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Factors affecting drug release from a pellet system coated with an aqueous colloidal dispersion

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Summary

The formulation of sustained-release pellets of dextromethorphan hydrobromide is described. The system used consisted of drug-coated sugar spheres which were then overcoated with the rate-controlling membrane. The membrane was produced by spray-coating with an aqueous dispersion of ethylcellulose containing hydroxypropyl methylcellulose. It is shown that adequate post-coating conditioning is important to ensure consistency of release rates. Conditioning at 60 °C for at least 1 h is necessary in order to ensure that the formulations produced show no ageing effects in release rates. Drug release could be made pH-independent by a choice of proper formulation.

Introduction

The use of solvents for film coating poses several disadvantages which have become more apparent in the last 25 years due to the introduction of spray coating systems containing large volumes of organic solvents. Pollution and solvent toxicity which have resulted in strict government regulations concerning solvent emissions together with the expense and explosion hazards of solvents have led to the renewed interest in water-based coatings.

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In the mid-seventies, work began to develop a new class of film-coating materials which could be more suitable for the needs of the pharmaceutical industry of the eighties and nineties (Onions, 1986a). The result of this research was the introduction of aqueous colloidal dispersions for film coating.

In the present study, a commercially available ethylcellulose (EC) aqueous colloidal dispersion will be investigated with a view to providing a solid dosage form with controlled-release properties.

Aqueous colloidal dispersions are also referred to as latices or pseudolatices. Physically, pseudolatices are indistinguishable from true polymer emulsions or latices. A true latex is formed from a synthetic polymer with a liquid monomer and is prepared by emulsion polymerisation (for exam-

ple, Eudragit® NE30D). Both latices and pseudolatices (for example, Eudragit® RS and RL30D) are or may be colloidal dispersions containing spherical, solid or semi-solid particles less than 1 μm in diameter and typically less than 0.1 μm in diameter. Both are fluid even at polymer concentrations of 20–40% w/w and both systems form films by the same mechanism. (Vanderhoff et al., 1966; Vanderhoff, 1970; Miller and Vadas, 1984; Onions, 1986a). The process of film formation involves deposition of the polymer from the aqueous colloidal dispersion, evaporation of water and concentration of the polymer spheres, coalescence of the spheres due to deformation and further fusion by adjacent polymer spheres by interdiffusion of the polymeric molecules to form a continuous homogenous film, the final stage of film formation being known as further gradual coalescence. The differences between pseudolatex and latex systems are, as stated by Banker and Peck (1981), that water-based true latices are limited to synthetic polymers with liquid-insoluble monomers that may be emulsified into water and may contain residual monomers and initiators, such as peroxides, surfactants and other chemicals used in the emulsion-polymerisation process. In contrast, pseudolatices may be prepared from virtually any existing water-insoluble polymer.

This study reports on the release of dextromethorphan hydrobromide (DMHB) from pellets coated with an EC aqueous colloidal dispersion. The effects of the additive hydroxypropylmethylcellulose (HPMC), storage and conditioning of the pellet system, prior to release studies, were investigated to elucidate their effect on the rate of drug release from the dosage form.

Materials and Methods

Materials

Hydroxypropylmethylcellulose (Shin-Etsu Chemical Co., Japan), citric acid (AR grade, BDH Ltd, U.K.), disodium hydrogen orthophosphate and potassium chloride (GPR grade, May and Baker, U.K.), ethylcellulose aqueous colloidal dispersion (FMC Corp., Philadelphia), triethylcitrate (Pfizer Inc., New York) and dextromethorphan hydrobromide (Sigma, U.K.) were obtained from the indicated sources.

Methods

Drug loading and coating of drug coated pellets

Drug loading The drug-loaded beads consisted of small sugar (65–85%)/starch (10–40%) spheres (Nupareil® seeds) of size 20–25 which had dextromethorphan hydrobromide impregnated onto them. 400 mg of the drug-loaded beads were weighed and placed in 80 ml of McIlvaine buffer pH 6.90, 1.0 M constant ionic strength, and shaken at 100 rpm for 48 h. The temperature was controlled to 37 ± 0.5 °C. Before ultraviolet analysis at a λ_{max} of 280 nm for DMHB the solutions were filtered through a 0.45 μm filter to obtain clear solutions. All experiments were performed in quadruplicate.

Coating of drug-loaded pellets The drug-loaded beads were coated with EC aqeuous colloidal solutions containing 0–12% w/w HPMC and 24% w/w of total polymer solids of triethylcitrate. The theoretical level of coating is 6.48% w/w, based on the sum of the weights of polymer solids and plasticiser divided by the batch size of drug coated Nu-pareil® seeds. The production methods currently available for pellet manufacture are discussed by Gamlen (1985). In this study batches of drug impregnated Nu-pareil® seeds, 1.3 kg per batch, were coated using the Uniglatt Laboratory Unit (Glatt Air Technique, NJ) which employs a bottom-spray coating process in a Wurster column (Porter, 1982; Mehta et al., 1986). Coating conditions were: an inlet temperature of 45–55 °C and an outlet temperature of 27–31 °C; coating mixtures were pumped to the atomiser at a rate of 3 ml/min operating at a spray pressure of 20 psi. The total coating time was 100–110 min. No post-coating drying was carried out.

Dissolution studies

The dissolution method was performed as described under the dissolution test for tablets and capsules (Appendix XIID, British Pharmacopoeia, Vol. 11, 1980) using an automated

lution assembly which consisted of an Apple IIe computer and TDS Software; Epson LX 86 printer; a peristaltic pump (Watson Marlow Ltd, U.K.); an LKB 4052 Ultrospec UV Spectrophotometer; a Caleva Model 7ST water bath fitted with variable-speed stirring unit and a Tempette Junior JE-8J (Techne, U.K.) heater and water bath. 500 ml of McIlvaine buffer, 1.0 M constant ionic strength, previously warmed to 37 °C was introduced into the six cylindrical flat-bottomed glass vessels. 800 mg of the coated pellets was placed in the baskets and lowered into the dissolution medium to between 18 and 20 mm of the bottom interior surface of the vessels. Rotational speed was adjusted to 100 rpm and the motor started. Sampling was performed automatically, at predetermined time intervals, using the above apparatus equipped with an eight-station cell holder of which six cells were flow-through. Ultraviolet detection was at a λ_{max} for DMHB of 280 nm. All experiments were performed in quadruplicate.

Effect of HPMC Pellets were coated with polymer dispersions containing 0–12% w/w HPMC using the method described previously. McIlvaine buffer pH 6.90 was used as the dissolution medium.

Effect of pH The effect of pH on the dissolution properties of the Uniglatt coated pellets containing 0 and 12% w/w HPMC was investigated. The pH values chosen were 6.90 and 2.10 using McIlvaine buffer.

Effect of storage and pellet conditioning The effect of storage and pellet conditioning, after initial film formation, was investigated. Dissolution studies were performed on the pellets after storage at room temperature for 4 months. The effect of conditioning on the dissolution properties of pellets containing 0, 4, 8 and 12% w/w HPMC at 60 °C for 1, 4 and 16 h, after initial film formation, was investigated. Pellets containing 2, 6 and 10% w/w HPMC were also studied after conditioning at 60 °C for 16 h. McIlvaine buffer pH 6.90 was used as the dissolution medium.

Scanning electron microscopy

Scanning electron microscopy, using the Jeol JSM 35CF scanning electron microscope, was carried out on the pellets before and after dissolution studies. The samples were mounted on stainless-steel stubs, of suitable dimensions, using double-sided adhesive tabs. The mounted samples were sputter coated before investigation under the electron microscope. Magnifications best suited to revealing the surface structure were selected.

Results and Discussion

Before discussing the factors affecting the in vitro release of drug from the pellet systems it is necessary to determine the actual drug loading on the pellets, as opposed to the theoretical drug loading, to enable the correct percentages of drug released, for the pellet systems to be calculated. The drug loaded beads were prepared by spraying 100 g of drug, in a solution of 60% dichloromethane and 40% methanol, onto 1 kg of beads using the Uniglatt Laboratory Unit. Thus, the theoretical yield was a drug loading of 10% w/w. The actual drug loading, calculated according to the method described previously was 8.76% w/w. It was then decided necessary to determine the actual drug loading on each of the batches of pellets coated with the different coating solutions containing 0–12% w/w HPMC, to investigate any difference there may be in the drug loading for each batch. It was found that for pellets coated with EC pseudolatex films containing 0–12% w/w HPMC the actual drug loading was $8.45 \pm 0.29\%$ w/w which is equivalent to $96.50 \pm 3.31\%$ of the actual drug loading calculated from the uncoated pellets. Thus calculation of the drug loading on the uncoated pellets gives an accurate value for the drug loading determined for each individual batch of coated pellets. In the following discussion the actual drug loading determined for each individual batch of coated pellets will be used as the value representing 100% of the drug released from the pellets.

Effect of HPMC

It is well known that addition of an additive to a polymer film will alter the permeability charac-

teristics of that film (Shah and Sheth, 1972; Donbrow and Samuelov, 1980; Lindholm and Justin, 1982; Lindholm et al., 1985; Ghebre-Sellasie et al., 1984; Ghebre-Sellasie et al., 1987). Figs 1 and 2 show the effect of increasing the proportion of HPMC in the polymer film coating from 0 to 12% w/w of the total polymer solids. Increasing the percentage of hydrophilic additive, in the film, increases the release rate of drug from the pellets. This effect has been found by several authors who have studied the effect of hydrophilic additives on spherical diffusion-controlled systems. Kannikoski et al. (1984) modified the properties of EC-coated verapamil HCl granules by the addition of HPMC. These authors found that the ratio of EC to HPMC had a major influence on drug release rate. Incorporation of 10% HPMC in the coating led to a 10–90% increase in the release rate of verapamil HCl, the variation in the percentage increase being attributed to the different nature of the plasticisers employed and the viscosity grade of EC. The increase in drug

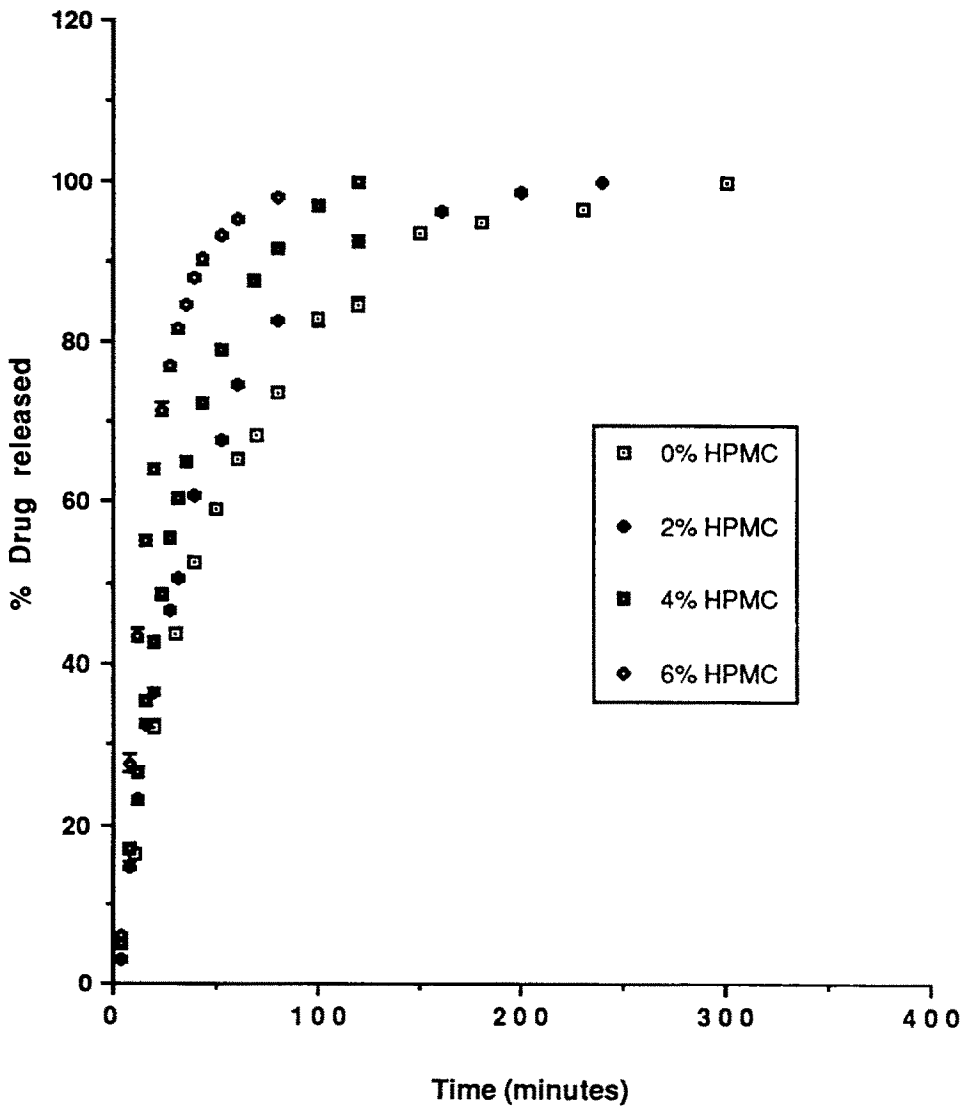

Fig. 1. The effect of HPMC on the permeation of DMHB across EC pseudolatex-coated pellets at pH 6.90.

release rate when the amount of HPMC was increased to 25% was of the order of 300–1000%. This effect was also found by Kohri et al. (1986) who reported that the release rate of nifedipine from granules composed of nifedipine, HPMC, EC and corn starch, increased with an increase in HPMC in the granules.

The release data in the present study were fitted to first-order kinetics and good fits were obtained (Table 1). Comparison of electron micrographs of pellets coated with an EC pseudolatex film containing 4% w/w HPMC, before and after dissolution, shows that after dissolution numerous pores and cracks were present in the polymer film coating (Fig. 3). This effect was evident for all of the pellets studied including pellets coated with an EC pseudolatex film containing no HPMC (Fig. 4). This observation would suggest that the cracks were not related to the presence of HPMC in the films or caused by the leaching of HPMC from the film but rather to an incompletely formed pseudolatex polymer film

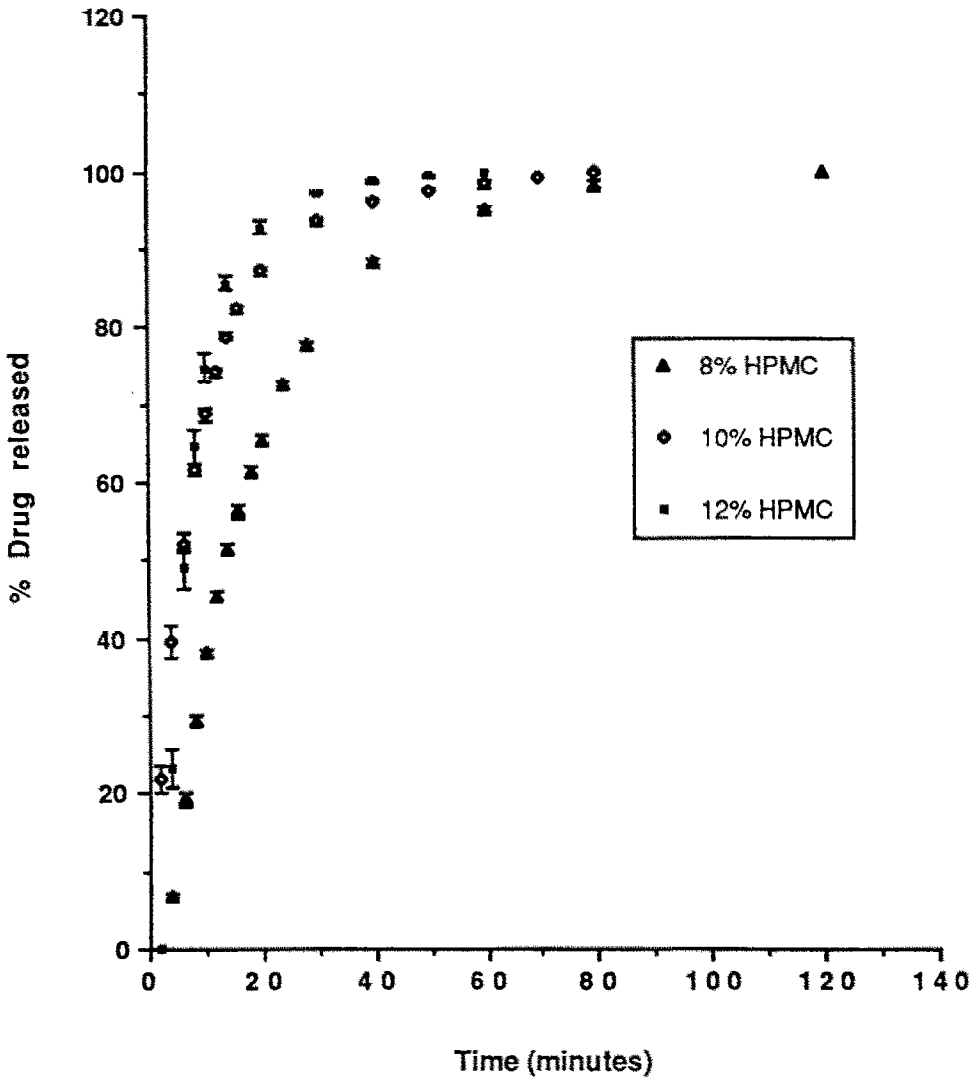

Fig. 2. The effect of HPMC on the permeation of DMHB across EC pseudolatex-coated pellets at pH 6.90.

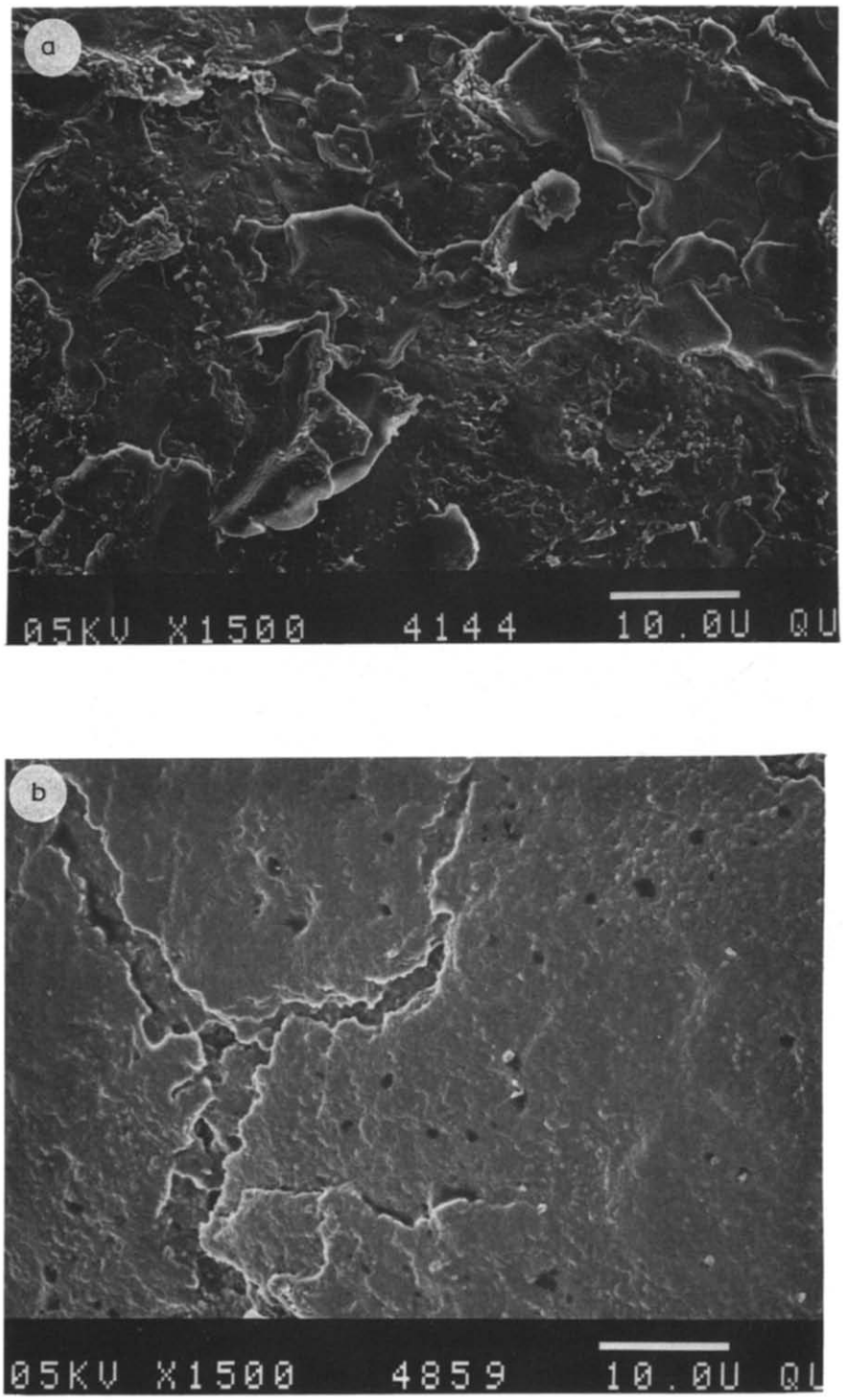

Fig. 3. Surface structure of EC pseudolatex-coated pellets containing 4% w/w HPMC: (a) before dissolution, ×1500 magnification; (b) after dissolution, ×1500 magnification.

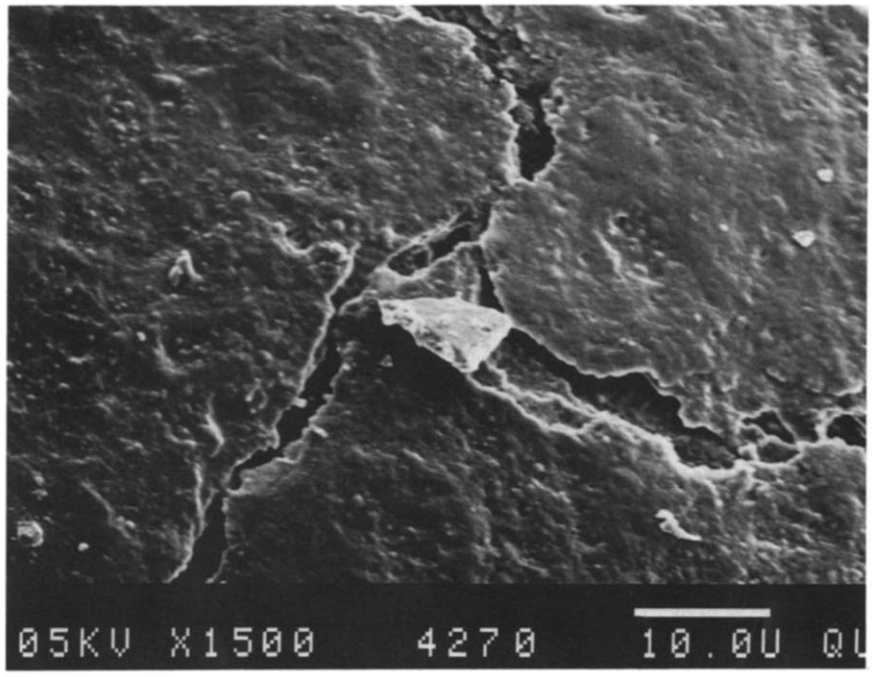

Fig. 4. Surface structure of EC pseudolatex-coated pellets containing no HPMC after dissolution; ×1500 magnification.

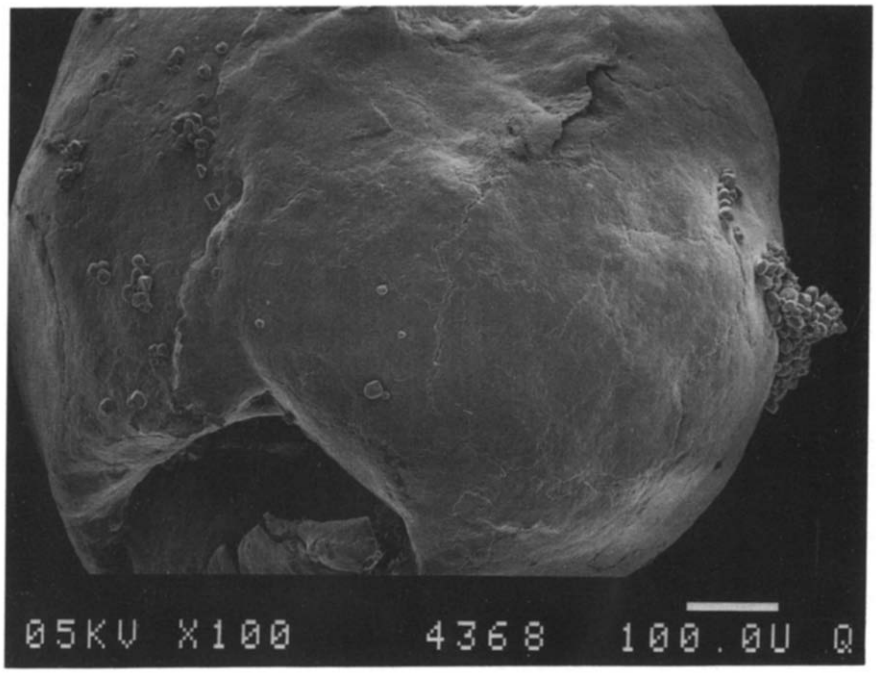

Fig. 5. Surface structure of EC pseudolatex-coated pellets containing 12% w/w HPMC after dissolution; ×100 magnification.

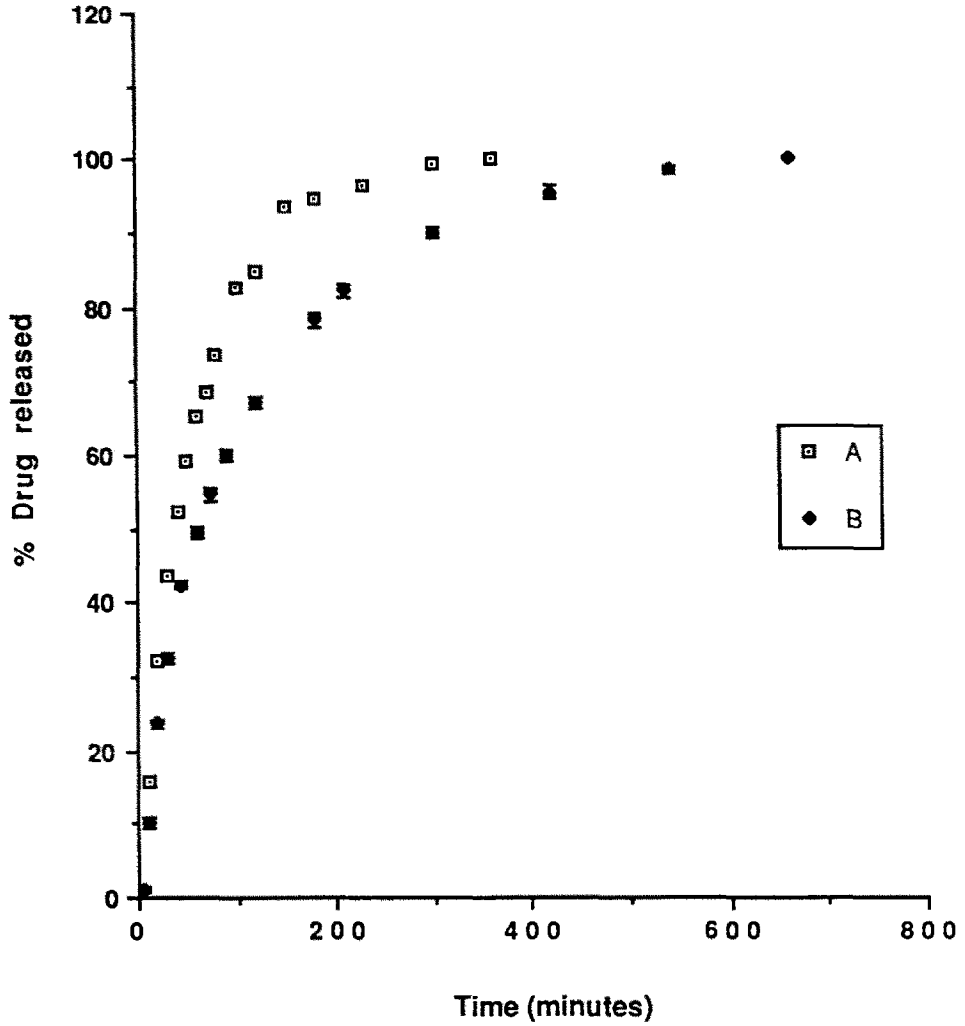

Fig. 6. The effect of storage for 4 months at room temperature on the release of DMHB from pseudolatex-coated pellets at pH 6.90: (A) 0% HPMC pellets with no storage; (B) 0% HPMC pellets stored at room temperature for 4 months.

coating. Previous electron microscopic investigation, in this laboratory, into cast films containing HPMC from both solvent based and pseudolatex based films, indicate that HPMC leaches when in contact with an aqueous medium to form pores, not cracks, in the polymer film structure. An electron micrograph of a pellet containing 12% w/w HPMC, taken after dissolution, shows that the polymer film coat contains large pores and cracks (Fig. 5) explaining the very rapid release from these pellets with complete drug release in sixty minutes. Drug release from these pellets, however, still obeys first-order kinetics (Table 1).

Approx. 80% of DMHB was released in 2 h from the pseudolatex-coated pellets containing no HPMC. This time period of release is unsuitable for a controlled prolonged release product.

At this stage it was thought that incomplete film formation could be responsible for the rapid drug release from the pellets. It was thus decided to investigate the effect of storage and certain conditioning procedures on the in vitro release of DMHB from the pseudolatex-coated pellets to see whether this would affect the polymer film

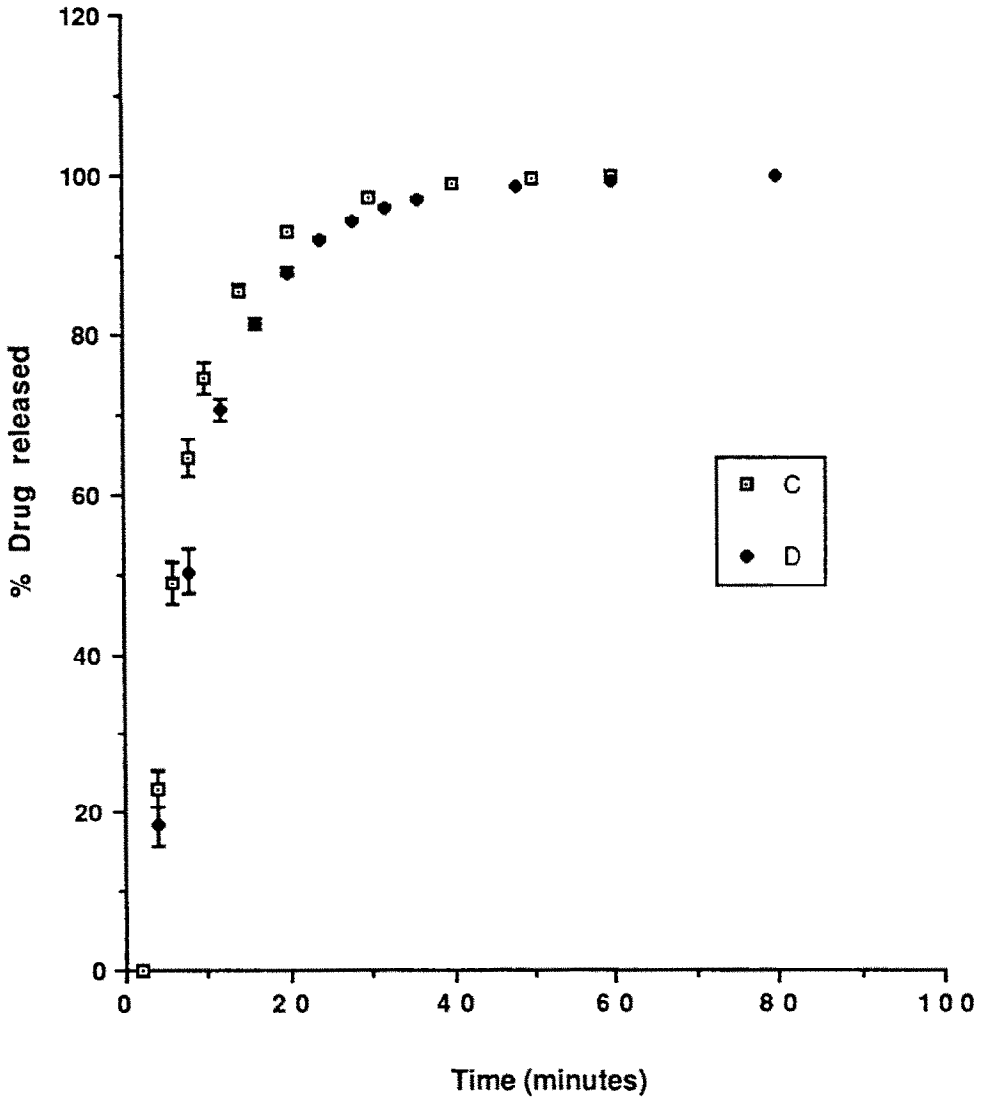

Fig. 7. The effect of storage for 4 months at room temperature on the release of DMHB from pseudolatex-coated pellets at pH 6.90. (C) 12% HPMC pellets with no storage; (D) 12% HPMC pellets stored at room temperature for 4 months.

coating structure and hence decrease the drug release rate from the pellets.

Effect of storage and conditioning on the coated pellets

Effect of storage It has been shown that pseudolatex films undergo a process of further gradual coalescence, after initial film formation, to form a homogeneous continuous film in which the contours of the individual particles are no longer visible (Miller and Vadas, 1984; Onions, 1986b). This process has been shown to be a function of the temperature of the film-forming process and duration of any post-spraying heating. Figs 6 and 7 show the effect of storage for 4 months at room temperature on the dissolution profiles of the pseudolatex-coated pellets containing 0 and 12% w/w HPMC, respectively. The release data were fitted to first-order release kinetics and the rate constants reported in Table

TABLE 1

The effect of HPMC on the rate of dextromethorphan hydrobromide release from EC pseudolatex-coated pellets

% w/w HPMC concentration	Rate constant ±S.D. (min^{-1}) ($\times 10^4$)	% Drug released for rate determination	r^2 (%)	Mean square error
0	158± 5	0–85	99.0	0.00346
2	217± 7	0–90	99.7	0.00182
4	318± 3	0–90	99.9	0.00012
6	559± 5	0–90	99.9	0.00096
8	557± 7	0–90	99.7	0.00089
10	1000±17	0–85	99.4	0.00238
12	1670±36	0–85	99.2	0.00481

2 for the range of pellets studied. Analysis of variance using a one-way ANOVA test showed that there was a significant difference in the rate of drug release from the coated pellets before and after 4 months storage at room temperature. The decrease in release rate can be related to further gradual coalescence. Initially, the pseudolatex coat of the pellets did not fully coalesce. With time, coalescence proceeds to produce a more continuous polymer film resulting in a decrease in drug release rate. Research by FMC (1983) on the storage conditions of pellets coated with an EC aqueous dispersion, with a theoretical coat loading of 16%, at room temperature and 37 °C showed that, after a 3 month storage period no pronounced change in release rate was observed in those pellets stored at room temperature. This result differed from that observed above where a decrease in release rate was noted for the pellets after a storage period of 4 months at room temperature. This difference may be explained by the fact that in the study performed by the FMC workers the pellets were slow coated at a rate of 2–3 ml of coating mixture pumped to the atomiser per min followed by normal coating at a rate of 12–14 ml/min at a temperature of 64–67 °C. The pellets were post-dried at 34–38 °C for 10 min, the total processing time being 90–95 min. The pellets in this study were coated at a rate of 3 ml/min at 45–55 °C for a total period of 100–110 min with no post-drying period. The temperature of the coating procedure by the FMC workers was 64–67 °C which allowed complete film formation at this stage as it is known that the process of further gradual coalescence is completed if the coating procedure is carried out at 60 °C. Thus storage, in this instance, would not change the properties of the polymer film coating and a decrease in release rate would not be observed. The pellets in this study were coated at 45–55 °C and thus on completion of the coating, further coalescence would not have been complete. Storage of these pellets would allow further gradual coalescence to proceed thus providing a possible explanation for the decrease in release rate on storage.

TABLE 2

The effect of storage for 4 months at room temperature on the rate of dextromethorphan hydrobromide release from sustained-release pellets

% w/w HPMC concentration	Rate constant ±S.D. (min^{-1}) ($\times 10^4$)	% Drug released for rate determination	r^2 (%)	Mean square error
0	78± 2	0–85	99.0	0.00678
2	75± 2	0–90	99.1	0.00686
4	166± 2	0–90	99.6	0.00251
6	323± 6	0–90	99.9	0.00088
8	409± 5	0–90	99.8	0.00063
10	825±10	0–90	99.7	0.00233
12	1160± 8	0–90	99.7	0.00285

Conditioning of the coated pellets If a plasticised EC pseudolatex film is applied to Nu-pareil® seeds at 60 °C or coated pellets dried for 1 h at 60 °C after initial film formation then the process of coalescence is essentially complete. Thus, it was decided to investigate the effect, on drug release rates, of conditioning pellets at 60 °C for predetermined time periods. Figs 8–10 show the effect of conditioning at 60 °C for 1, 4 and 16 h for pellets containing 0, 8 and 12% w/w HPMC. The release data were fitted to first-order release kinetics. The release rate constants are given in Table 3 for the range of pellets and conditioning times studied. EC pseudolatex-coated pellets containing no HPMC conditioned at 60 °C for 1, 4 and 16 h and those containing 2 and 4% w/w

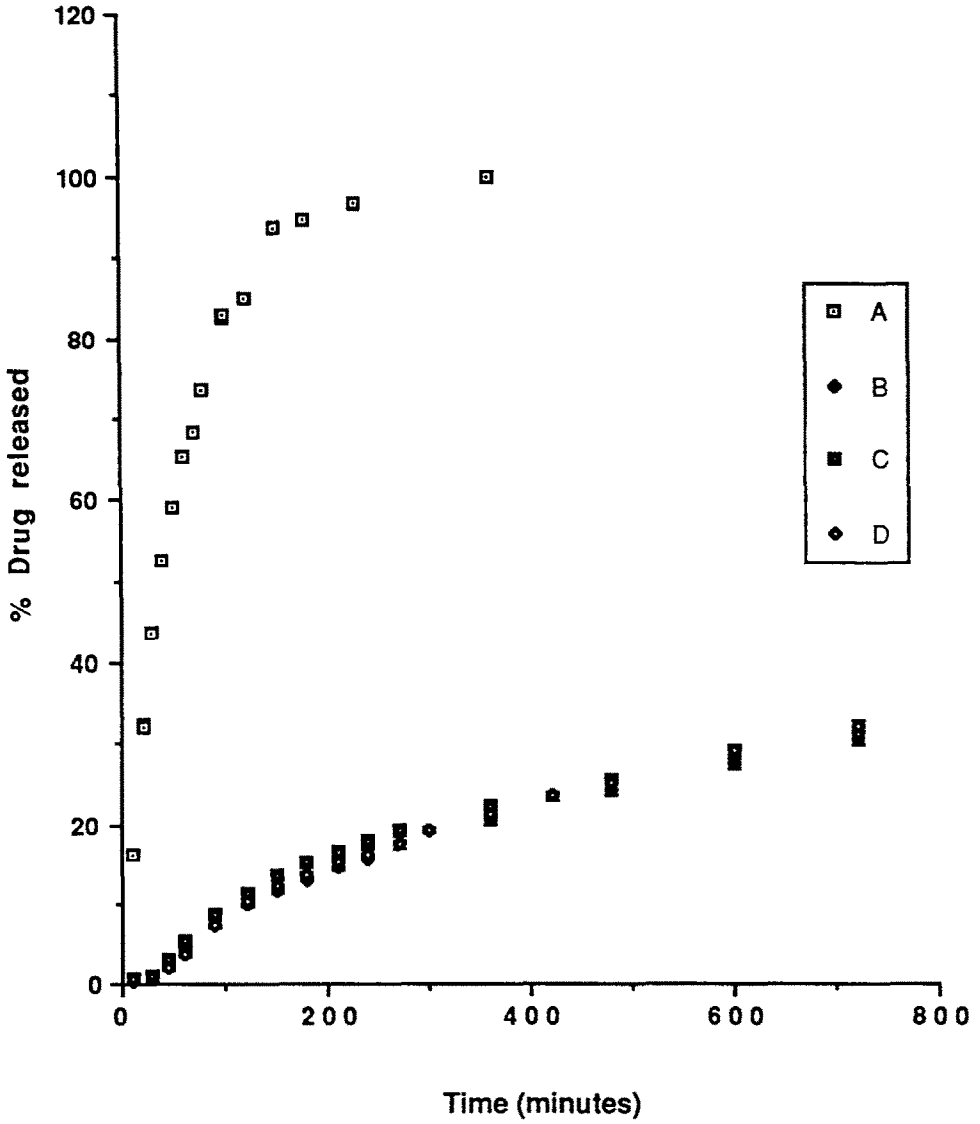

Fig. 8. The effect of conditioning on the release of DMHB from pseudolatex-coated pellets at pH 6.90. (A) 0% HPMC pellets with no conditioning; (B) 0% HPMC pellets conditioned at 60 ° C for 16 h; (C) 0% HPMC pellets conditioned at 60 ° C for 4 h; (D) 0% HPMC pellets conditioned at 60 ° C for 1 h.

HPMC conditioned at 60 ° C for 16 h showed no adherence to first-order release kinetics.

From the drug release rate constants it can be seen that conditioning of the pellets has a marked effect on the release of DMHB from the spherical systems. This effect was also observed by Goodhart et al. (1984) for phenylpropanolamine HCl release from EC pseudolatex-coated pellets. A faster drug release rate was observed for coated pellets dried for 48 h at 45 ° C as opposed to pellets dried for an additional 96 h at 65 ° C. The authors related this effect to the fact that as the drying temperature was decreased the hardness of the polymer particles increased resulting in resistance to deformation with the effect that an incomplete polymer film coating was obtained as

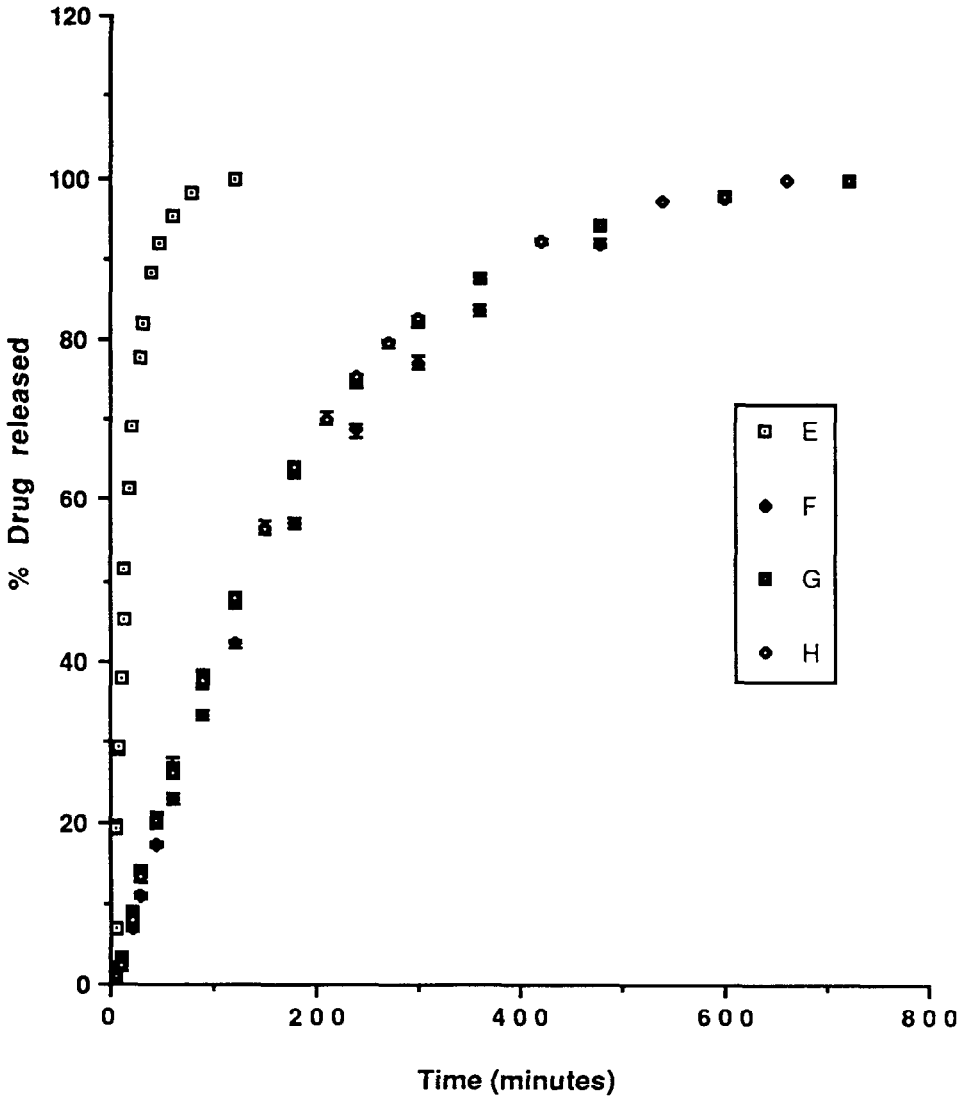

Fig. 9. The effect of conditioning on the release of DMHB from pseudolatex-coated pellets at pH 6.90: (E) 8% HPMC pellets with no conditioning; (F) 8% HPMC pellets conditioned at 60 ° C for 16 h; (G) 8% HPMC pellets conditioned at 60 ° C for 4 h; (H) 8% HPMC pellets conditioned at 60 ° C for 1 h.

opposed to additional drying at a higher temperature producing a more homogenous film with lower diffusivity. These authors also found that additional drying of the pellets at 65 ° C for 96 h promoted further gradual coalescence and thus further decreased the drug release rate from the pellets. This effect can be compared to that found in the above study, that is conditioning of the pellets at 60 ° C resulted in a decrease in drug release rate which can be related to the formation of a complete film in which the individual polymer particles have coalesced and in which further gradual coalescence is complete.

Thus, it can be seen that conditioning of the pellets at 60 ° C produces a decrease in the release rate of DMHB from the pellets. This effect was most evident at zero or low HPMC content. For example in 5 h 100% of DMHB was released

from EC pseudolatex-coated pellets with no conditioning, as opposed to only 18% of DMHB released from those pellets which had been conditioned for 16 h at 60 °C. The difference in release rate decreased with an increase in HPMC content until at 12% w/w HPMC the release rate is 100% in 1 h for the unconditioned pellets and 80% in 1 h for the pellets conditioned for 16 h at 60 °C. Drug content analysis of the pellets, conditioned at 60 °C for 16 h, was carried out to ensure that the decrease in drug release rate was not caused by a loss of drug loading during the conditioning at the elevated temperatures. It was found that drug loading for the conditioned pellets containing 0–12% w/w HPMC was 96.31 ± 3.22% of the intended drug loading. From this it can be concluded that the decrease in release rate from the conditioned pellets is not due to drug loss but rather to the effect of temperature on the pseudolatex film coating of the pellets.

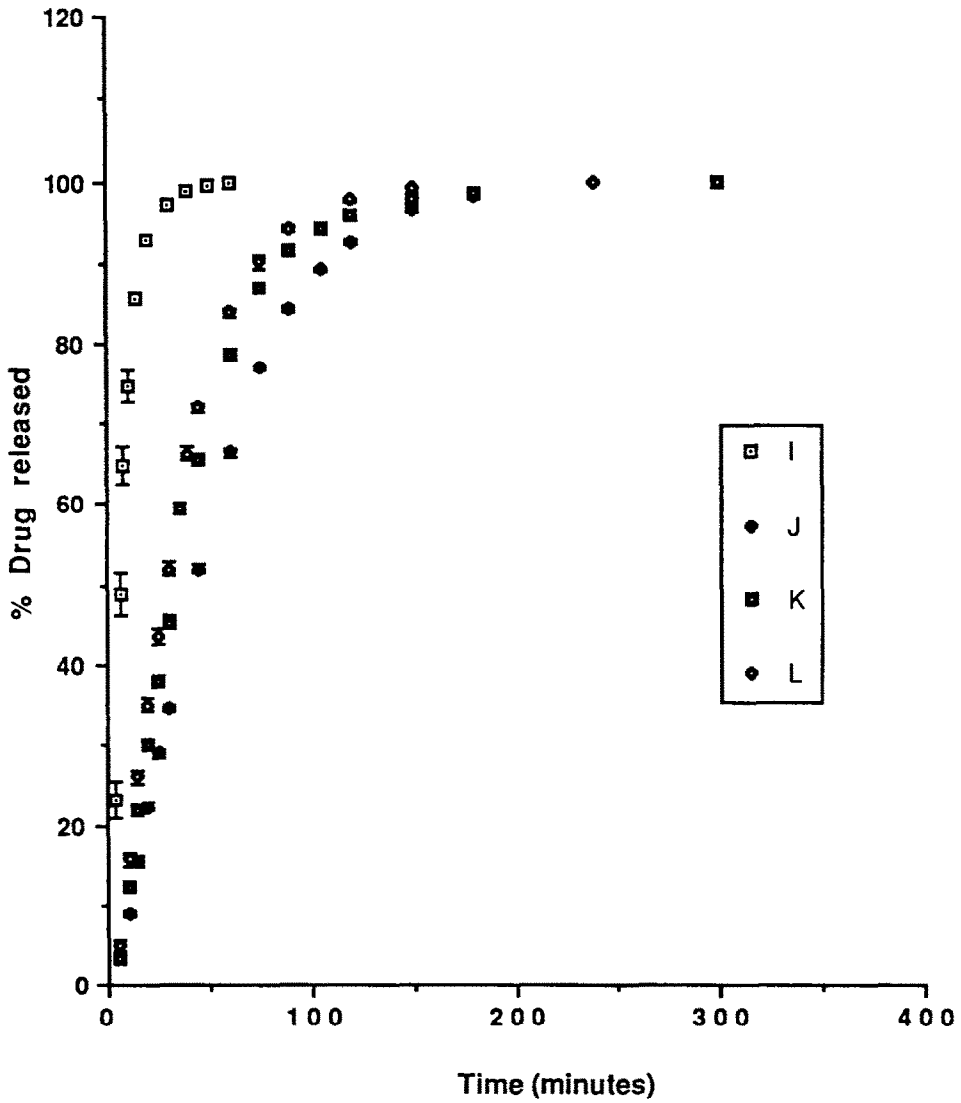

Fig. 10. The effect of conditioning on the release of DMHB from pseudolatex-coated pellets at pH 6.90: (I) 12% HPMC pellets with no conditioning; (J) 12% HPMC pellets conditioned at 60 °C for 16 h; (K) 12% HPMC pellets conditioned at 60 °C for 4 h; (L) 12% HPMC pellets conditioned at 60 °C for 1 h.

Electron micrographs indicate marked differences in film structure.

Conditioning of the pellets resulted in the production of a multi-unit dosage form which showed potential as a controlled release system with respect to the duration of action. Pellets with 6% w/w HPMC in the pseudolatex coating released 80% of the drug in approx. 10 h. Thus, by altering the coating conditions of the pellets, together with the storage and conditioning procedures after initial coating it would be possible to produce dosage forms which may ultimately be administered as a once or twice daily dosage regime.

From this study it can be seen that temperature is an important factor in the coalescence of the individual polymer spheres coated with pseudolatex dispersions. In order to produce consistent drug release profiles from the coated pellets it is necessary to ensure that the individual polymer spheres have fully coalesced. Otherwise, a variable drug release may be obtained. To ensure that the pellets are coated correctly, it is neces-

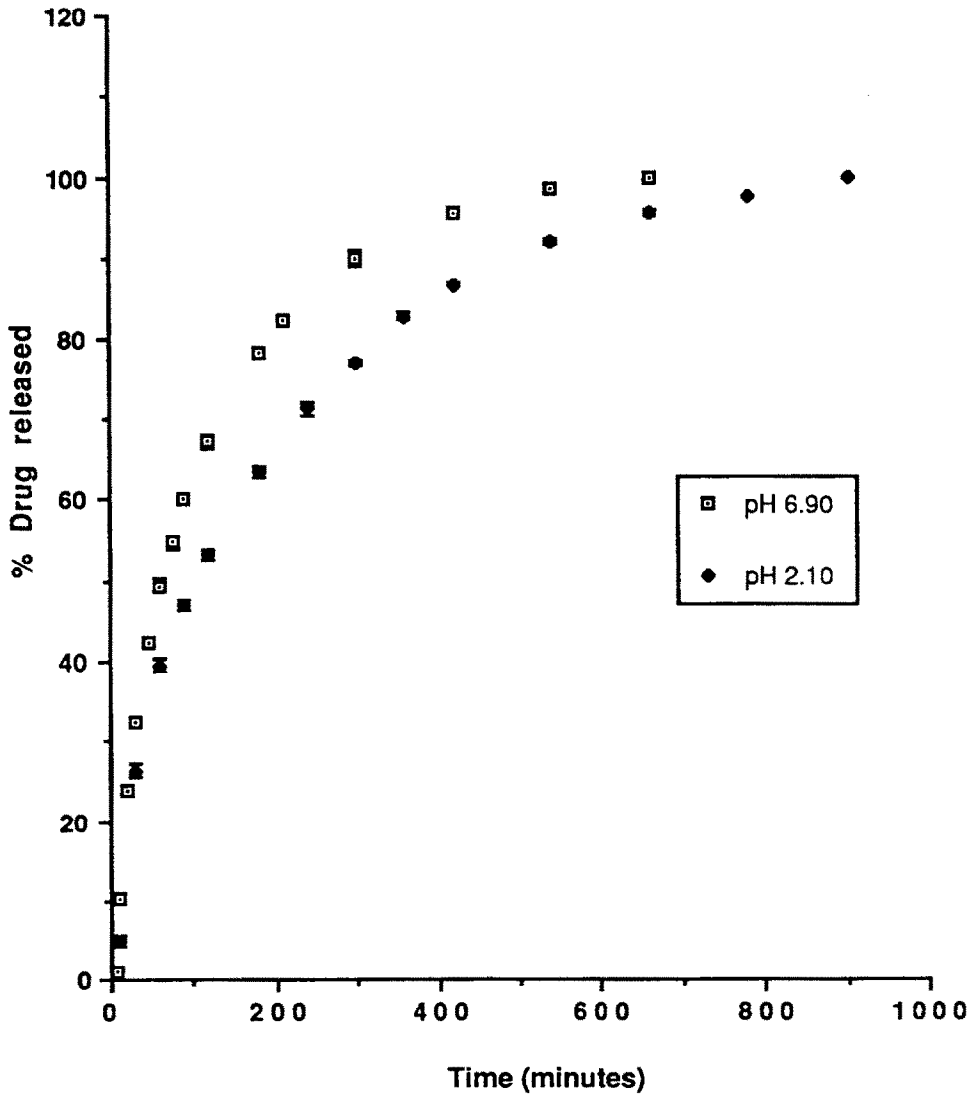

Fig. 11. The effect of pH on the permeability of pellets containing no HPMC to DMHB.

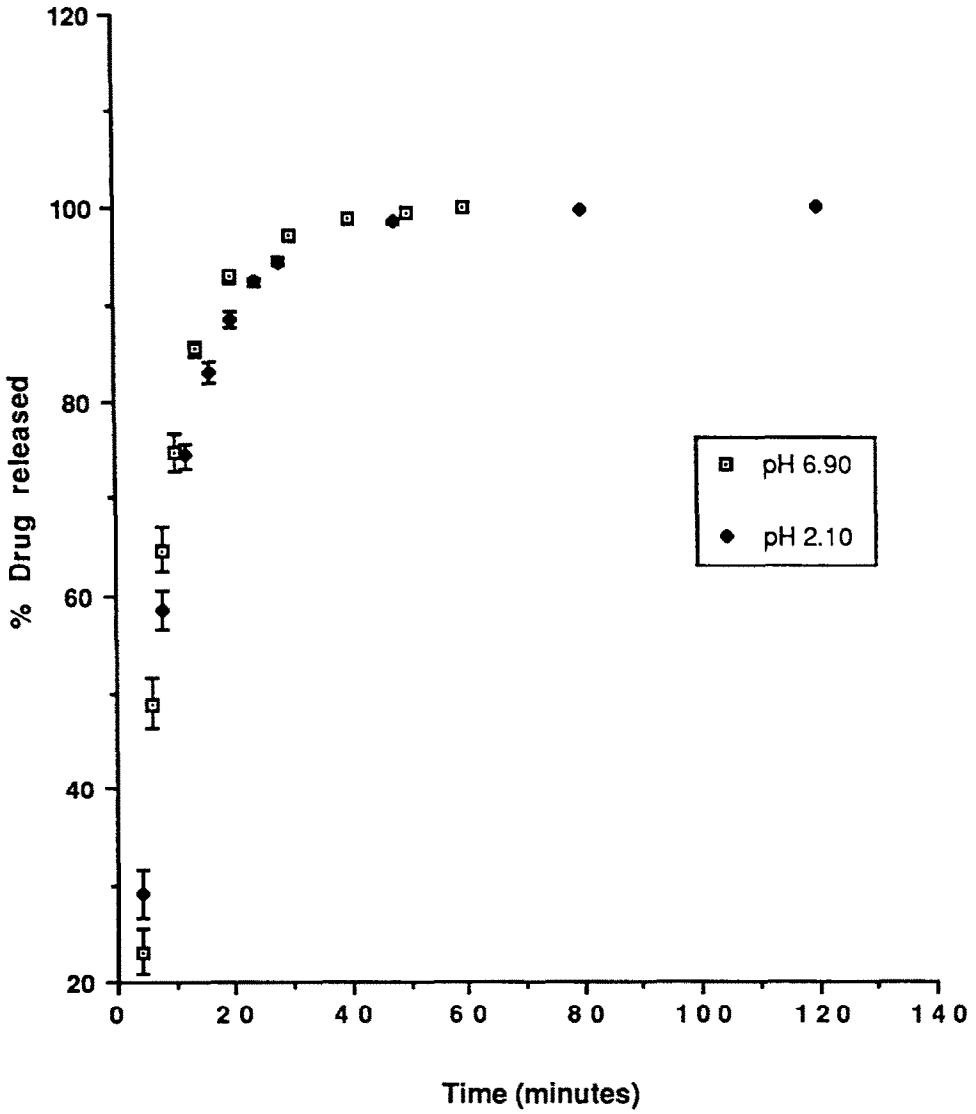

Fig. 12. The effect of pH on the permeability of pellets containing 12% w/w HPMC to DMHB.

sary to coat the pellets at a temperature sufficient to promote further gradual coalescence and to include a post-spraying drying period into the coating procedure.

Effect of pH

The effect of pH on the rate of drug release from EC pseudolatex coated pellets containing 0 and 12% w/w HPMC was investigated. Figs 11 and 12 show the effect of pH on the two sets of pellets. The release rate constants, based on first-order release kinetics are given in Table 4, with the corresponding r^2 values. Analysis of variance showed that there was no significant difference in the release rate constants for the pellets containing 12% w/w HPMC at the two experimental pH values ($F_{1,6,\alpha=0.05} = 5.99$, $F_t = 3.69$) although a significant difference in the release rate constants was observed for the pellets containing no HPMC ($F_{1,6,\alpha=0.05} = 5.00$, $F_t = 1246$).

The pK_a of DMHB was found to be 9.12 using

TABLE 3

The effect of pellet conditioning on the rate of release of dextromethorphan hydrobromide from pellets

% w/w HPMC concentration	Rate constant ± S.D. (min^{-1}) ($\times 10^5$)	% Drug released for rate determination	r^2 (%)	Mean square error
4_1 [a]	107 ± 4	0–55	99.7	0.00019
4_4	104 ± 1	0–55	99.1	0.00053
6_{16}	260 ± 4	0–85	99.9	0.00037
8_1	608 ± 8	0–90	99.9	0.00024
8_4	590 ± 11	0–90	99.9	0.00027
8_{16}	537 ± 28	0–90	99.8	0.00066
10_{16}	2310 ± 74	0–90	99.7	0.00189
12_1	3122 ± 56	0–90	99.4	0.00286
12_4	2992 ± 101	0–90	99.6	0.00291
12_{16}	2262 ± 22	0–90	99.5	0.00397

[a] Subscripts in column 1 refer to the number of hours conditioned at 60 °C.

the potentiometric method of Levy and Rowland (1971) employing non-logarithmic linear titration curves. At the experimental pH value of 6.90, 0.60% of DMHB is in the unionised form and at pH 2.10 a negligible amount of DMHB is in the unionised form. This difference in the percentage of the unionised form of the drug could explain the higher release rate constant at the higher pH value if the main transport process is partitioning of the drug into the polymer structure as in the case of the pellets containing 0% w/w HPMC. Another possible explanation for the difference in release rates at the two pH values, was proposed by Goodhart et al. (1984) who investigated the effect of pH on the release of phenylpropanolamine HCl from EC pseudolatex coated pellets. They suggested that, as the pK_a of phenylpropanolamine is 9.04, a pH-dependent release in the physiological pH range would not be expected. However, experimental data showed a faster release rate in basic media than in acidic media. They suggested that the pH effect could be attributed to the presence of sodium lauryl sulphate in the aqueous dispersion formulation. Sodium lauryl sulphate has a pK_a of 1.9 and the authors postulated that this could effect the partitioning of phenylpropanolamine HCl into the simulated gastrointestinal fluids by virtue of its state of ionization under acidic or basic conditions.

This effect of pH on release rate was also found by Chang et al. (1987) for the release of theophylline from pellets coated with an EC aqueous dispersion. Theophylline is a weak base with a pK_a of 0.7. At the two experimental pH values of 6.7 and 1.2, theophylline is 99.99 and 75.96% unionised, respectively. Thus, as was found by the authors, the release rate was greatest for theophylline at the pH corresponding to the highest unionised to ionised drug ratio (pH 6.7). A similar effect was observed by Serajuddin and Rosoff (1984) for the pH-dependent release of papaverine HCl, pK_a 6.5, from sustained-release pellets.

The EC pseudolatex pellets containing 12% w/w HPMC show no significant difference in the release rate constants at the two experimental pH values (Table 4). On contact with the dissolution medium, the HPMC leaches from the polymer film causing the formation of pores which are evident in the electron micrograph taken at a magnification of 1500 (Fig. 13). Lower magnification (Fig. 5) also reveals the presence of cracks in the polymer film. The presence of pores and

TABLE 4

The effect of pH on the permeability of pellet coatings to dextromethorphan hydrobromide

Pseudolatex-coated pellet system	pH	Rate ± S.D. (min^{-1}) ($\times 10^4$)	% Drug released for calculation of rate	r^2	Mean square error
0% HPMC	2.10	44 ± 1	0–90	99.5	0.00403
0% HPMC	6.90	78 ± 2	0–90	99.7	0.00678
12% HPMC	2.10	1118 ± 6	0–90	99.5	0.00359
12% HPMC	6.90	1160 ± 8	0–90	99.7	0.00285

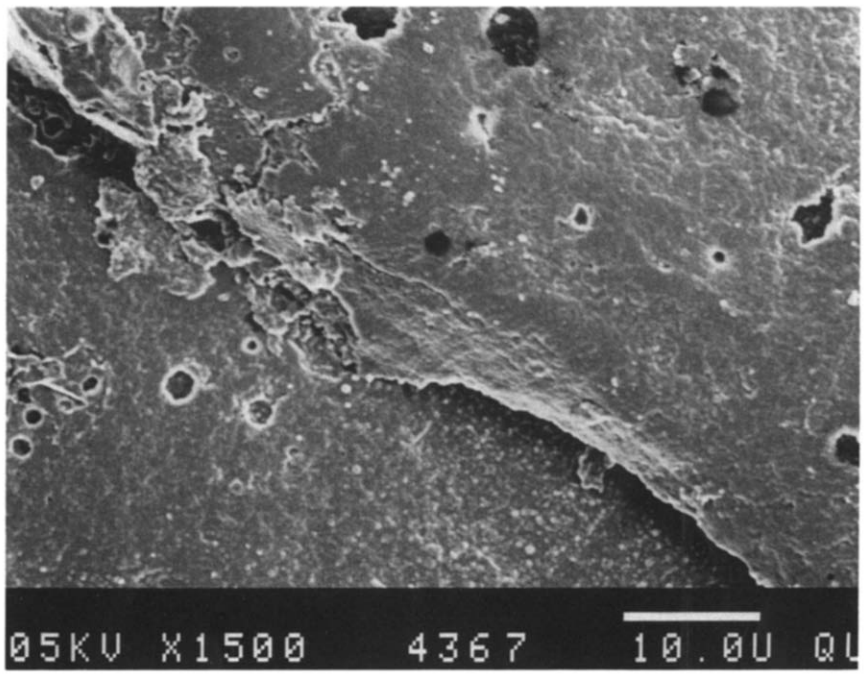

Fig. 13. Surface structure of pellets containing 12% w/w HPMC after dissolution at ×1500 magnification.

cracks in the film coating ensures that diffusion of the drug, from the core to the surrounding sink medium occurs through the solvent filled pores and is therefore independent of pH, assuming as is correct in this instance, the drug is in solution.

In conclusion it has been shown that EC pseudolatex coated pellets containing HPMC do have the capacity to provide good controlled-release systems assuming the pellets have been coated according to certain requirements which are necessary to ensure formation of a completely homogeneous film with a consistent degree of coalescence.

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