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The influence of polymeric excipients on drug release from hydroxypropylmethylcellulose matrices

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Summary

The effect of various polymers and ion-exchange resins on drug release from hydroxypropylmethylcellulose (HPMC) matrices has been evaluated. Non-ionic polmers did not significantly alter release rates. Ionic polymers, however, were capable of retarding the release of oppositely charged molecules, but the effect was small. Ion-exchange resins had a profound effect. It is believed that, provided the drug and the resin are oppositely charged, they will bind together in situ within the HPMC matrix, leading to reduced drug release rates. The drug is liberated once sufficient ions are available to displace it from the binding site. It was not surprising, therefore, to find that the ionic strength of the dissolution fluid affected the action of the resin. Nevertheless, the HPMC matrix was shown to have an inherent buffering capacity, which allowed a virtually pH independent release profile to be obtained.

Introduction

Hydroxypropylmethylcellulose (HPMC) is one of a number of cellulose ethers commonly used in the formulation of controlled-release dosage forms. These polymers hydrate in water forming a gel layer at the matrix periphery. Drug is liberated by a combination of diffusion through and erosion of the gel (Huber et al., 1966). HPMC offers the advantages of being non-toxic and relatively inexpensive; it can be directly compressed into matrices and the many grades available allow a wide latitude in the ability to tailor desired drug-release profiles (Alderman, 1984).

A previous paper described how ionic surfactants can retard the release of drugs from HPMC matrices by forming drug/surfactant complexes (Feely and Davis, 1988). The surfactant is effective when both it and the drug are ionised and when they have opposite charges. Cationic surfactants are too toxic to be administered repeatedly to humans, therefore a non-toxic alternative is required to retard the release of anionic drugs. The most suitable excipients are likely to be those which can bind to the drug ionically, reducing either the solubility of the drug and/or its rate of diffusion through the matrix gel layer.

Various ionic polymers have been found to alter drug release profiles. Badawi et al. (1980) found that salicylic acid diffusion was inhibited by

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interacting with a cationic methacrylate copolymer and para-amino salicylic acid was retarded by both cationic and anionic copolymers. Similarly, Lapidus and Lordi (1968) observed that the release rate of chlorpheniramine was significantly lower than that of sodium salicylate from sodium carboxymethylcellulose (SCMC) matrices. They attributed this response to a drug/polymer interaction between the chlorpheniramine and the carboxymethylcellulose.

Ion-exchange resins are also capable of binding drugs leading to a sustained-release effect (Chaudhry and Saunders, 1956), and so these materials too have potential in retarding drug release from HPMC matrices.

This paper deals with the characterisation of the effect that various polymeric excipients have upon drug release from HPMC matrices. Specific reference is made to the retardation of anionic compounds.

Materials and Methods

Materials

Methocel K100M (Colorcon Limited, Orpington, U.K.) was the HPMC grade used. The Methocel K range has a 22% methoxyl and an 8% hydroxypropyl content. A 2% aqueous solution of the K100M grade has a viscosity of approximately 100 000 cP at 20 °C (Dow technical literature on 'Methocel', 1982). The test drugs were chlorpheniramine maleate BP (Pharmax Ltd., Bexley, U.K.), sodium salicylate BP (Thornton and Ross Ltd., Huddersfield, U.K.) and the potassium salt of phenoxymethylpenicillin (Penicillin V) (Sigma Chemical Co., St. Louis, U.S.A.). Lactose (Whey Products, Crewe, U.K.) was employed as a diluent.

Two non-ionic polymers were examined, hydrophilic polyethylene glycol (PEG) 6000 and hydrophobic ethylcellulose (both from BDH Chemicals Ltd., Poole, U.K.). Two ionic polymers were also tested, cationic diethylaminoethyl (DEAE) dextran (Sigma Chemical Co., St. Louis, U.S.A.) and anionic SCMC (BDH Chemicals, Ltd., Poole, U.K.).

The ion-exchange resins employed were Amberlite IRA 410 and IRA 120 (both BDH Chemicals Ltd., Poole, U.K.), Amberlite IRA 47 and CG 50, and Dowex 2X-8 (all Sigma Chemical Company, St. Louis, U.S.A.). Some of the relevant physical and chemical properties of these resins are summarised in Table 1.

Resin preparation

The ion-exchange resins were washed before use by repeatedly soaking (for 20 min) in 2 N sodium hydroxide solution (NaOH) and 2 N hydrochloric acid solution (HCl). The final soak regenerated the resin; cation exchangers were regenerated in 2 N HCl, anion exchangers required 2 N NaOH (i.e. H^+ and OH^- counter ions). If the salt form of the resin was required (i.e. the Na^+

TABLE 1

Some properties of the ion-exchange resins tested

Resin	Cation or anion exchanger	Matrix composition	Active group	Strong or weak exchanger	Exchange capacity (wet) (meq/ml)	Percent crosslinked	pH (range)
Amberlite IRA 410	anion	crosslinked polystyrene-divinylbenzene matrix	quaternary ammonium	strong	1.40	8	1–12
Dowex 2X8	anion	crosslinked polystyrene-divinylbenzene matrix	quaternary ammonium	strong	1.33	8	1–14
Amberlite IRA 47	anion	epichlorhydrin/ammonia condensation product	tertiary amino	weak	2.4	–	0– 7
Amberlite IR 120	cation	crosslinked polystyrene-divinylbenzene matrix	sulfonic acid	strong	1.9	8	1–14
Amberlite CG 50	cation	crosslinked polyacrylic-divinylbenzene matrix	carboxylate	weak	3.5	–	5–14

and Cl^- counter ions) then the final soak was in 2 N NaOH for cation exchangers and 2N HCl for anion exchangers.

Matrix preparation

Each powder was sieved and the 125–180 μm size fraction was used. Matrices were prepared to the following general formula:

HPMC	70% w/w
Drug	15% w/w
Polymer excipient	X% w/w
Lactose	15 – X% w/w

where X had a value of 0, 5, 10 or 15. The ingredients were mixed and the blend was directly compressed, using 5 mm diameter flat-faced punches, on a Manesty F3 single punch tabletting machine. The upper punch compaction pressure used was 170 N mm^{-2} ($\pm$20 N mm^{-2}). Each matrix weighed 50 mg ($\pm$3 mg).

Dissolution studies

The release of drug from HPMC matrices was monitored using a method based upon the USP (1980) paddle apparatus. 900 ml of dissolution medium was introduced into each of 5 one-litre glass vessels. The temperature of the medium was maintained at 37 °C ($\pm$1 °C) and the paddle speed was set to 100 rpm. Dissolution was continuously recorded using a spectrophotometer (Kontron, model Uvikon 810) connected to a microcomputer (Commodore model 8032). The dissolution fluids used are listed in Table 2.

TABLE 2

pHs and dissolution strengths of the dissolution fluids employed

Dissolution fluid	pH	Ionic strength
Hydrochloric acid 0.1 N	ca. 1	0.1
Hydrochloric acid $2.5 \cdot 10^{-3}$ N	2.6	$2.5 \cdot 10^{-3}$
Formic acid/potassium hydroxide buffer	3.4	0.01
Phosphate buffer	7.0	0.01
Phosphate buffer in saline	7.0	0.1

Results and Discussion

Non-ionic polymers

The effect of adding 15% w/w of either PEG 6000 or ethylcellulose on chlorpheniramine release from HPMC matrices was compared against two controls; one containing 15% w/w lactose as diluent and a polymer control containing HPMC (85%) and drug (15%) only. Neither polymer greatly altered the chlorpheniramine release profiles (Fig. 1). The PEG 6000 profile was similar to that of the polymer control, whereas the ethylcellulose profile emulated that of the lactose control formulation.

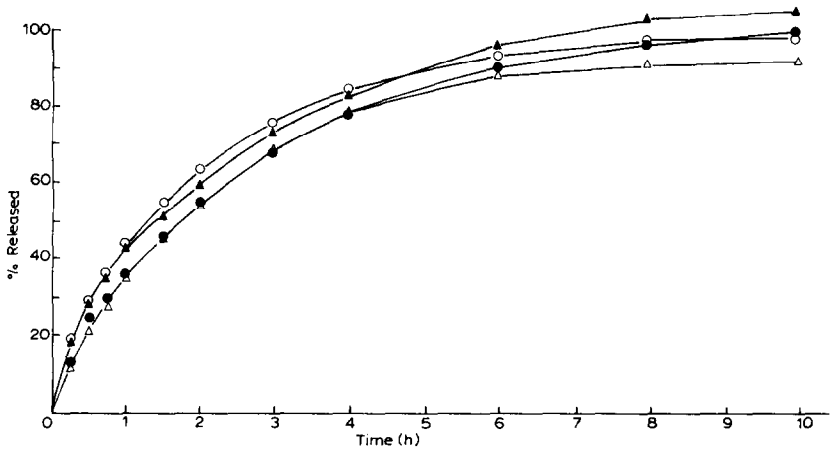

Fig. 1. Effect of non-ionic polymer excipients on chlorpheniramine release from K100M matrices (pH 7). (○), lactose control, (●), polymer control, (△), 15% w/w PEG 6000; (▲), 15% w/w ethylcellulose.

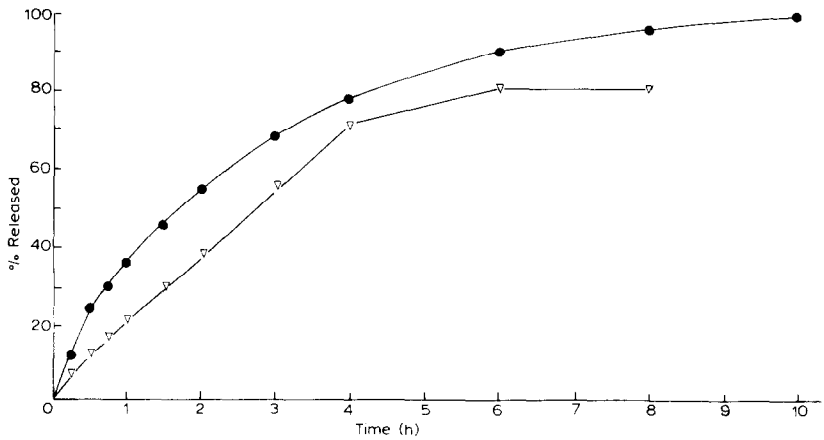

Fig. 2. Effect of SCMC on chlorpheniramine release from K100M matrices (pH 7). (●), polymer control; (▽), 42.5% w/w SCMC.

Lapidus and Lordi (1968) studied the effect that lactose (water-soluble) and tricalcium phosphate (poorly water-soluble) had on drug release from HPMC matrices. The observed increase in rate of drug liberation was similar for both excipients, providing they did not constitute more than 33% of the formulation. In our experiment, ethylcellulose appears to have behaved as an inert diluent, whereas PEG 6000 acted more like a swellable polymer (i.e. HPMC).

Ionic polymers

Matrices consisting of 15%w/w chlorpheniramine maleate and 85% of a 50 : 50 HPMC : SCMC polymer blend were tested by dissolution into pH 7 buffer. These matrices gave a zero order drug release profile; the chlorpheniramine molecule being liberated more slowly than from the control matrices (containing 85% of pure HPMC) (Fig. 2).

SCMC is a hydrophilic swellable polymer similar to HPMC and has been widely used as a base for controlled release matrices (Baveja et al., 1985). When blended with a non-ionic polymer (such as HPMC), a synergistic effect occurs whereby the resultant viscosity is considerably higher than anticipated, due to hydrogen bond-induced cross-linking (Walker and Wells, 1982). This condition is unlikely to explain why SCMC retards chlorpheniramine release since it has already been shown that gel viscosity has little effect upon drug

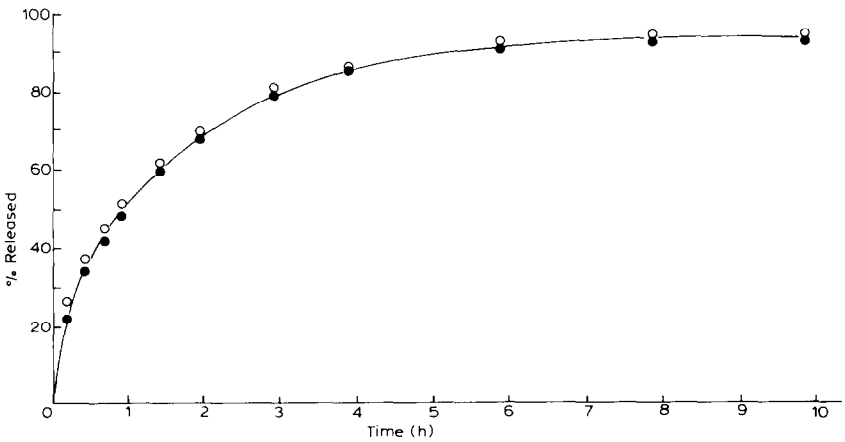

Fig. 3. Effect of SCMC on chlorpheniramine release from K100M matrices (pH 1). (○), polymer control; (●), 42.5% w/w SCMC.

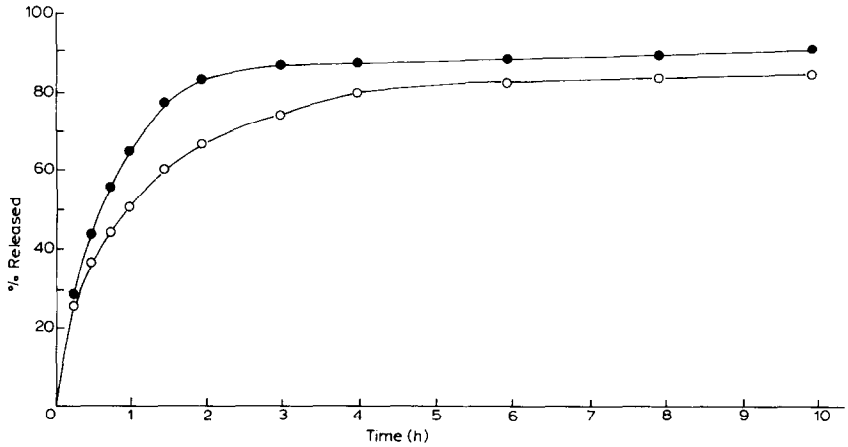

Fig. 4. Effect of SCMC on sodium salicylate release from K100M matrices (pH 7). (○), polymer control; (●), 42.5% w/w SCMC.

release when high-molecular-weight grades of HPMC are employed (Ford et al., 1985a and b; Feely and Davis, 1988). A more probable explanation is that the chlorpheniramine cation complexes with the cationic SCMC backbone as indicated by Lapidus and Lordi (1968).

In order to provide evidence for this theory two more dissolution experiments were performed. Firstly, the effect of SCMC on chlorpheniramine release into pH 1 dissolution medium and secondly, the effect of SCMC on sodium salicylate release (pH 7) were investigated. There was no retardation of drug in either experiment (Figs. 3 and 4), thus supporting the drug/polymer binding theory. Below pH 3, SCMC reverts to its unionised acidic form which is water-insoluble; electrostatic binding is no longer possible and the carboxymethylcellulose therefore behaves as an inert, insoluble diluent. Similarly, no interaction occurs between sodium salicylate and SCMC since they are both anionic in pH 7 media.

The near-zero order release profile obtained with the SCMC-containing matrices can be attributed to a change in the principal mechanism controlling drug release. Normally, drug diffusion is more rapid than gel erosion and a root time release profile is obtained. However, since chlorpheniramine/SCMC binding inhibits drug diffu-

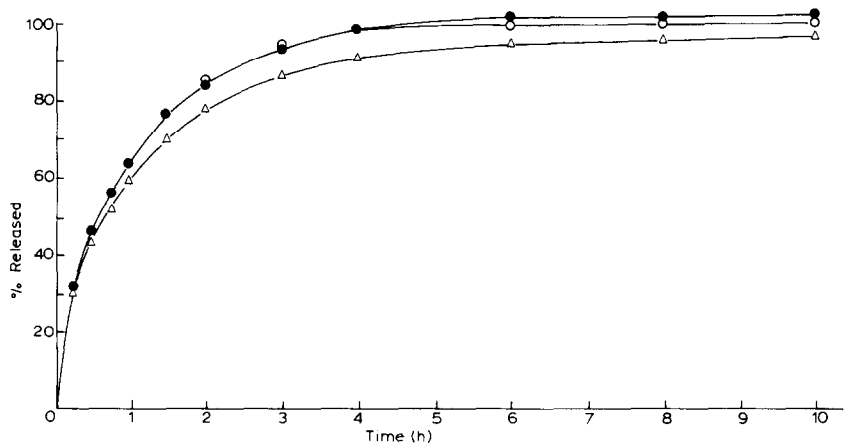

Fig. 5. Effect of DEAE dextran on sodium salicylate release from K100M matrices (pH 7). (○), lactose control; (●), Polymer control; (△), 15% w/w DEAE dextran.

sion and because SCMC is fast hydrating, gel erosion is the prominent drug-releasing mechanism for these matrices. A near-zero order profile is observed because the rate of gel erosion remains constant provided the surface area of the matrix does not change dramatically.

Finally, the effect of 15% w/w DEAE dextran (a cationic polymer) on the release of an anionic drug (sodium salicylate) was investigated. A small decrease in the drug release rate into pH 7 media was observed (Fig. 5), but as expected this effect was reversed in pH 1 dissolution fluid due to the sodium salicylate reverting to its unionised form.

Summarising all these results, it is apparent that ionic polymers can delay drug release from HPMC matrices but the effects are not usually very dramatic.

Ion-exchange resins

Ion-exchange resins were incorporated into HPMC matrices in an effort to reduce drug release rates. Different types of resin were tested under various conditions in order to determine the advantages (if any) of a resin/HPMC formulation over a conventional sustained-release ion-exchange system.

The rate of penicillin V release from HPMC matrices was reduced in the presence of Amberlite IRA 410 anion-exchange resin (Fig. 6). The extent of the inhibition was related to the amount of resin present and this is reflected in the values for the release rate constant, k, obtained by calculating the gradient of the percentage release vs. root time curve. A plot of k against the weight percentage of the resin in the matrix produced a straight line (Fig. 7) with a gradient of -0.238 $min^{-1/2}$. This value characterises the retarding ability of IRA 410 on penicillin V release from Methocel K100M matrices in pH 7 buffer. A number of such gradients obtained for different

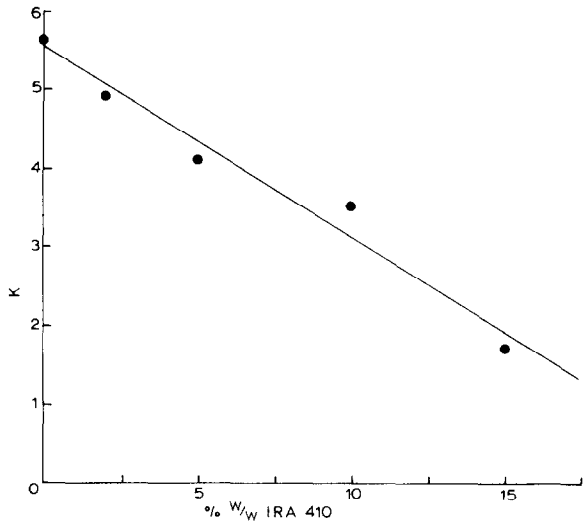

Fig. 7. Plot of k vs % w/w Amberlite IRA 410 for penicillin V release from K100M matrices (pH 7). Slope = -0.238 $min^{-1/2}$; intercept = 5.55 $min^{-1/2}$; correlation coefficient = 0.985.

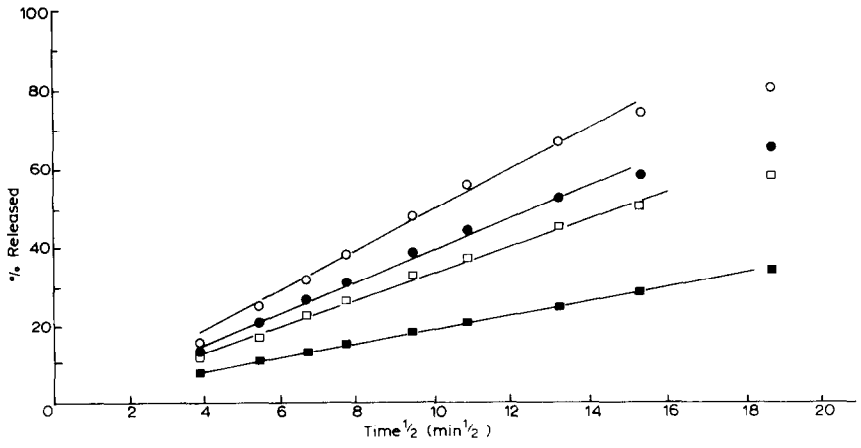

Fig. 6. Effect of Amberlite IRA 410 on penicillin V release from K100M matrices (pH 7). (○), 0% w/w; (●), 5% w/w; (□), 10% w/w; (■), 15% w/w.

TABLE 3

Linear regression analysis of the k vs % w/w resin plots

Resin	Drug	pH	Slope ($min^{-1/2}$)	Intercept ($min^{-1/2}$)	Corr. coeff.
Amberlite IRA 410 (Cl^-)	Pen V	7	−0.238	5.55	0.985
Dowex 2X8 (Cl^-)	Pen V	7	−0.279	5.32	0.980
Dowex 2X8 (Cl^-)	Sod sal	7	−0.244	6.56	0.994
Amberlite IRA 47 (Cl^-)	Sod sal	7	−0.277	6.51	0.994
Amberlite IRA 47 (OH^-)	Sod sal	7	−0.091	6.54	0.966
Amberlite IRA 120 (H^+)	CPM	7	−0.297	5.83	0.990
Amberlite IRA 120 (H^+)	CPM	1	−0.233	5.78	0.974

See e.g. Fig. 7.

drug and resin combinations is listed in Table 3. A value of $-0.279\ min^{-1/2}$ was obtained for similar matrices containing Dowex 2X-8 anion-exchange resin. This indicates that Dowex 2X-8 was more retarding than Amberlite IRA 410, despite the latter having a slightly higher exchange capacity (Table 1). One possible reason for the difference in potency is that the Dowex resin has a more favourable distribution of reactive binding sites.

The effect of a weakly basic anion-exchange resin (Amberlite IRA 47) on sodium salicylate release was compared to that of a strongly basic resin (Dowex 2X-8). Surprisingly, the weakly basic resin was more effective at retarding anion release (Table 3). This is most probably explained by the fact that Amberlite IRA 47 has a much higher exchange capacity than Dowex 2X-8, so on a weight-for-weight basis the former should have more binding sites available which may offset any disadvantage due to weak binding.

The nature of the resin counter ion may be important because certain ions may be more difficult to displace than others. Once it has been displaced, the counter ion itself may have an effect upon the HPMC gel structure. Sodium ions may dehydrate the polymer which could lead to precipitation of the HPMC causing disruption of the matrix integrity. Hydrogen ions may protonate the HPMC which would also reduce the hydration of the polymer (Lapidus and Lordi, 1966).

Amberlite IRA 47 did not retard sodium salicylate release as much when present in the basic (OH^-) form compared to the salt (Cl^-) form (Table 3). This result can be explained by the

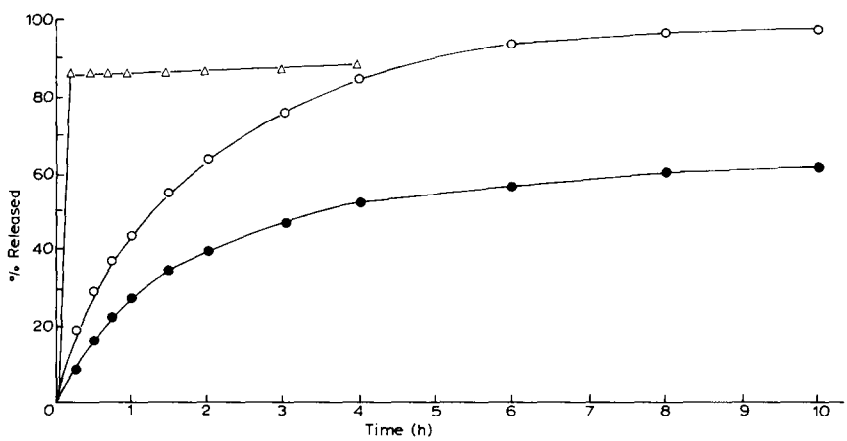

Fig. 8. Effect of Amberlite CG 50 counter ion on chlorpheniramine release from K100M matrices (pH 7). (○), lactose control; (●), 15% w/w H^+; (△), 15% w/w Na^+.

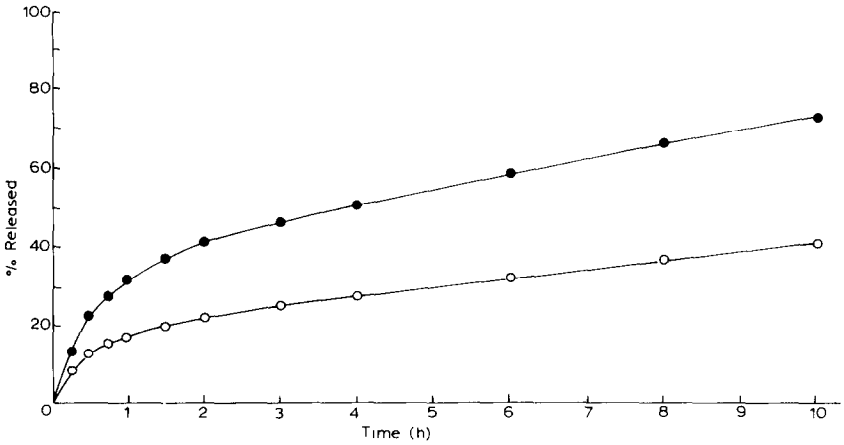

Fig. 9. Effect of 15% w/w Amberlite IR 120 on chlorpheniramine release from K100M matrices in different ionic strength dissolution media (pH 7). (○), 0.01 ionic strength; (●), 0.1 ionic strength.

fact that weakly basic resins have a strong affinity for hydroxyl ions (BDH technical information on ion-exchange resins, 1977) which would inhibit the binding of the salicylate anion. Drug release is delayed to some extent by the basic form of the resin because exchange is still possible due to the large excess of salicylate ions in the matrix.

The experiment was repeated for a weakly acidic cation exchange resin (Amberlite CG 50). Chlorpheniramine release was inhibited when the resin was in its acidic (H^+) form, but the HPMC matrix disintegrated almost immediately when the resin was used as its salt (Na^+) form (Fig. 8). It is likely that the sodium ions were quickly displaced by the drug and buffer cations; the large amount of free sodium could then 'salt out' the HPMC, preventing gel formation and hence leading to matrix disintegration.

The pH and the ionic strength of the dissolution medium is a crucial factor in regulating the release of drugs from sustained-release ion-exchange resin formulations (Chaudhry and Saunders, 1956). Experiments were therefore performed to evaluate the effect that changes in these two parameters have upon drug release from HPMC/resin matrices. Chlorpheniramine release

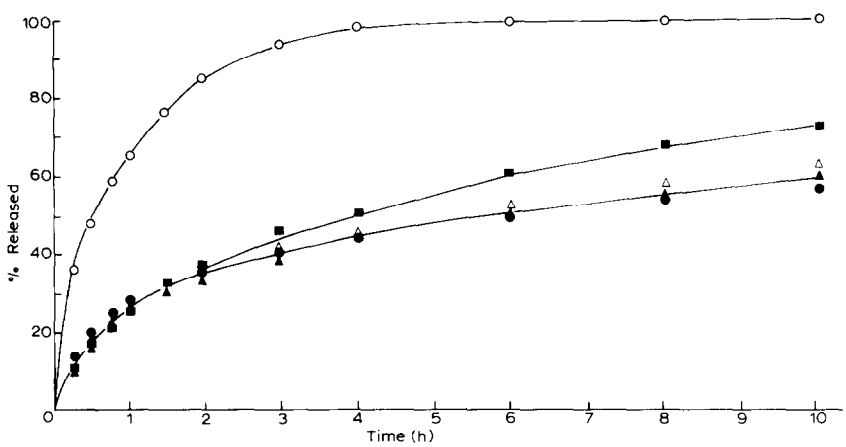

Fig. 10. Effect of media pH on the release of sodium salicylate from K100M matrices containing 15% w/w Dowex 2X-8 resin. (○), lactose control pH 7; (△), pH 7; (●), pH 3.4; (▲), pH 2.6; (■), pH 1.

from matrices containing Amberlite IR 120 cation-exchange resin was more rapid into a high ionic strength fluid ($I = 0.1$) than into media with low ionic strength ($I = 0.01$) (Fig. 9). This was expected since the presence of more sodium ions in the high-ionic-strength medium would encourage the displacement of the chlorpheniramine from the resin and promote release.

In order to study the effect of media pH, HPMC matrices containing sodium salicylate and Dowex 2X-8 resin were tested in pH 7, pH 3.4, pH 2.6, and pH 1 dissolution fluids. Excluding the pH 1 data, the drug release profiles were very similar at each pH (Fig. 10). Salicylic acid has a pKa of 3.0 so the drug will be principally in its ionised form above pH 3.0 but should revert more to its acidic, unionised form in solutions with a pH lower than 3. Although sodium salicylate should theoretically be only 30% ionised in pH 2.6 media, a significant retardation of the drug was still observed. These results imply that the HPMC gel has a certain buffering capacity which renders the system pH independent. The different release profile observed in pH 1 media is likely to be due to the higher ionic strength of this media compared to that of the other dissolution fluids used (Table 2).

Conclusions

The following conclusions can be drawn from the results of this study:

(i) Ionic polymers can be incorporated into HPMC matrices to retard the release of oppositely charged drugs, but the effect is not very dramatic. Non-ionic polymers are no more effective than the HPMC polymer itself.

(ii) The release of ionised drugs from HPMC matrices can be delayed by incorporating an ion-exchange resin into the formulation. The drug binds to the resin, in situ, and the former is released when sufficient ions are available to displace the drug from its binding site.

(iii) Although the HPMC/resin system is susceptable to changes in the ionic strength of the dissolution environment, it offers certain advantages over conventional sustained-release resin systems. One advantage is that no prior soaking of the resin in a solution of the drug is required. Secondly, a wide range of release profiles can be obtained without coating the resin particles (i.e. by changing the HPMC : resin ratio). Finally, the HPMC appears to have a certain buffering capacity which can render the system pH independent.

Acknowledgements

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