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Biphasic drug release: the permeability of films containing pectin, chitosan and HPMC

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Abstract

The permeabilities of mixed films of pectin/chitosan/HPMC have been studied to assess their value in producing a dosage form with biphasic drug release characteristics. The inclusion of chitosan enhanced the properties of the films, rendering them stable at all physiological pH values. Pectin/HPMC films were soluble at pH values above 3.0. All pectin/chitosan/HPMC films were permeable to a model drug, paracetamol. HPMC initially increased the permeability of the films and subsequently reduced it at higher concentrations. The minimum permeability was obtained at pH 3 and at an HPMC level of 5% where the potential for polyelectrolyte complex formation between pectin and chitosan exists. The permeabilities of the films increased when they were exposed to pectinolytic enzymes, a system designed to mimic conditions in the colon. The film formulation thus show the potential for biphasic delivery with an initial, controllable slow phase that can be manipulated by changes in the formulation followed by a faster phase under conditions pertaining in the colon.

Keywords: Biphasic release; Mixed films; Permeability; Pectin; Chitosan

1. Introduction

Much of the emphasis on oral controlled drug delivery has been to develop dosage forms that exhibit a constant release of drug over extended time periods. In certain circumstances, different rates of delivery as the dosage form traverses the gastrointestinal tract (GIT) may be advantageous (Turner-Warwick, 1988; Lemmer, 1991; Willich et al., 1992). The development of systems to obtain biphasic release patterns has been described in the literature. Conte et al. (1989) used a three layer tablet consisting of an immediate release layer, a barrier layer which was slowly broken down to allow the release of a second pulse of drug from the third layer. The dissolution profiles from this device showed immediate release followed by a lag phase followed by a slower second release of drug. Plasma levels of drug showed two peaks mimicking the dissolution profile. Maggi et al. (1999) described a two layer system in which one layer gave immediate release and the second provided extended release from a hydroxypropylmethylcellulose (HPMC) matrix. Changes in the

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formulation of the matrix layer allowed different extended profiles to be achieved.

Macleod et al. (1999a) have described a coating system for a tablet that gives a sigmoidal release profile, the rate of release increasing when the system enters the colon. Such a system may provide a more uniform drug absorption pattern over extended time periods. The coating consists of a mixture of pectin, chitosan and HPMC. Pectin and chitosan can interact to form a polyelectrolyte complex (PEC) (Macleod et al., 1999b) and this maintains the integrity of the film and allows limited diffusion of drug through the film. On encountering colonic conditions, degradation of the pectin (Ashford et al., 1993) and possibly the chitosan (Hirano et al., 1990; Tozaki et al., 1997) occurs enhancing drug release. HPMC was included in the coating formulation to improve the ductility of the films.

This paper investigates the permeability characteristics of mixed films of pectin/chitosan/HPMC intended for sigmoidal delivery. The work extends that of Macleod et al. (1999a,b) in that the influence of the inclusion of chitosan, pH of medium and HPMC content, on the permeability of films was studied.

2. Materials and methods

2.1. Materials

Pectin USP was a gift from Citrus Colloids (Hereford, UK), High molecular weight Chitosan (Chitosan HM) was obtained from Sigma–Aldrich (Dorset, UK). HPMC was received as Methocel E4M Premium grade from Colorcon (Kent, UK). Paracetamol was chosen as a model neutral drug for the permeability studies and was obtained from Sigma (St. Louis, USA). Hydrochloric acid (reagent grade) was supplied by Fisher Scientific (Loughborough, UK). Citric acid monohydrate, di-sodium hydrogen orthophosphate, potassium dihydrogen orthophosphate and glycerol were general purpose reagents from BDH (Poole, UK). All other chemicals used were of analytical reagent grade.

2.2. Gel preparation

Aqueous gels of pectin USP (2% w/w), chitosan HM (1% w/w) and HPMC (1% w/w) were prepared by dispersing the required amount of material in 0.1 M HCl. Samples were left overnight to dissolve stirring continuously with a mechanical stirrer (Heidolph type RZRI, Germany) until uniform gels were obtained. The gels were used as stocks for the preparation of the mixed films.

2.3. Preparation of mixed films

Five film formulations of pectin USP/chitosan HM, in a fixed ratio of 6:1, containing 0–20% HPMC were prepared. A further set of five formulations of pectin USP containing 0–20% HPMC without chitosan were prepared as controls. The film formulations were prepared by initial mixing of the pectin and HPMC gels followed by stirring for 15 min. Chitosan gel was then added (if required) and the mixture stirred for a further 15 min. Glycerol (20% w/w-related to the total polymer content) was added as a plasticiser and mixed for 1 h. Samples were then placed in a water bath at 70 °C and shaken at 60 strokes/min for 1 h to remove all air bubbles.

Portions of the film formulations (50 g) were cast in plastic petridishes (9 cm diameter) and dried at 55 °C for 40 h in an oven. The films were allowed to cool, removed from the petridishes and stored in a desiccator at room temperature until use.

2.4. Permeability studies

Drug permeation tests were conducted with Teflon diffusion cells consisting of donor compartment and acceptor compartments. Film samples measuring 3×3 cm were cut with a scalpel and the film thickness measured at six different places with a micrometer (Moore and Wright, England). Samples with mean thickness values in the range 100–150 μm were selected and mounted between the donor and acceptor compartments. The volume of both compartments was 6.0 ml.

Paracetamol (10^{-3} M) was used as the permeant (donor) in test solutions of pH 1.5 (0.1 M

HCl), pH 3.0 McIlvaine's citric acid–phosphate buffer and pH 5.0 and 6.4 Sorensen's phosphate buffer solution. Solutions spanning the pH range of 1.5–6.4 were chosen as they are likely to be encountered in the GIT. The acceptor cells contained blank solutions. To simulate colonic conditions, pectinolytic enzymes at a concentration of 2 ml/l (Pectinex Ultra SP-L 26,000 pg/ml, Novo Nordisk Ferment, Switzerland) were added to the acceptor and donor cells at pH 6.4. The diffusion cell was placed in a water bath maintained at 37 °C and shaken at a rate of 40 strokes/min. The contents of the donor and acceptor cells were collected at 30 min intervals and replaced with fresh solutions for a period of 4 h. The contents of the acceptor cells were assayed spectrophotometrically for paracetamol at 243 nm (Cecil 1020 UV spectrophotometer, Cambridge, England). Each permeation experiment was repeated three times and the data plotted as the cumulative amount of drug permeated as a function of time.

The permeability coefficients (P) of the various film formulations were calculated using the equation below (Chowdary and Naidu, 1992; Rao and Diwan, 1997).

$$P = \frac{K_{app} H}{A}$$

where K_{app} is the rate of drug diffusion which is obtained from the slope of the linear drug permeation profiles, H is the film thickness (cm) and A is the surface area of the film (cm^2). The permeability coefficients can be regarded as being obtained under pseudo-steady state conditions, as the membrane will be changing by dissolution and swelling during the experiment.

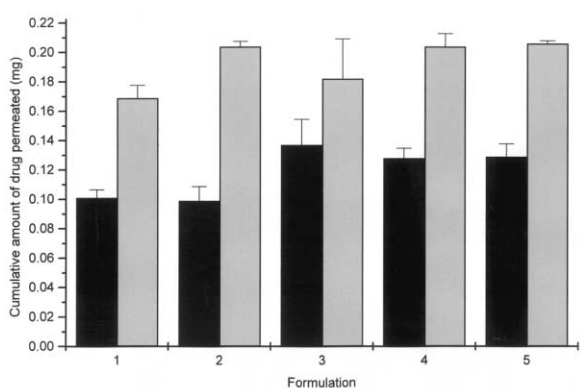

Fig. 1. Influence of chitosan on drug permeation rate of pectin/HPMC films. Total amount of paracetamol permeated: ■ = films containing chitosan and □ = films without chitosan.

3. Results and discussion

The optimum ratio of pectin to chitosan for the formation of a PEC will vary with pH as the ionisation states of the components change (Macleod et al., 1999a). Under the conditions used for film formation (0.1 M HCl) no PEC will form, but when the prepared films are exposed to different pH values, PEC formation becomes possible. The 6:1 ratio of pectin to chitosan represents a reasonable compromise of the optimum ratios for the pH values encountered in the GIT.

Paracetamol was chosen as a model neutral drug so that variation in drug permeation would not be due to ionisation but be attributed to the physicochemical properties of the films and the changes they undergo in the diffusion media. The choice of a model neutral drug was particularly important as Sawayanagi et al. (1982) found greater permeabilities through chitosan membranes for acidic drugs than basic drugs. The addition of HPMC to the mixed pectin/chitosan film formulations was to improve the physicochemical properties of the films such as film ductility (Macleod et al., 1999a,b), toughness and elasticity (Peh and Wong, 1999). The expectation is that such films will provide appropriate controlled release of the drug in the small intestine and that the permeability properties will increase significantly when exposed to the pectinolytic enzymes present in the colon (Fernandez-Hervas and Fell, 1998).

Fig. 1 shows the influence of chitosan on the cumulative amount of drug permeated in 1 h through pectin/HPMC films at pH 1.5. The rate of permeation through the films of pectin/HPMC was much higher than that of pectin/chitosan/HPMC. Previous studies have shown that no PEC is formed between pectin and chitosan at pH 1.5 (Macleod et al., 1999a) as only the chitosan will

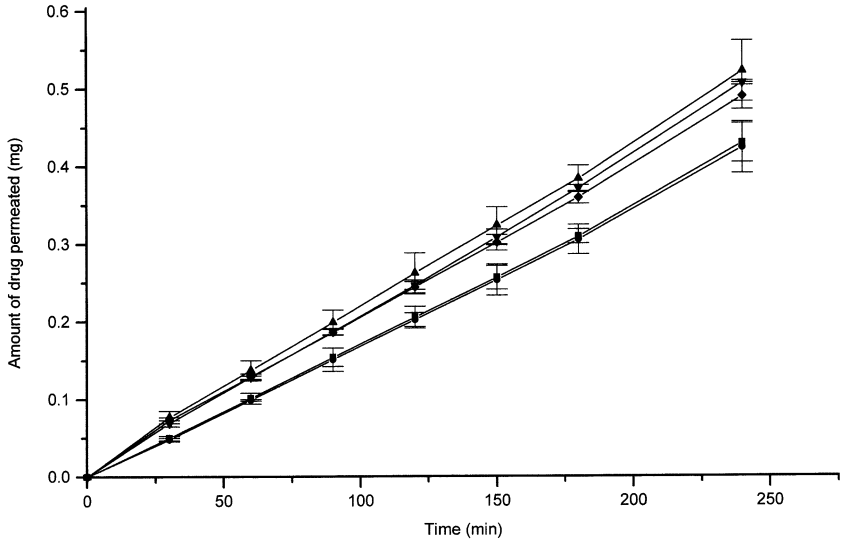

Fig. 2. Permeation of paracetamol through mixed films of pectin, chitosan and HPMC in pH 1.5 (0.1 M HCl solution). Ratio of HPMC and pectin/chitosan in films: ■ = 0% HPMC:100% pectin/chitosan; ● = 5% HPMC:95% pectin/chitosan; ▲ = 10% HPMC:90% pectin/chitosan, ▼ = 15% HPMC:85% pectin/chitosan; and ◆ = 20% HPMC:80% pectin/chitosan.

be ionised. The reduction in the permeability of pectin/HPMC films with the inclusion of chitosan is not, therefore, due to PEC formation but may involve other linkages of chitosan with pectin and HPMC. Films of pectin/HPMC, unlike those of pectin/chitosan/HPMC lost their integrity by dissolution in media of pH 3.0, 5.0, and 6.4 where ionisation of both pectin and chitosan will occur. Hence drug permeability in pectin/HPMC films was indeterminate in these media. Pectin/chitosan/HPMC films were thus more stable over a wider range of pH values presumably due to the formation of an insoluble PEC between chitosan and pectin (Meshali and Gabr, 1993; Macleod et al., 1999a) which tends to restrict the rate of drug permeation through mixed pectin/chitosan/HPMC films and also enhances the mechanical properties of the films. Yin et al. (1999) studied the properties of PEC films of chitosan and gelatin and found that chitosan improved the tensile strength of complex films. Lee et al. (1999) observed PEC formation between chitosan and poly(acrylic acid) and found that, even in a swollen state, the hydrogels possessed good mechanical properties. Pectin/chitosan/HPMC films are therefore more suited for controlled release of drugs than pectin/HPMC films.

All the pectin/chitosan/HPMC films were permeable to paracetamol. Figs. 2–5 show the relationship between amount of drug permeated and time in media of different pH, the linear plots allowing calculation of the permeability coefficient. Table 1 shows the effect of pH and HPMC content on the permeability coefficient of paracetamol in mixed pectin/chitosan films. The permeability coefficients of the films generally increased when the HPMC content was increased from 0–10%. Further increase in HPMC resulted in a reduction in film permeability. The minimum permeability was attained in media of pH 3.0 and in films containing 5% HPMC. Drug permeation through polymer membranes is generally described in terms of two mechanisms: the 'pore' mechanism and the 'partition' mechanism (Zentner et al., 1978; Nakatsuka and Andrady, 1992). In the 'pore' mechanism, drugs permeate the polymeric membrane by diffusion through pores within the membrane at a rate controlled mainly by the pore size of the membrane and the molecular volume of the drug. The 'partition' mechanism involves drug dissolution in the polymer structure followed by drug diffusion along and between the

polymer segments that make up the membrane structure. In practice, drug permeation probably occurs by both mechanisms but one is more likely to predominate (Zentner et al., 1978). The current films are hydrophilic and contain water soluble components. The drug is relatively water soluble

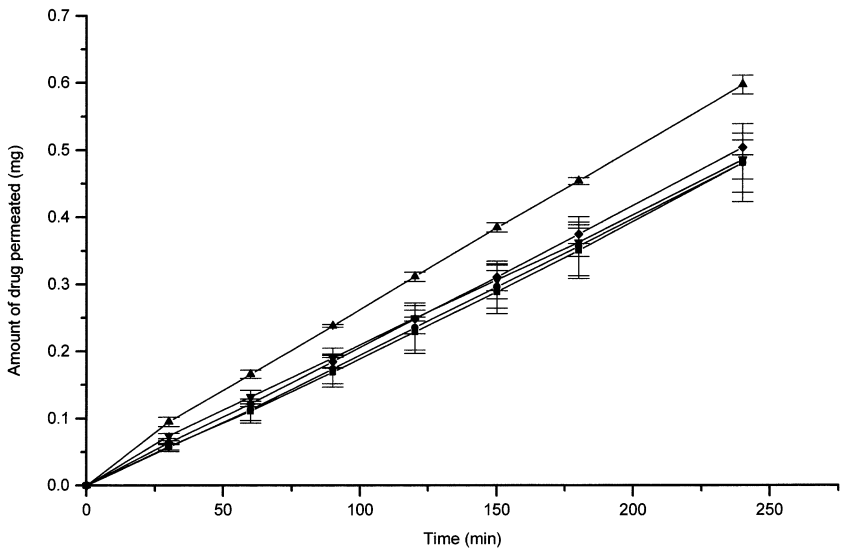

Fig. 3. Permeation of paracetamol through mixed films of pectin, chitosan and HPMC in pH 3.0 McILvaine's citric acid–phosphate buffer solution. Ratio of HPMC and pectin/chitosan in films: ■ = 0% HPMC:100% pectin/chitosan; ● = 5% HPMC:95% pectin/chitosan; ▲ = 10% HPMC:90% pectin/chitosan; ▼ = 15% HPMC:85% pectin/chitosan; and ◆ = 20% HPMC:80% pectin/chitosan.

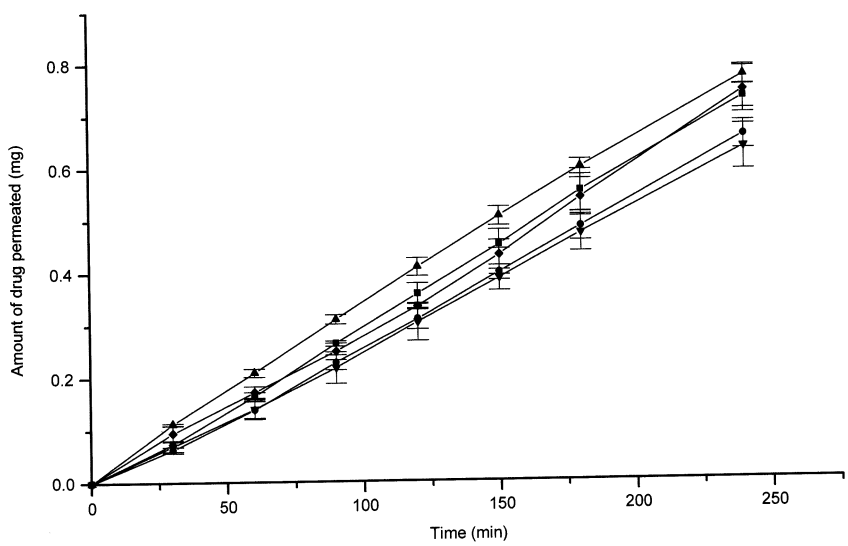

Fig. 4. Permeation of paracetamol through mixed films of pectin, chitosan and HPMC in pH 5.0 Sorensen's phosphate buffer solution. Ratio of HPMC and pectin/chitosan in films: ■ = 0% HPMC:100% pectin/chitosan; ● = 5% HPMC:95% pectin/chitosan; ▲ = 10% HPMC:90% pectin/chitosan; ▼ = 15% HPMC:85% pectin/chitosan; ◆ = 20% HPMC:80% pectin/chitosan.

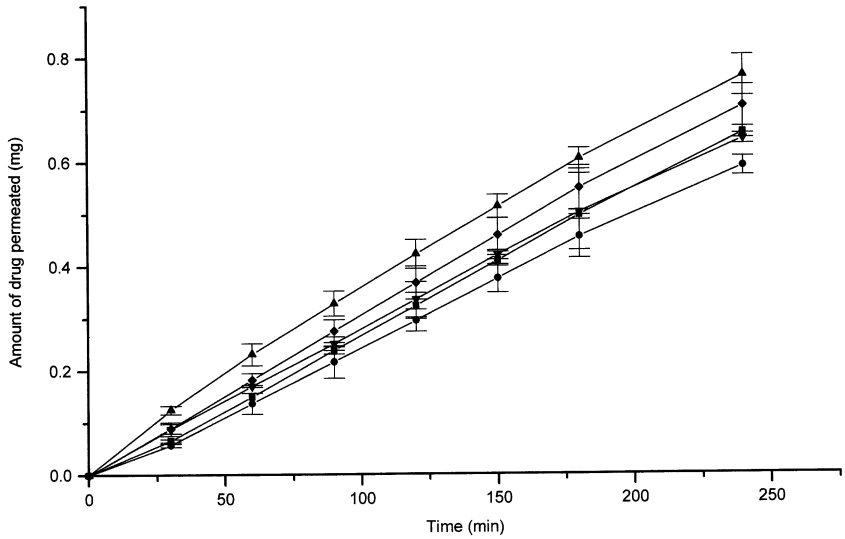

Fig. 5. Permeation of paracetamol through mixed films of pectin, chitosan and HPMC in pH 6.4 Sorensen's phosphate buffer solution. Ratio of HPMC and pectin/chitosan in films: ■ = 0% HPMC:100% pectin/chitosan; ● = 5% HPMC:95% pectin/chitosan; ▲ = 10% HPMC:90% pectin/chitosan; ▼ = 15% HPMC:85% pectin/chitosan; and ◆ = 20% HPMC:80% pectin/chitosan.

Table 1
The influence of pH and HPMC on the permeability of mixed films of pectin and chitosan (mean ± S.D., $n = 3$)

% HPMC	Permeability coefficient $\times 10^6$ (mg/min/cm) at pH			
	1.5	3.0	5.0	6.4
0	4.52 ± 0.31	4.46 ± 0.13	8.93 ± 0.31	5.13 ± 0.38
5	4.70 ± 0.29	5.08 ± 0.17	6.79 ± 0.25	6.72 ± 0.14
10	6.06 ± 0.15	6.09 ± 0.20	8.59 ± 0.19	8.11 ± 0.21
15	5.03 ± 0.16	4.43 ± 0.18	6.82 ± 0.26	6.13 ± 0.40
20	4.87 ± 0.13	4.61 ± 0.13	6.95 ± 0.29	6.19 ± 0.22

so drug permeation is likely to take place mainly through water filled pores. HPMC will presumably dissolve, creating pores in the film, leading to increased permeability but higher concentrations may reduce the free water volume and increase the viscosity causing the permeability to decrease. The minimum permeability was attained in media of pH 3.0 where there would be maximal interaction between ionised carboxylic acid groups in pectin ($pK_a = 3.6$–4.1) and ionised amino groups in chitosan ($pK_a = 6.3$) resulting in the formation of insoluble PEC.

Table 2 compares the permeability coefficients of the films in media of pH 6.4 with and without

Table 2
Effect of pectinolytic enzymes (2 ml/l) on the permeation of paracetamol through pectin/chitosan/HPMC films into pH 6.4 Sorensen's phosphate buffer (mean ± S.D., $n = 3$)

Formulation	Permeability coefficient $\times 10^6$ (mg/min/cm)	
	No enzyme	With enzyme
1	5.13 ± 0.38	9.41 ± 0.21
2	6.72 ± 0.14	9.72 ± 0.19
3	8.11 ± 0.21	10.72 ± 0.64
4	6.13 ± 0.40	10.24 ± 0.20
5	6.19 ± 0.22	9.38 ± 0.47

the addition of pectinolytic enzymes. In all cases, the addition of pectinolytic enzymes increases the permeability of the films to paracetamol. This implies that the pectin in the film is accessible to the enzyme causing breakdown, the creation of a more porous structure and hence an increase in permeability.

The permeabilities of pectin/chitosan/HPMC films to a model drug, paracetamol, can thus be manipulated by changes in the HPMC composition of the films. Increases in the permeabilities arising on exposure to pectinolytic enzymes confirms the potential of this type of formulation for sigmoidal delivery with an initial slow phase followed by a more rapid phase consistent with the dosage form entering the colon.

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