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Research paper

Effect of ion exchange resins on the drug release from matrix tablets

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Abstract

Ion exchange resins were incorporated into hydroxypropylmethylcellulose (HPMC) matrix tablets to modify the release of oppositely charged drugs. The drug release from HPMC tablets containing drug-resin complexes was significantly slower than from HPMC tablets containing drug without resin. A physical mixture of drug and ion exchange resin (cationic drug, propranolol HCl, with the cation exchange resin, Amberlite® IRP 69, or the anionic drug, sodium diclofenac, with the anion exchange resin, cholestyramine (Duolite® ATP-143)) resulted in almost the same drug release as tablets containing preformed drug-resin complexes. Upon contact with the dissolution medium, a gel layer formed rapidly around the solid tablet core and the complex between the drug and the resin formed in situ within the gelled regions. No effect of pH of the dissolution medium (0.1 N HCl or pH 7.4 phosphate buffer) or resin counterion was observed with the strong cation exchanger, Amberlite® IRP 69. The resin was dissociated at both pH-values, allowing drug binding. With the weak cation exchange resin, Amberlite® IRP 88, in situ complex formation and retardation was only observed in pH 7.4 buffer but not in 0.1 N HCl because of the non-ionization of the carboxyl groups. The drug release depended also on the amount and particle size of the resin particles and the type of carrier. The use of smaller resin particles eliminated the burst release seen with larger resin particles. Upon comparing different carrier materials, a rapid formation of the gel layer was important for the in situ complex formation. The drug release was in the order of Gelucire 54/02 (glyceryl palmitostearate) > polyethylene oxide 400K > HPMC K15M.

Keywords: Controlled release; Hydrophilic carriers; Hydroxypropylmethylcellulose; Ion exchange resins; Matrix tablets

1. Introduction

Oral controlled drug delivery systems based on matrix-type tablets are generally prepared by blending a drug and carrier material followed by compression. The carrier materials can be classified into water-insoluble carriers such as polymers (e.g. ethyl cellulose, acrylate derivatives) or lipids (e.g. Gelucires) and water-soluble carriers. Water-soluble carriers (e.g. cellulose ethers, such as hydroxypropyl methylcellulose, polyoxyethylene oxide) have the advantage of complete erosion/dissolution and therefore no accumulation in the GI-tract as this is potentially possible with water-insoluble polymers.

Hydroxypropylmethylcellulose (HPMC) is the dominant hydrophilic carrier used in matrix tablets. HPMC-tablets hydrate upon contact with water and a rate-controlling gel layer forms around a solid inner core. A rapid formation of the gel layer is a prerequisite for the retardation of the drug release, otherwise, hydrophilic drugs would be released rapidly. The effect of various formulation factors such as drug:HPMC ratio, solubility and particle size of the drug, particle size and viscosity grade of HPMC and added excipients on the drug release has been investigated [1–5]. The drug release mechanism depends primarily on the solubility of the drug. Water-soluble drugs are generally released by diffusion through a swollen gel layer while water insoluble drugs are released by erosion of the gel layer.

The drug release from hydrophilic matrix tablets has been modified through the use of mulitlayered systems [6], or addition of other excipients. Many drugs incorporated into HPMC matrices are hydrophilic and carry cationic or anio-

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nic functional groups. The effect of the addition of anionic surfactants, polymers and ion exchange resins on the release of cationic drugs was investigated [7,8]. Ion exchange resins reduced the drug release most effectively.

Ion exchange resins are crosslinked water-insoluble polymers carrying ionizable functional groups. The resins have been used in various pharmaceutical applications, primarily for taste masking and for controlled release systems in liquid form [9–12]. In tablet formulations, ion exchange resins have been used as disintegrants because of their swelling ability.

The objective of this study was to investigate the effect of ion exchange resins as release modifiers in matrix formulations containing oppositely charged drugs.

2. Experimental

The following chemicals were obtained from commercial suppliers and used as received: propranolol HCl (Sigma, St. Louis, MO, USA), diclofenac sodium (Lederle Arzneimittel, Wolfratshausen, Germany), guaifenesin (Julius Redel, Cesra-Arzneimittelfabrik, Baden-Baden, Germany), Amberlite® IRP 69 (sodium polystyrene sulfonate; USP), Amberlite® IRP 88 (polacrillin potassium; USP), Duolite® ATP 143 (cholestyramine resin; USP) (Röhm and Haas Company, Philadelphia, PA, USA), Dowex® 50 WX 8 (styrene-DVB-copolymer) (Serva Feinbiochemica, Heidelberg, Germany), hydroxypropylmethylcellulose (Methocel® E4M, K4M, K15M and K100M Premium Grade), methylcellulose (Methocel® A4M Premium Grade) (Colorcon, Nordmann Rassmann, Hamburg, Germany), polyethyleneoxide (Polyox® 400K) (Union Carbide, Danbury, CT, USA), Gelucire 54/02 (mixture of mono-, di-, triglycerides of C16 and C18 fatty acids, Tm = 54°C, HLB = 2) (Gattefosse, Enghien-Les-Bains, France).

Before use, the resins were washed twice with deionized water followed by drying in a desiccator. In order to obtain smaller particles of Amberlite® IRP 69, an aqueous slurry of the resin was transferred into a ball mill (U.S. Stoneware, East Palestine, OH, USA) and milled for 24 h. The ground resin particles were recovered by centrifugation followed by drying (Beckman centrifuge model TJ-6; Spinco Division, Palo Alto, CA, USA). To obtain different size fractions of Amberlite® IRP 69 or of the drug-resin complex particles, the resin particles were immersed in water for 24 h in order to be fully hydrated. The hydrated resin particles were then wet sieved through an analytical sieve set (U.S. Standard Sieve Series, Newark Wire Cloth, Newark, NJ, USA). The following size fractions were obtained: <45, 45–106, 106–150 and >150 μm. Each particle size fraction was then dried in a desiccator. Amberlite® IRP 69 was in the sodium salt form and Amberlite® IRP 88 in the potassium salt form. The acid forms of the two resins were obtained through conversion of the salt form with 1.0 N HCl, followed by washing with deionized water and drying in a desiccator.

The drug-resin complex was formed by a batch method, whereby the resin particles (Amberlite® IRP 69 or Duolite® ATP 143) were added to an aqueous drug solution (propranolol HCl or diclofenac sodium) and agitated for 24 h [13]. The drug-resin particles were separated by centrifugation, washed with deionized water to remove unbound drug, and dried in a desiccator. The amount of drug bound to the resin was calculated as the difference between the initial and the remaining amount of drug assayed spectrophotometrically in the supernatant (propranolol HCl, $\lambda = 290$ nm; diclofenac Na, $\lambda = 276$ nm). The loading capacity was calculated as the (amount of drug bound to the resin, mg/amount of resin, mg) $\times$ 100% and was between 95 and 100% for both resin-drug systems.

The active ingredients (drug, drug-ion exchange complex, or drug and ion exchange resins) and HPMC were blended with a pestle in a porcelain mortar by geometric dilution. Tablets (200 mg, 13 mm diameter) were prepared by compressing the powder blend manually (Specac Hydraulic Press P/N 25.011; Specac, Kent, UK; compaction force 5 tons, holding time 15 s). The standard tablet contained either 20 mg drug or 40 mg drug-resin complex (containing 20 mg drug) or 20 mg drug and 20 mg resin. HPMC was added to obtain a tablet weight of 200 mg.

The following variables affecting the drug release from matrix tablets containing drug without resin, drug-resin complex or a physical mixture of drug and resin were investigated: the particle size of the drug-resin complex or the resin to form the in situ complex (<45 μm, 45–106 μm, 106–150 μm and >150 μm); amount of resin (10, 20, 30 or 40 mg of Amberlite® 69), type of resins (strong cation exchanger (Amberlite® IRP 69 and Dowex® 50 WX 8), weak cation exchanger (Amberlite® IRP 88)), counter ion of resin (acid form; hydrogen form for Amberlite® IRP 69 and Amberlite® IRP 88 and salt form; sodium ion for Amberlite® IRP 69 and potassium ion for Amberlite® IRP 88), viscosity grade of HPMC (Methocel® K4M, K15M and K100M); type of polymer (Methocel® A4M, E4M and K4M); type of carrier (Gelucire 54/02, Methocel® K15M and Polyox® 400K), type of exchangers and drugs.

The USP XXIII rotating paddle method (37°C, 50 rev./min, 900 ml of deionized water, 0.1 M HCl or 0.1 M pH 7.4 phosphate buffer USP, $n = 3$, coefficient of variation $< 5\%$) was used to study the drug release from matrix tablets. The samples (2 ml, replaced with fresh medium) were withdrawn at predetermined time intervals, filtered and assayed spectrophotometrically (propranolol HCl, $\lambda = 290$ nm; guaifenesin, $\lambda = 272$ nm; diclofenac Na, $\lambda = 276$ nm).

3. Results and discussion

The release of drug from HPMC tablets containing (A) drug without resin, (B) propranolol-Amberlite® IRP 69 complexes and (C) a physical mixture of propranolol HCl

and Amberlite® IRP 69 in water, 0.1 N HCl and 0.1 M pH 7.4 buffer is shown in Fig. 1. The drug was released fastest from resin-free HPMC tablets, with the release not being influenced by the release medium (Fig. 1A). The release was mostly controlled by diffusion rather than erosion of the HPMC-layer since propranolol HCl is a water-soluble drug. In contrast, the release of drug from HPMC tablets containing drug-resin complexes was significantly slower (Fig. 1B). The drug was not released in water, since there were no counterions in the medium to replace drug ions from the ion exchange resin within the gelled matrix. The drug was released in 0.1 N HCl and 0.1 M pH 7.4 phosphate buffer, indicating that the drug release was initiated by an ion exchange process. The counterions present in the dissolution media diffused through the gel layer to replace the drug, which was then released by diffusion through this gel layer.

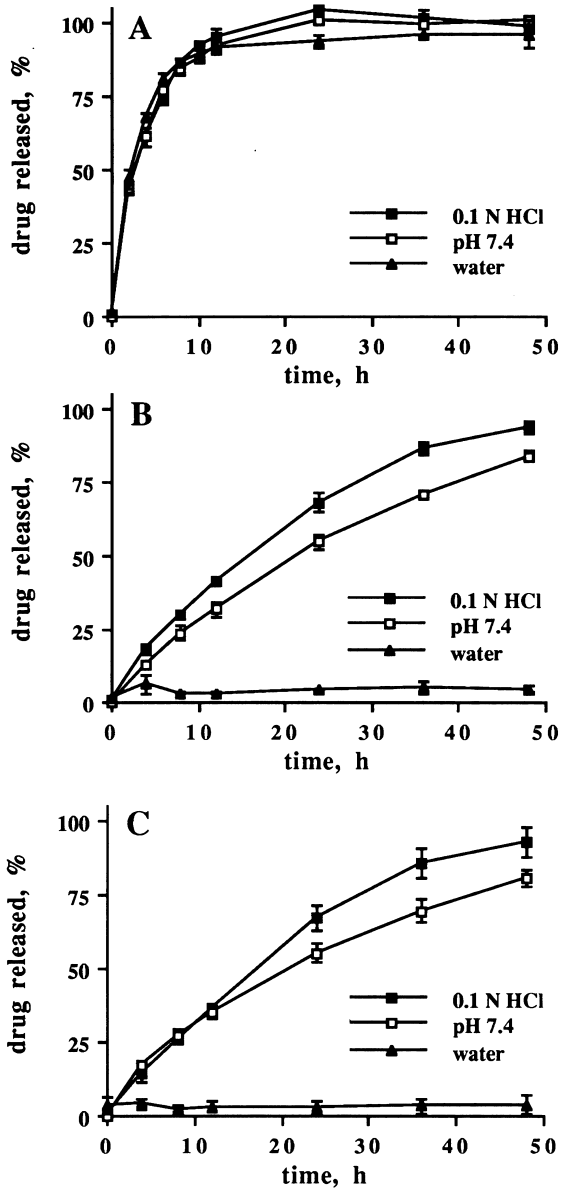

Fig. 1. Release of propranolol from HPMC K15M tablets containing (A) propranolol HCl, (B) propranolol-Amberlite IRP 69 complex and (C) a physical mixture of propranolol HCl and Amberlite IRP 69 in different media.

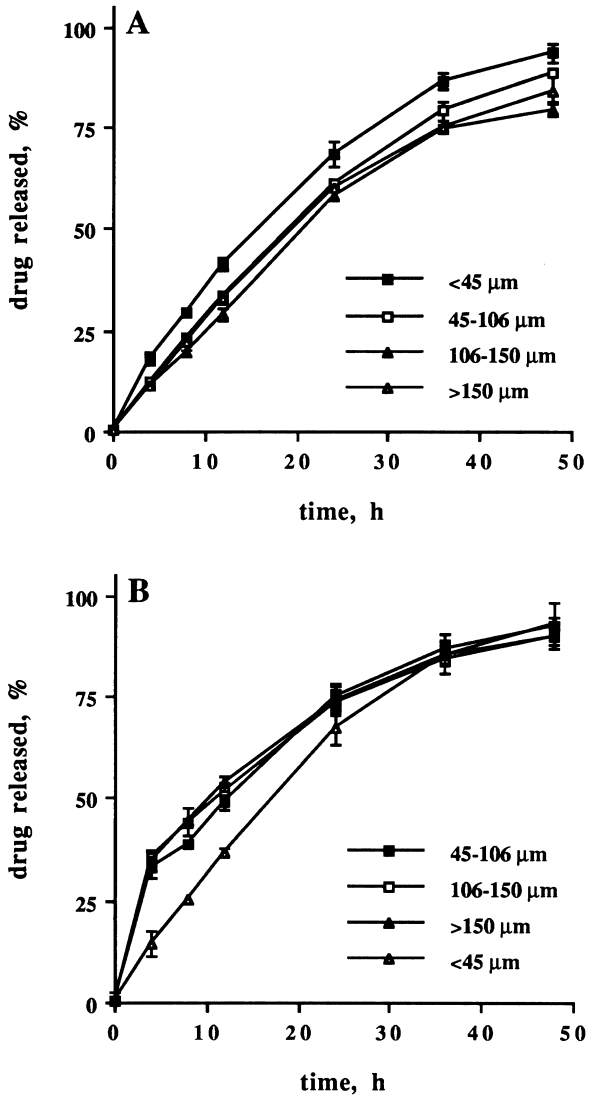

Fig. 2. Effect of size of (A) propranolol-Amberlite IRP 69 complex, (B) Amberlite IRP 69 in a physical mixture with propranolol HCl on the drug release from HPMC K15M tablets (medium 0.1 N HCl).

Interestingly, a similar sustained release pattern could be obtained by just using a physical mixture of drug and ion exchange resin rather than a preformed drug-resin complex (Fig. 1C). Upon contact with the dissolution medium, a gel layer formed rapidly around the solid tablet core. The complex between the drug and the resin formed in situ within the gelled regions [10]. The drug was then replaced by the counterions of the dissolution medium and released through diffusion through the gel layer. As with the preformed drug-resin complex, almost no drug was released in deionized water, indicating complete in situ binding of the drug to the resin. The ‘in situ’ method is advantageous with regard to simplifying the manufacturing process when compared to the use of preformed complexes. The steps involved in the

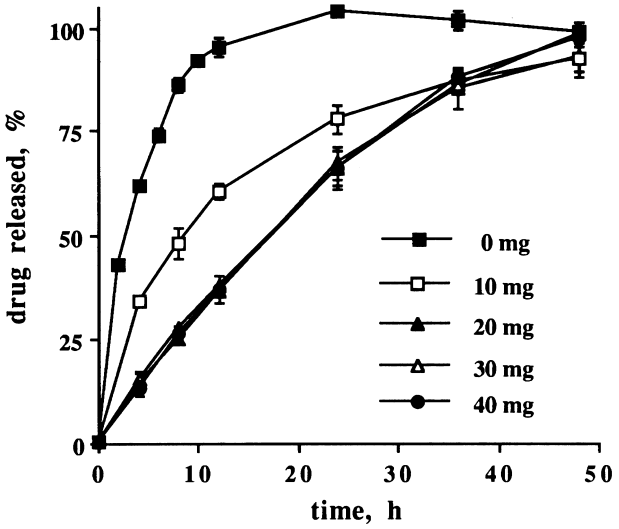

Fig. 3. Effect of the amount of Amberlite IRP 69 on the propranolol release from HPMC K15M tablets containing a physical mixture of Amberlite IRP 69 and propranolol HCl (medium 0.1 N HCl).

complex formation such as loading, washing and drying of the resin can be eliminated through the in situ formation of the complex.

The effect of the size of the drug-loaded or drug-free resin particles on the drug release is shown in Fig. 2. The different size fractions of the drug-resin complexes were obtained by using different size fractions of Amberlite® IRP 69 to form the complex with the drug. For the in situ complex formation, different size fractions of Amberlite® IRP 69 were incorporated together with drug powder into the HPMC tablets. With drug-resin complexes, the release was slightly faster for the smallest size fraction. With the physical mixture, an opposite trend was observed. An initial burst phase was observed with resin particles larger than 45 μm. The unbound drug could diffuse through the gel or it could bind to the resin and then be released through ion exchange and diffusion. The rate of drug binding increases with decreasing particle size of the resin. More drug was therefore bound to the smaller resin particles in a shorter period of time (larger surface area at the same weight fraction), thus explaining the slower release and the absence of the burst phase with the smaller sized resin particles. The use of smaller resin particles therefore eliminated the burst seen with larger resin particles.

The effect of the amount of resin (10, 20, 30 or 40 mg) at a constant drug loading (20 mg) on the drug release is shown in Fig. 3. The drug release initially decreased with increasing amount of resin, with no further decrease being observed at levels in excess of 20 mg resin. This amount apparently was enough to bind the drug in situ.

Depending on the functional group, ion exchangers can be classified into strong or weak ion exchangers. Three different cation exchangers, Amberlite® IRP 69 and Dowex® 50 WX8 (strong cation exchangers with sulfonate

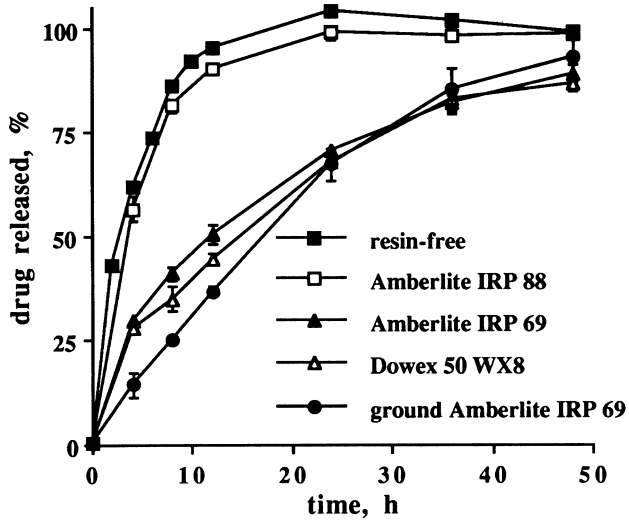

Fig. 4. Effect of the type of resin on the propranolol release from HPMC K15M tablets containing a physical mixture of drug and resin (medium 0.1 N HCl).

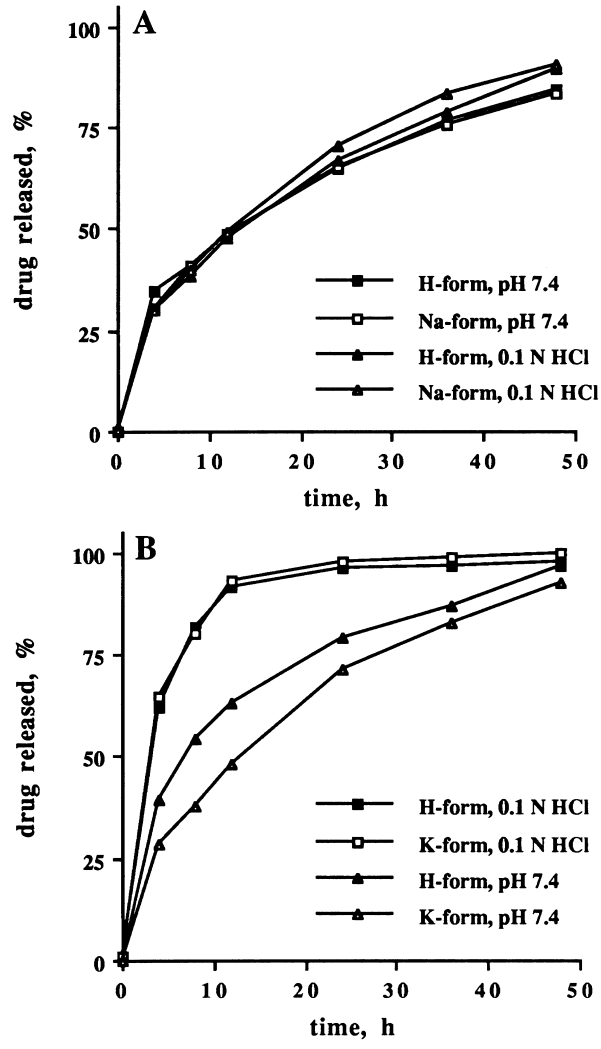

Fig. 5. Effect of counterions of (A) Amberlite IRP 69 and (B) Amberlite IRP 88 on the propranolol release from HPMC K15M tablets containing a physical mixture of the resin and propranolol HCl.

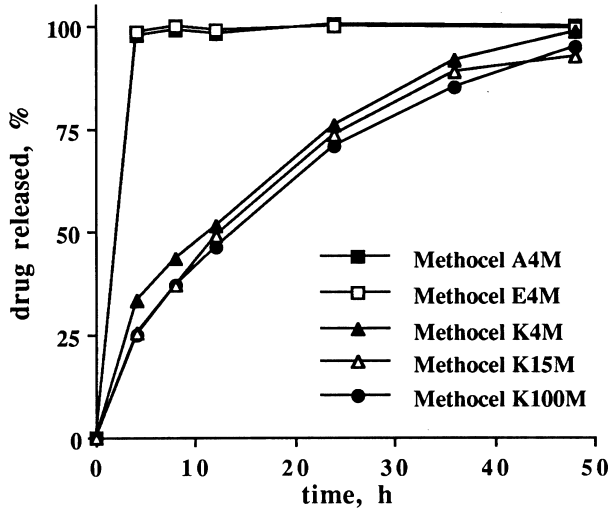

Fig. 6. Effect of type of cellulose ether (methyl cellulose or HPMC) and HPMC viscosity grade on the propranolol release from HPMC tablets containing a physical mixture of Amberlite IRP 88 and propranolol HCl (medium pH 7.4 phosphate buffer).

groups with sodium counter ions for Amberlite® IRP 69 and H^+-counterions for Dowex® 50 WX8) and Amberlite® IRP 88 (weak cation exchanger with carboxyl groups with K^+-counter ions) were evaluated (Fig. 4). The use of Amberlite® IRP 69 and Dowex® 50 WX8 resulted in similar release profiles. The drug release from HPMC tablets containing Amberlite® IRP 88 was similar to the release from HPMC tablets containing drug without resin, indicating no significant in-situ complex formation. The carboxyl groups of Amberlite® IRP 88 were undissociated in 0.1 N HCl; the drug was therefore not bound to the resin.

The effect of resin counterion (H^+ or Na^+ or K^+) and the pH of the dissolution medium on the release from the strong and weak cation exchangers, Amberlite® IRP 69 or 88, is shown in Fig. 5. No effect of pH of the dissolution medium or counterion was observed with the strong cation exchanger, Amberlite® IRP 69 (Fig. 5A). The resin was dissociated at both pH-values, allowing drug binding. With the weak resin, Amberlite® IRP 88, the release was faster in 0.1 N HCl for both ion forms because of the non-ionization of carboxyl groups at low pH (Fig. 5B). The retardation in the drug release in pH 7.4 phosphate buffer could be explained with the ionization of the carboxyl groups and the drug binding to the resin. Using the resin in the H^+ form gave a faster release when compared to the release from tablets containing the resin in the potassium form. This could be due to differences in the internal pH of the gel layer. Replacing H^+ ions with the drug will result in a lower pH within the gel when compared to the replacement of the potassium ion. The lower pH could have increased the solubility of the

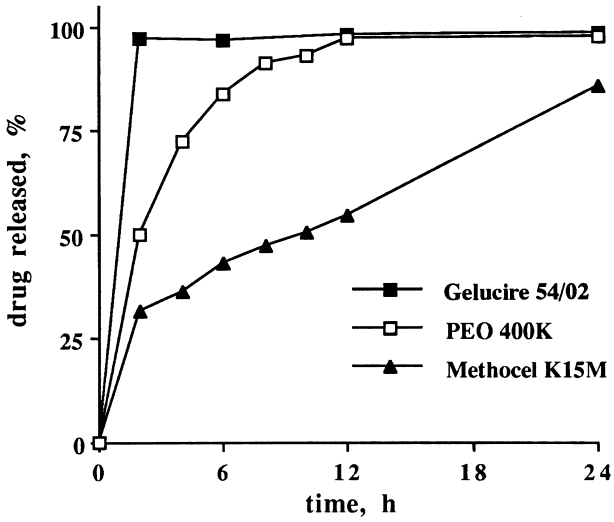

Fig. 7. Effect of type of carrier on the propranolol release from matrix tablets containing a physical mixture of Amberlite IRP 88 and propranolol HCl (medium pH 7.4 phosphate buffer).

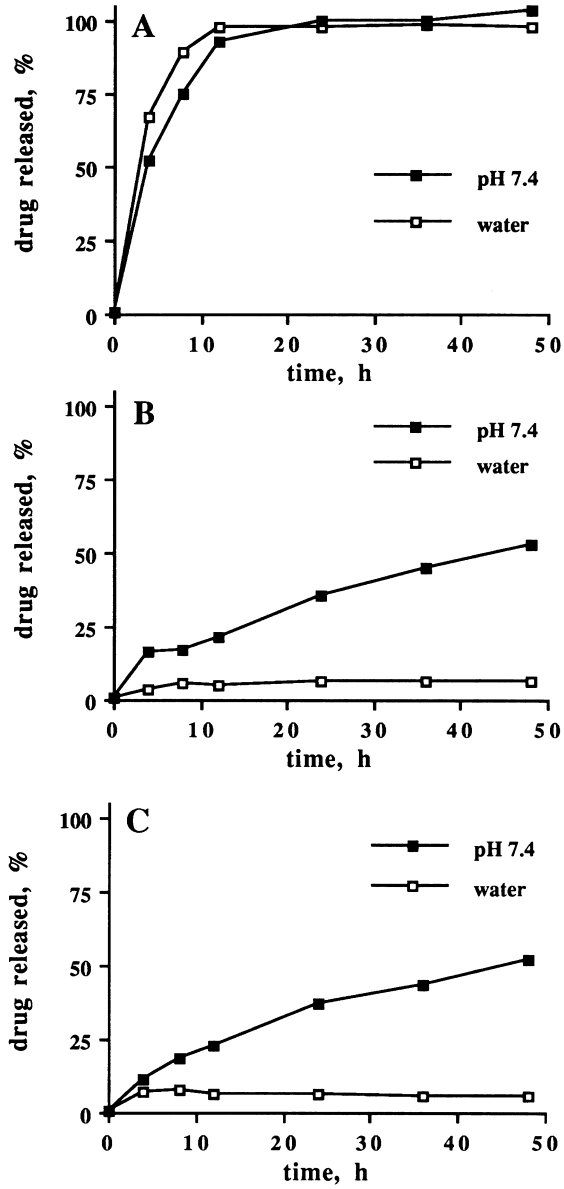

Fig. 8. Release of diclofenac from HPMC K15M tablets containing (A) diclofenac Na, (B) diclofenac-Duolite ATP 143 complex and (C) a physical mixture of diclofenac Na and Duolite ATP 143.

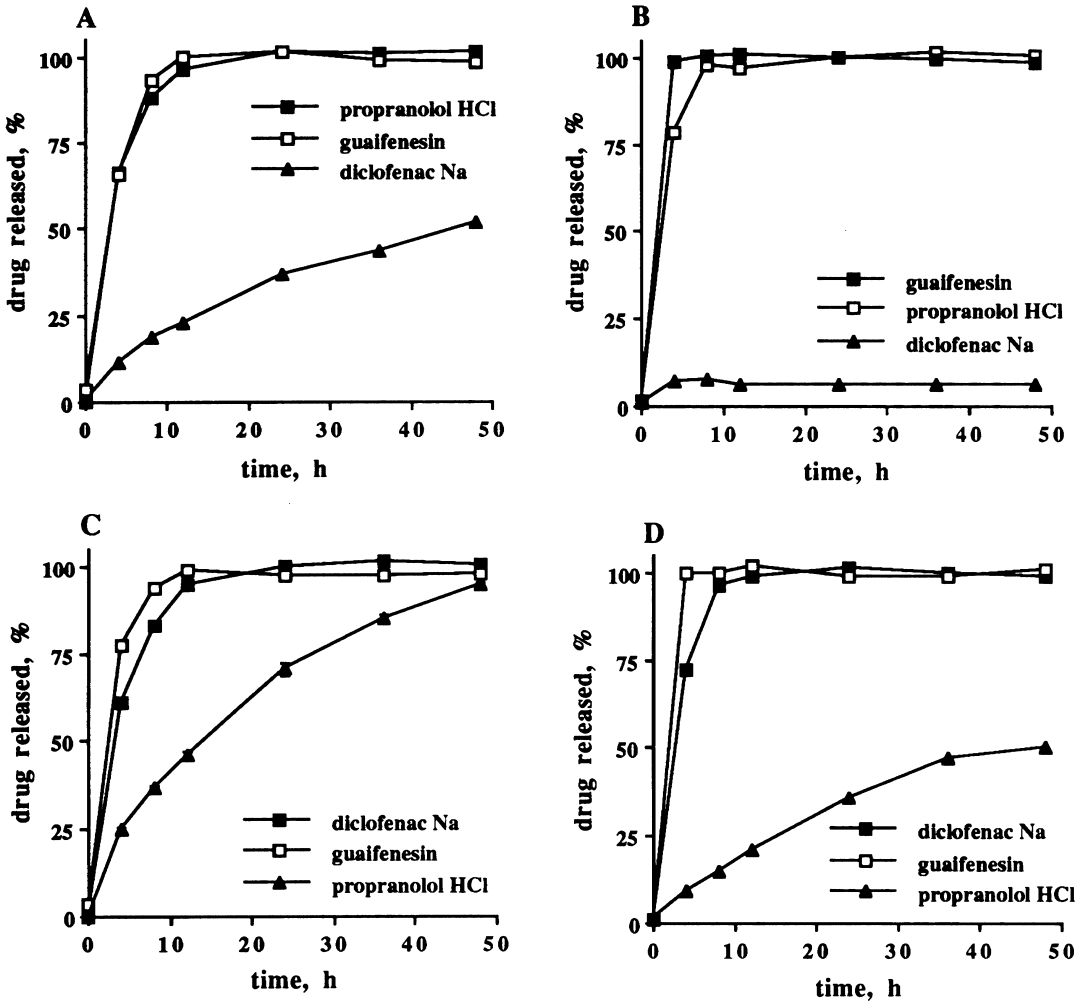

Fig. 9. Effect of type of drug and resin on the drug release from HPMC K15M tablets containing a physical mixture of (A) drug and Duolite ATP 143 (medium pH 7.4), (B) drug and Duolite ATP 143 (medium water), (c) drug and Amberlite IRP 88 (medium pH 7.4) and (D) drug and Amberlite IRP 88 (medium water).

drug in the aqueous gel layer and lowered the dissociation of the resin and therefore the binding of the drug. The faster release could possibly be explained by these two factors.

The drug release from cellulose ether matrix tablets can be controlled by the type of polymer and its molecular weight. The release from tablets containing a physical mixture of Amberlite IRP 88 and propranolol HCl and different viscosity grades of HPMC (Methocel K4M, 15M, 100M), a HPMC grade with a different degree of substitution (Methocel E4M) or methyl cellulose (Methocel A4M) was compared (Fig. 6). The rate of the drug release from hydrophilic matrices depends to a large extent on how quickly the gel layer is formed, in particular with water-soluble drugs. If the polymer hydrates too slowly, the dissolution medium will penetrate into the tablet, the drug will dissolve and will be released quickly. The rapid formation of a gel layer is also crucial for the development of the in-situ ion exchange complex. A fixed viscosity (supplier's specification: 4000 cP, 2% polymer solution in water) of the Methocel series A (methylcellulose), and Methocel E and K (HPMC) was utilized to investigate the effect of type of cellulose ether. The release was slower with HPMC K4M than with the A and E series which agreed with the relative rate of hydration of the polymers. HPMC E4M has a higher degree of substitution with methoxyl groups when compared to the HPMC K4M. Tablets based on Methocel® A and E disintegrated shortly after exposure to the medium because of the slow rate of hydration and the disintegrating effect of the resin. Amberlite® IRP 88 has been used as a disintegration agent to increase the dissolution rate of tablets because of its large swelling ability in aqueous solution. In contrast, a quick gel formation and intact tablets were observed with tablets prepared with the rapidly gelling HPMC K4M. The viscosity of HPMC had no influence on the drug release. It has been reported in the literature, that the drug release is not further retarded above a critical molecular weight [1].

Besides the cellulose ethers, two other carrier materials, Gelucire 54/02 and polyethylene oxide (Polyox® 400K) were examined (Fig. 7). Gelucires have been used as water-insoluble carrier materials in tablet dosage forms, while polyethylene oxide has similar applications as HPMC, it also swells and forms a gel layer in contact

with aqueous media. The drug release was in the order Gelucire 54/02 > polyethylene oxide 400K > HPMC K15M. Gelucire 54/02 does not hydrate when exposed to water, a gel does not form and the tablets disintegrated quickly because of the swelling pressure of the ion exchange resin. The complex did not form in situ. With Polyox® 400K, the gel formed quickly, however, it was not as strong as that of HPMC K15M (as qualitatively determined with a glass rod by squeezing the hydrated tablets) and therefore eroded faster.

In order to generalize the retardation of drug release from HPMC-matrices through the incorporation of ion exchangers and the in-situ complex formation within the matrix, the anionic drug, sodium diclofenac and the anion exchange resin, cholestyramine (Duolite® ATP-143) were evaluated. Cholestyramine is a strong anion exchanger with quaternary ammonium groups attached to a styrene-divinylbenzene copolymer. The release of drug from HPMC tablets containing drug without resin, the drug-resin complexes or a physical mixture of the drug and resin in water or pH 7.4 buffer is shown in Fig. 8. The release was not determined in 0.1 N HCl because of the low solubility of the drug. Similar trends as seen with propranolol HCl and Amberlite IRP-69 were observed. The release of drug without resin was rapid (Fig. 8A), while the release from the preformed (Fig. 8B) or in-situ formed complexes (Fig. 8C) was retarded. The negligible release of drug in water confirmed the in situ complex formation from the physical mixture between Duolite® ATP 143 and sodium diclofenac.

In order to further verify the in-situ complex formation, a cation exchanger, Amberlite® IRP 88 or an anion exchanger, cholestyramine, was incorporated with different drugs in HPMC tablets. The drugs used fell into three categories: (1) a cationic drug, propranolol HCl, (2) an anionic drug, sodium diclofenac or (3) a non-ionic drug, guaifenesin. As expected, a rapid release was observed with the non-ionic drug, guaifenesin, and when drug and resin carried the same charge (Fig. 9A–D). This strongly confirmed that the slow release from HPMC tablets containing a physical mixture of oppositely charged drug and resin was the result of the in situ complex formation. In water, propranolol HCl was released faster from tablets containing the weak cation exchanger Amberlite IRP 88 (Fig. 9D) when compared with tablets containing Amberlite IRP 69 (Fig. 1C).

In conclusion, the addition of ion exchange resins to HPMC-matrices significantly modified the release of oppositely charged drug molecules. A complex between the drug and resin formed in-situ within the gelled matrix and retarded the drug release. The drug release could be varied with the type of carrier material and ion exchange resin and the drug:resin ratio.

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