag times t_{lag} of the fits of release data to the different kinetic models are shown in Tables 2–4. No results are reported for the 4% coating load due to insufficient data points for regression analysis. The release rates decreased as the coating loads increased irrespective of the kinetic model used. On the other hand, increasing the HPMC E15 content in the coats increased the release rates at equivalent coating loads. For example, the first-order release rate was more than three times faster when the HPMC E15 content was 10% compared to when the HPMC E15 content was 5% at the coating load of 20%. Therefore, the ratio of HPMC to Surelease had a major effect on the release rate of the drug. Similar to Surelease-coated pellets (14), a lag time was observed before establishing the controlled-release profiles. The duration of lag time increased with increasing coating load, but decreased as the amount of HPMC E15 in the coats increased.

Correlation coefficients r of the fits of metoclopramide hydrochloride release data to different kinetic models are also shown in Tables 2–4. The correlation coefficients for the best statistical fits revealed that the first-order kinetic model is probably the most applicable model to all the release data. The coating load and also the HPMC E15 content in the film did not appear to change the kinetic model, which provided the best fit for the data.

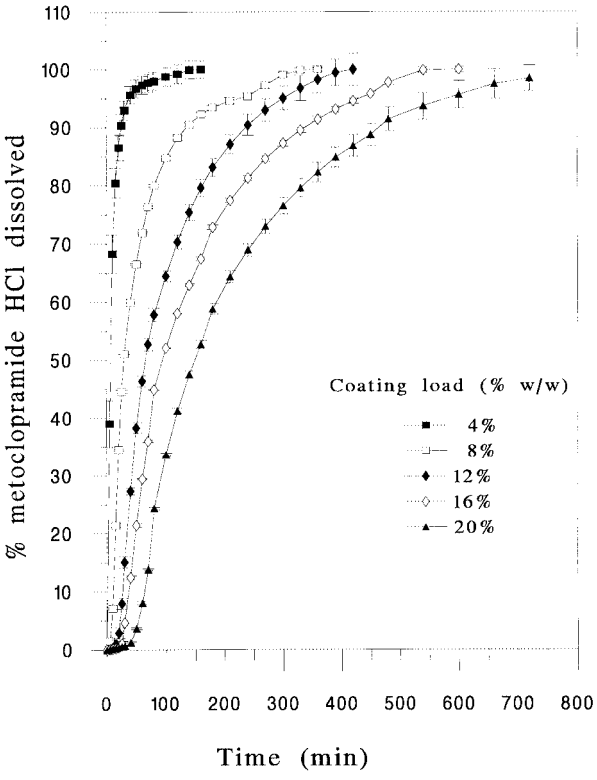

Figure 2. Effect of coating load on the release of metoclopramide HCl from pellets coated with Surelease containing 7.5% HPMC E15.

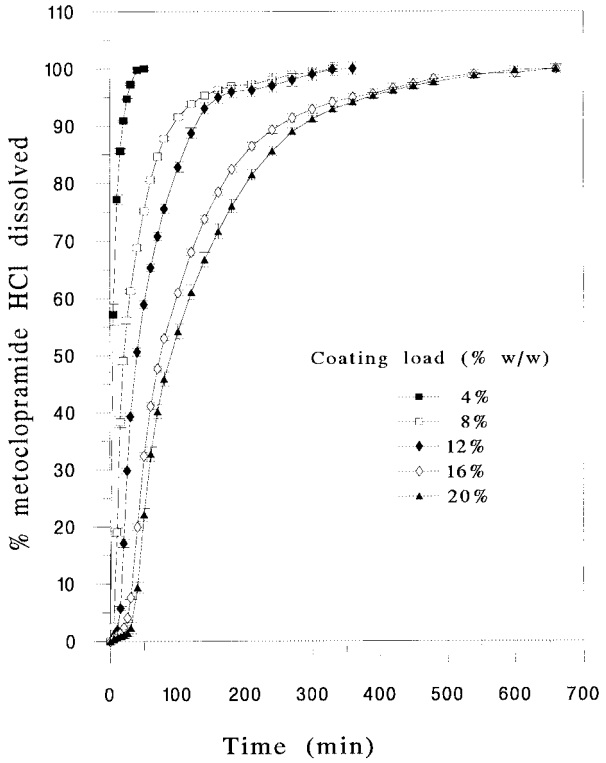

Figure 3. Effect of coating load on the release of metoclopramide HCl from pellets coated with Surelease containing 10% HPMC E15.

Table 2

Values of Release Constants K, *Correlation Coefficients* r, *and Lag Times* (t_{lag}) *Obtained from Data Corresponding to 15%–60% Release of Metoclopramide Hydrochloride from Pellets Coated with Surelease Containing 5% HPMC E15, Using Equations 1–3*

Model	[a]	8%	12%	16%	20%
Zero order	K_1	0.85 ± 0.01	0.33 ± <0.01	0.20 ± 0.0	0.16 ± 0.01
	r	0.977	0.980	0.981	0.985
	$P<$	0.001	0.001	0.001	0.001
	$(t_{lag})_1$	−3.2 ± 0.60	−4.9 ± 1.6	9.5 ± 4.5	43.1 ± 9.4
Square root	K_2	11.5 ± 0.1	7.4 ± 0.1	5.8 ± 0.0	5.6 ± 0.2
	r	0.992	0.993	0.987	0.995
	$P<$	0.001	0.001	0.001	0.001
	$(t_{lag})_2$	9.1 ± 0.3	26.7 ± 0.6	52.2 ± 2.4	95.1 ± 9.6
First order	K_3	0.0152 ± 0.0002	0.0059 ± 0.0001	0.0034 ± 0.0001	0.0028 ± 0.0001
	r	0.995	0.997	0.997	0.998
	$P<$	0.001	0.001	0.001	0.001
	$(t_{lag})_3$	7.6 ± 0.1	25.5 ± 1.1	53.2 ± 0.9	101.0 ± 11.2

[a] The units of the rate constants are as follows: K_1, %min^{-1}; K_2, %min$^{-1/2}$; K_3, min^{-1}. Units of the lag times that correspond to different equations (1–3) $(t_{lag})_1$, $(t_{lag})_2$, and $(t_{lag})_3$ are minutes. P is the degree of significance.

Tables 5–7 summarize the values of K, n, and l obtained from Eq. 4. Coating load had no apparent effect on the value of n for Surelease-coated pellets containing different amounts of HPMC E15. Generally, the values of n for pellets coated with mixtures of Surelease and 5% HPMC were slightly higher than those observed for pellets coated with mixtures of Surelease and 7.5% or 10% HPMC. To gain an insight into the release mechanism, the values of n were averaged, and the mean value of n was 0.57 ± 0.09. The value of release exponent n indicates that diffusion is the predominant mechanism controlling the release of metoclopramide hydrochloride from pellets coated with Surelease/HPMC E15.

Diclofenac Sodium Release from Pellets Coated with Surelease Containing Hydroxypropylmethylcellulose E15

Figures 4–6 show the release of diclofenac sodium from pellets coated with Surelease containing 5%, 7.5%,

Table 3

Values of Release Constants K, *Correlation Coefficients* r, *and Lag Times* (t_{lag}) *Obtained from Data Corresponding to 15%–60% Release of Metoclopramide Hydrochloride from Pellets Coated with Surelease Containing 7.5% HPMC E15, Using Equations 1–3*

Model	[a]	8%	12%	16%	20%
Zero order	K_1	1.22 ± 0.02	0.70 ± <0.01	0.40 ± 0.01	0.31 ± 0.00
	r	0.961	0.969	0.950	0.979
	$P<$	0.002	0.001	0.001	0.001
	$(t_{lag})_1$	−7.9 ± 0.05	−0.01 ± 1.2	3.2 ± 2.5	18.1 ± 1.7
Square root	K_2	13.7 ± 0.2	11.1 ± 1.2	8.4 ± 0.1	7.7 ± 0.1
	r	0.981	0.987	0.979	0.992
	$P<$	0.001	0.001	0.001	0.001
	$(t_{lag})_2$	4.0 ± 0.1	14.6 ± 0.6	25.5 ± 0.6	45.7 ± 0.9
First order	K_3	0.0239 ± 0.0001	0.0126 ± 0.0001	0.0074 ± 0.0001	0.0055 ± 0.0001
	r	0.989	0.992	0.996	0.997
	$P<$	0.001	0.001	0.001	0.001
	$(t_{lag})_3$	2.4 ± 0.5	13.9 ± 0.6	24.7 ± 0.3	46.1 ± 0.5

[a] See Table 2 footnote for values.

Table 4

Values of Release Constants K, *Correlation Coefficients* r, *and Lag Times* (t_{lag}) *Obtained from Data Corresponding to 15%–60% Release of Metoclopramide Hydrochloride from Pellets Coated with Surelease Containing 10% HPMC E15, Using Equations 1–3*

Model	[a]	8%	12%	16%	20%
Zero order	K_1	2.04 ± 0.02	1.15 ± <0.00	0.66 ± 0.01	0.53 ± 0.01
	r	0.965	0.971	0.973	0.975
	$P<$	0.01	0.001	0.001	0.001
	$(t_{lag})_1$	−1.9 ± 0.6	−0.3 ± 0.5	2.7 ± 1.1	0.4 ± 1.3
Square root	K_2	18.0 ± 0.2	14.3 ± 1.0	11.0 ± 0.1	9.7 ± 0.1
	r	0.982	0.985	0.987	0.987
	$P<$	0.01	0.001	0.001	0.001
	$(t_{lag})_2$	3.7 ± 0.2	8.8 ± 0.2	17.8 ± 0.5	19.8 ± 0.6
First order	K_3	0.0361 ± 0.0001	0.0212 ± 0.0002	0.0119 ± 0.0001	0.0096 ± 0.0001
	r	0.987	0.993	0.993	0.993
	$P<$	0.01	0.001	0.001	0.001
	$(t_{lag})_3$	2.8 ± 0.3	8.7 ± 0.1	16.97 ± 0.7	20.3 ± 0.09

[a] See Table 2 footnote for values.

Table 5

Values K_4, (t_{lag}), n *Based on Equation 4 Calculated in the Range 15%–60% Metoclopramide Hydrochloride or Diclofenac Sodium Release from Surelease Containing Pellets Coated with 5% HPMC E15*

	Metoclopramide HCl			Diclofenac Na		
Coating Load	K_4 (%min^{-1})	(t_{lag}) (min)	n	K_4 (%min^{-1})	(t_{lag}) (min)	n
8%	5.00	13.40	0.63	6.27	2.81	0.87
12%	2.18	36.90	0.68	0.97	13.50	1.15
16%	1.84	72.50	0.64	0.14	16.20	1.46
20%	0.80	104.00	0.75	0.04	20.20	1.55

Table 6

Values K_4, (t_{lag}), n *Based on Equation 4 Calculated in the Range 15%–60% Metoclopramide Hydrochloride or Diclofenac Sodium Release from Surelease Containing Pellets Coated with 7.5% HPMC E15*

	Metoclopramide HCl			Diclofenac Na		
Coating Load	K_4 (%min^{-1})	(t_{lag}) (min)	n	K_4 (%min^{-1})	(t_{lag}) (min)	n
8%	9.36	9.46	0.55	Not enough data points		
12%	5.04	23.20	0.61	1.69	10.10	1.08
16%	6.03	46.00	0.50	0.05	6.59	1.66
20%	4.59	64.80	0.52	0.04	11.60	1.59

Table 7

Values K_4, (t_{lag}), n *Based on Equation 4 Calculated in the Range 15%–60% Metoclopramide Hydrochloride or Diclofenac Sodium Release from Surelease Containing Pellets Coated with 10% HPMC E15*

	Metoclopramide HCl			Diclofenac Na		
Coating Load	K_4 (%min^{-1})	(t_{lag}) (min)	n	K_4 (%min^{-1})	(t_{lag}) (min)	n
8%	20.50	9.18	0.36	Not enough data points		
12%	7.26	14.40	0.59	2.65	3.21	1.06
16%	5.91	28.60	0.55	1.15	8.66	1.09
20%	7.39	38.50	0.48	0.22	9.90	1.35

and 10% HPMC E15, respectively. At each coating composition, as the coating load increased, the release of diclofenac sodium decreased.

The release rates K and lag times t_{lag} of the fits of diclofenac sodium release data to different kinetic models are shown in Tables 8–10. Due to insufficient data points for regression analysis, no results were obtained for 4% coating load for all pellets and also for the 8% coating containing 7.5% or 10% w/w HPMC E15. Release rates decreased as the coating loads increased. Similar to metoclopramide hydrochloride pellets, inclusion of HPMC E15 in the coat increased the release rates of diclofenac sodium compared to those coated with only Surelease. Release rates were similar for pellets coated with Surelease containing 5% and 7.5% HPMC E15. Increasing the HPMC E15 content in the film to 10% increased the release rates. Addition of 5% HPMC E15 into Surelease film increased the first-order release rate by a factor of four compared to those coated with Surelease only at the 20% coating load (14). When the HPMC E15 content in

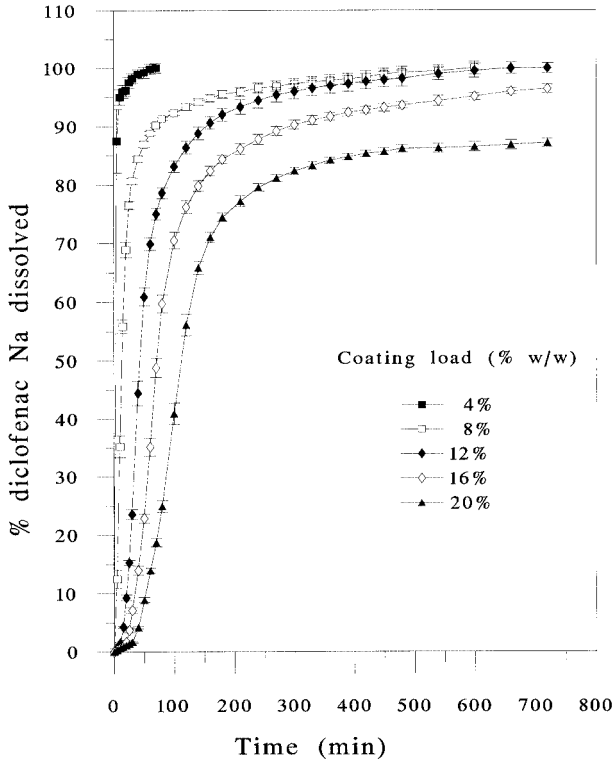

Figure 4. Effect of coating load on the release of diclofenac sodium from pellets coated with Surelease containing 5% HPMC E15.

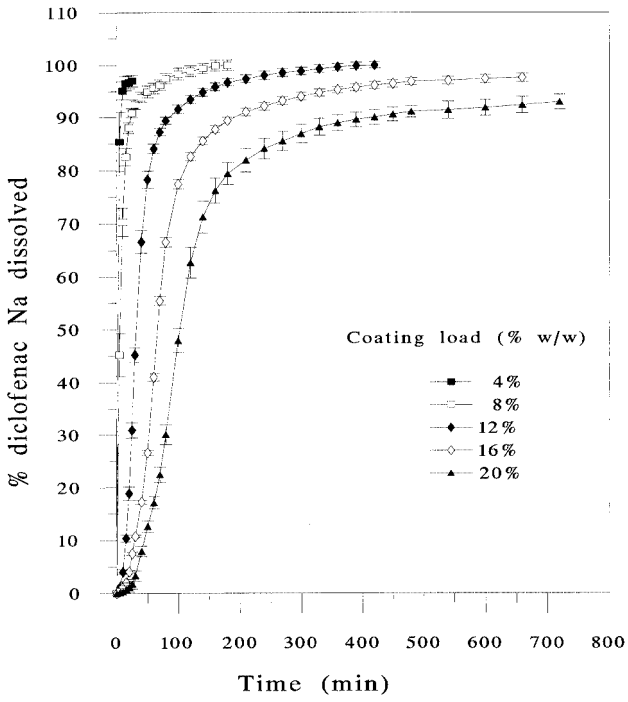

Figure 5. Effect of coating load on the release of diclofenac sodium from pellets coated with Surelease containing 7.5% HPMC E15.

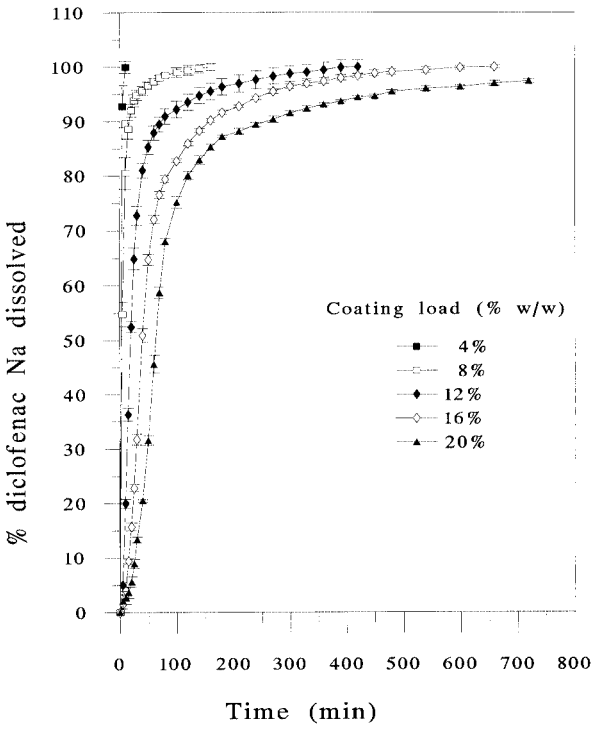

Figure 6. Effect of coating load on the release of diclofenac sodium from pellets coated with Surelease containing 10% HPMC E15.

the film reached 10%, the first-order release rate (Table 10) was 1.5 times faster than from pellets containing 5% HPMC E15 (Table 8) at the 20% coating load. Again, the inclusion of HPMC E15 decreased the lag times before the controlled-release profiles were established. Contrary to pellets loaded with metoclopramide hydrochloride, the inclusion of 5% HPMC E15 considerably increased the release rate of diclofenac sodium. In addition, the lag time decreased from about 80 min to about 30 min after the inclusion of 5% HPMC E15 into the Surelease coat for pellets with a 20% coating load.

Correlation coefficients r of the fits of diclofenac sodium release data to different kinetic models are shown in Tables 8–10. The correlation coefficients for the best statistical fits revealed that the zero-order kinetic model is probably the most applicable to all the release data. Coating load and HPMC E15 content of the coat did not change the best kinetic model.

Tables 5–7 summarize the values of K, n, and t_{lag} obtained from Eq. 4. The coating load and HPMC E15 content in the film had no apparent effect on the mechanism of diclofenac sodium release. The mean value of n is 1.28 ± 0.25. A comparison of release exponent n with those obtained for pellets coated with Surelease solely (14) showed that different mechanisms control drug release from pellets coated with Surelease/HPMC E15 blends and those coated only with Surelease. The values of n indicate a dissolution controlled-release mechanism for pellets coated with Surelease/HPMC E15 blends. Therefore, it may be concluded that, in systems in which numerous pores are present in the coat, diffusion of drug

Table 8

Values of Release Constants K, *Correlation Coefficients* r, *and Lag Times* (t_{lag}) *Obtained from Data Corresponding to 15%–60% Release of Diclofenac Sodium from Pellets Coated with Surelease Containing 5% HPMC E15, Using Equations 1–3*

Model	[a]	8%	12%	16%	20%
Zero order	K_1	3.8 ± 0.1	1.9 ± 0.1	1.2 ± 0.1	0.68 ± 0.01
	r	0.993	0.998	0.998	0.997
	$P<$	0.01	0.01	0.001	0.001
	$(t_{lag})_1$	1.2 ± 0.4	16.7 ± 0.2	29.3 ± 0.6	40.9 ± 0.7
Square root	K_2	25.6 ± 0.6	22.3 ± 0.8	17.9 ± 0.4	13.4 ± 0.3
	r	0.990	0.997	0.994	0.996
	$P<$	0.01	0.01	0.001	0.001
	$(t_{lag})_2$	3.1 ± 0.2	18.9 ± 0.1	32.3 ± 0.5	47.3 ± 0.4
First order	K_3	0.0697 ± 0.0021	0.0313 ± 0.0016	0.0191 ± 0.0009	0.0119 ± 0.0005
	r	0.988	0.996	0.989	0.994
	$P<$	0.01	0.01	0.001	0.001
	$(t_{lag})_3$	3.4 ± 0.3	20.6 ± 0.3	34.9 ± 0.3	52.1 ± 0.6

[a] See Table 2 footnote for values.

Table 9

Values of Release Constants K *Correlation Coefficients* r*, and Lag Times (t_{lag}) Obtained from Data Corresponding to 15%–60% Release of Diclofenac Sodium from Pellets Coated with Surelease Containing 7.5% HPMC E15, Using Equations 1–3*

Model	[a]	12%	16%	20%
Zero order	K_1	2.3 ± 0.1	1.2 ± 0.1	0.74 ± 0.5
	r	0.998	0.992	0.995
	$P<$	0.001	0.001	0.001
	$(t_{lag})_1$	11.2 ± 0.3	23.9 ± 0.3	36.6 ± 1.3
Square root	K_2	2.37 ± 0.5	16.7 ± 0.2	13.3 ± 0.9
	r	0.994	0.983	0.987
	$P<$	0.001	0.001	0.001
	$(t_{lag})_1$	12.8 ± 0.2	26.5 ± 0.3	41.3 ± 1.1
First order	K_3	0.0370 ± 0.0069	0.0202 ± 0.0005	0.0124 ± 0.0011
	r	0.988	0.975	0.982
	$P<$	0.01	0.001	0.001
	$(t_{lag})_3$	14.3 ± 0.2	29.5 ± 0.2	45.2 ± 1.1

[a] See Table 2 footnote for values.

is a rapid process and is not the rate-limiting step. In this case, it is probable that the rate of pore formation controls the drug release.

Leaching of Hydroxypropylmethylcellulose E15 from Surelease Film

To understand the mechanisms of the enhancement of the release rate of the drugs through the Surelease coat following the addition of HPMC E15, studies were performed on free films containing 7.5% HPMC E15, representative of Surelease/HPMC E15 films. The amount of HPMC E15 leached from the Surelease/HPMC E15 films was 45.5% ± 2.1% after 30 min as determined by weight loss. However, no weight loss was detected from Surelease films. This suggests that, as pellets undergo dissolution, HPMC E15 in the coat would dissolve and leach out, leaving pores through which the drug may be released. These results are in accord with those published by Donbrow and Samuelov (10) and Lindholm et al. (17)

Table 10

Values of Release Constants K *Correlation Coefficients* r*, and Lag Times (t_{lag}) Obtained from Data Corresponding to 15–60% Release of Diclofenac Sodium from Pellets Coated with Surelease Containing 10% HPMC E15, Using Equations 1–3*

Model	[a]	12%	16%	20%
Zero order	K_1	3.0 ± 0.1	1.7 ± 0.1	1.2 ± 0.1
	r	0.999	0.998	0.996
	$P<$	0.001	0.001	0.001
	$(t_{lag})_1$	2.8 ± 0.4	10.9 ± 0.3	20.5 ± 0.3
Square root	K_2	24.7 ± 0.8	19.5 ± 0.3	16.6 ± 0.4
	r	0.997	0.997	0.989
	$P<$	0.001	0.001	0.001
	$(t_{lag})_2$	5.6 ± 0.2	14.2 ± 0.2	24.1 ± 0.2
First order	K_3	0.0554 ± 0.0023	0.0299 ± 0.0009	0.0205 ± 0.0004
	r	0.993	0.995	0.986
	$P<$	0.01	0.001	0.001
	$(t_{lag})_3$	6.4 ± 0.3	15.6 ± 0.9	27.2 ± 0.4

[a] See Table 2 footnote for values.

for the effects of polyethylene glycol or polysorbate 20 in ethylcellulose films, respectively. However, these results contradict those published by Donbrow and Samuelov (10) for the effect of HPC as an additive in ethylcellulose films. These authors stated that the increase in permeation through the ethylcellulose/HPC film was due to retention of the HPC in the film and the formation of swollen hydrated channels. The differences between the results of this study and those performed by Donbrow and Samuelov may be due to the differences in the type of cellulose ethers used. The reduced interaction of HPMC with ethylcellulose due to its increased substitution (18) may be responsible for the leaching of HPMC from these films.

Surface Morphology of the Pellets

The surfaces of the coated pellets were examined by scanning electron microscopy, as described previously (14), before and after dissolution. The surface characteristics of either the metoclopramide hydrochloride or diclofenac sodium pellets coated with Surelease films containing different amounts of HPMC E15 at high coating loads such as 20% w/w, were similar before and after dissolution. Due to the porous nature of the coat, it was not possible to distinguish between pores resulting from dissolution of HPMC and pores that already existed in the coat.

However, at the lower 8% w/w coating load, there were some cracks present on the surface of some of the pellets after dissolution (Fig. 7). These cracks were not observed for pellets coated with Surelease only (14). The development of these cracks at low coating loads may be explained as follows: As the retention of the HPMC in the ethylcellulose/HPMC blend depends on the coating thickness (19), it is more likely that, at a low coating load (e.g., 8% w/w), the dissolution and leaching of HPMC occurs through the full thickness of the coat. However, at the higher coating load (e.g., 20% w/w), with increased coating thickness, the possibility of retention of HPMC in the inner layers is more than at the lower coating load. Leaching of HPMC provides some weak points in the membrane, which cause it to be ruptured under the internal stresses as water penetrates the core. However, at a high coating load, the support provided by the inner layers of the coat prevents development of these cracks.

The results of this study indicate that the addition of the hydrophilic polymer HPMC E15 increased the release rate of both drugs from pellets coated with Surelease. Studies on free films revealed that the HPMC dissolved; consequently, the formation of pores in the film was probable. These pores, which might facilitate the ingress of water into the pellets and release of the drug from the pellets, were responsible for the faster release rates of drugs. These blends show phase separation (18) and may be considered as physical blends resulting in pore formation due to the dissolution of water-soluble HPMC E15 and leaching from the coat.

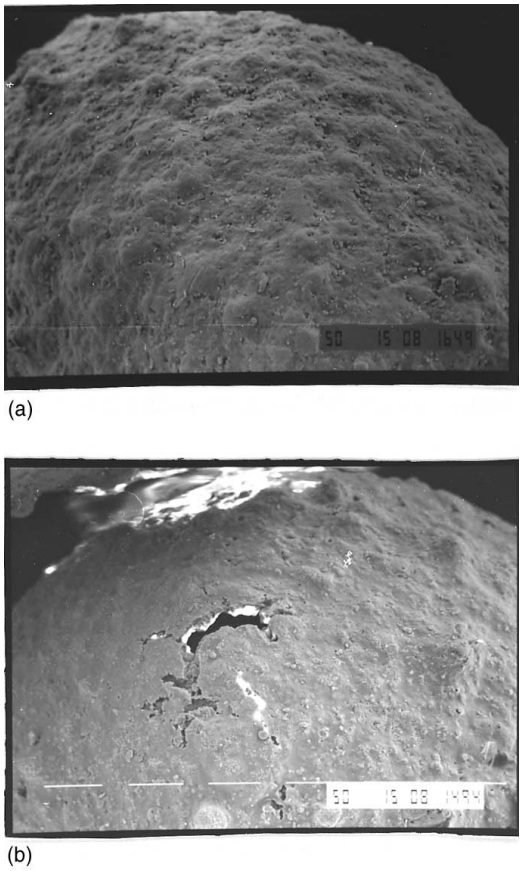

Figure 7. Micrographs of diclofenac sodium pellets coated with Surelease containing 7.5% HPMC E15 at 8% coating load: (a) before dissolution; (b) after 5 h dissolution (×150).

Comparison Between Rates and Mechanisms of Metoclopramide Hydrochloride and Diclofenac Sodium Release from Pellets Coated with Surelease/ Hydroxypropylmethylcellulose E15

It has been reported that, despite its lower water solubility, diclofenac sodium was released more quickly than metoclopramide hydrochloride from pellets coated with Surelease (14). In this study, addition of HPMC E15 to

Surelease increased the release of diclofenac sodium more than metoclopramide hydrochloride (Tables 2–4, 8–10). The values of *n* were higher for diclofenac sodium than for metoclopramide hydrochloride, indicating different mechanisms for the release of these drugs. Release of metoclopramide hydrochloride was controlled mainly via diffusion. However, the contribution of diffusion as a rate-limiting step in the release of diclofenac sodium was reduced.

One explanation that may describe the faster release of diclofenac sodium is that the mechanism involved in the release of these drugs from Surelease-coated pellets is diffusion through the intact polymeric film. In this case, drugs of low water solubility may be released more rapidly than expected (20). However, when the drug is released via diffusion through water-filled pores or channels within the coat, the solubility of the drug in water will be a significant factor in determining the release rate (20). However, the differences observed in the release rates of the two drugs here are not due to the differences in their diffusion rates through the polymer film. Other possible causes, such as drug-excipient interactions, are under study to explain the differences between release behavior of these two drugs from Surelease-coated pellets.

CONCLUSIONS

The release rates of both metoclopramide hydrochloride and diclofenac sodium increased with increasing the amount of hydrophilic polymer HPMC E15 in the Surelease coating. The ratio of Surelease to the HPMC E15 had a major effect on the drug release rate. High proportions of HPMC E15 component in Surelease membrane caused a rapid release of drugs even at high coating loads. This effect was related to the leaching of the HPMC from the Surelease film, which led to the formation of pores. The pores were thought to act as points for entry of dissolution medium through the film into the core and consequent dissolution and release of drug from the pellets. The release rate of diclofenac sodium was unexpectedly faster than that of metoclopramide hydrochloride. The mechanism of release of these two drugs was also different. The different release behavior of these drugs may be related to possible drug-excipient interactions.

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