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Studies on indomethacin inserts prepared by water-soluble polymers☆ II. The relation between dissolution rate and swelling behaviour

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Abstract

Inserts containing indomethacin were prepared using water-soluble polymers such as hydroxypropyl cellulose, methylcellulose, hydroxypropyl methylcellulose and polyvinyl alcohol by the film casting method. According to the different characteristics of the polymer used, these inserts exhibit different release kinetics and swelling behaviour. In this study, we examined the relation between swelling behaviour of the polymer and the release of the indomethacin from inserts. Thus an electrical device for measuring the thickness of the hydrated inserts was developed. The thickness of the hydrated inserts was measured by this electrical device at selected time intervals for release studies. The results were interpreted from normalised increases in thickness of the hydrated insert. The mechanism of drug release was identified by means of the value of the ratio R/F, calculated according to the equation developed by Peppas. When the ratio R/F of the insert decreased, drug release from the insert became diffusive. As the normalised thickness of the insert increased, the rate of drug release decreased.

Keywords: Indomethacin; Ophthalmic insert; Hydroxypropyl cellulose; Methylcellulose; Hydroxypropyl methylcellulose; Polyvinyl alcohol; Swelling; Electrical device

1. Introduction

Soluble ophthalmic inserts are composed of a water-soluble polymeric support containing drug(s) or not, the latter being incorporated as dispersion or a solution in the polymeric support. The inserts can be used for topical or systemic therapy. In comparison with the traditional ophthalmic preparations (i.e. eye drops or eye ointments), water soluble ophthalmic inserts present some advantages such as

- increased contact time and thus improved bioavailability,
- possibility of providing prolonged drug release and thus better efficacy,
- reduction of systemic side effects and thus reduced adverse effects,
- reduction of the number of administrations and thus better patient compliance.

They also offer the advantage of being entirely soluble so that they do not need to be removed from the site of application [1].

It is possible to modify the release behaviour of these inserts by the introduction of swellable polymeric excipients such as hydroxypropyl cellulose (HPC), methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), and polyvinyl alcohol (PVA) which possess different weight equilibrium swelling degrees, or by the use of polymers of different grades of viscosity.

According to the different characteristics of the polymer used, these drug delivery systems exhibit different release kinetics and swelling behaviour [2]. As the swelling behaviour of such systems will be directly related to the drug release mechanism, it is important to understand such behaviour.

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Drug release from these polymers follows two mechanisms: drug diffusion through the swelling gel layer and release by matrix erosion of the swollen layer [3]. Therefore, quantifying the percent contributions of diffusion and erosion to the overall drug release is important.

Nakano et al. [4] indicated that the release of theophylline from HPC matrices decreased as the viscosity grade of the HPC increased. However, Ford et al. [5] reported that release rates are unaffected by the viscosity grade of the polymer. Bettini et al. [2] reported that drug release is slightly influenced by the viscosity of the polymer. Colombo et al. [6] have demonstrated that the release of drug from swelling systems is directly related to the increase in surface area during swelling.

The goals of the present work were to study the insert swelling and release of indomethacin from inserts containing polymers (HPC, MC, HPMC, PVA) having different functional groups and viscosity grades, in order to establish a relationship between swelling behaviour and drug release kinetics.

Accurate measurement of the thickness of the hydrated inserts was carried out using a special experimental device capable of imposing an axial swelling during release.

2. Experimental

2.1. Materials

Indomethacin (Selectchemie A.G. Switzerland) was used as a model drug in inserts. Hydroxypropyl cellulose (Hercules Ltd. UK) had low (100.000 Da; HPC-L) and medium (300.000 Da; HPC-M) molecular weights. Methylcellulose (25 cP, Sigma Chemical Co., USA), hydroxypropyl methylcellulose (100 cP, Sigma Chemical Co., USA), polyvinyl alcohol (MW 67.000; Moviol 8-88 Hoechst AG., Frankfurt/Main) were used as polymers. Glycerin and polyethylene glycol 300 (PEG 300) (Dolder Ltd., Switzerland) were added to inserts as plasticisers.

2.2. Methods

2.2.1. Preparation of inserts by film casting method

Inserts containing HPC, MC, HPMC and PVA at the different ratios were prepared (Table 1). Glycerin and PEG 300 were used as a plasticisers. Plasticisers and polymers were dissolved in water. Indomethacin was dispersed in this polymer solution. The solution was poured into Petri dishes. The solvent (water) was allowed to evaporate for 24–48 h at 40°C [7]. Circular inserts of 6 mm diameter were cut from the resulting films with a cork borer, each containing 1% indomethacin, 15% plasticiser, and 84% polymer (w/w).

2.2.2. Measuring the thickness of hydrated inserts by an electrical device

The thickness of hydrated inserts was measured by an electrical device. We modified this electrical device, developed by Fatt [8], for our study.

The electrical device consists of a micrometer (a), source power (12 V) (b) and avometer (50 mA) (c). The gel thickness measuring scheme is shown in Fig. 1. The insert was placed on stainless steel plate and immersed in pH 7.4 buffer solution. The thickness of the hydrated insert was measured by this electrical device at selected time intervals for release studies.

Before making any hydrated insert thickness measurement, the dehydrated insert thickness was measured. This reading was recorded at the beginning. To measure at any time t, the hydrated insert on the stainless steel plate was placed on the non-conductor fibre and the upper conductor was brought into contact with the hydrated insert by rotating the micrometer barrel. Contact was indicated by deflection of the avometer needle. The micrometer reading was then taken. This determination was repeated four times. The swell change of each insert was calculated as the normalised thickness (h_t/h_0) (where h_0 is the insert thickness at the beginning and h_t is the thickness of the hydrated insert at time t). Calculated values were then plotted versus time.

Table 1
Composition of inserts

Indomethacin (%)	Plasticiser (15%)	Polymer	Polymer composition (%)
1	Glycerin	HPC-L	84
1	Glycerin	HPC-M	84
1	Glycerin	HPC-L/HPC-M	42/42
1	PEG 300	MC	84
1	PEG 300	HPC-L/MC	21/63
1	PEG 300	MC/HPC-L	21/63
1	PEG 300	HPMC	84
1	PEG 300	PVA	84
1	PEG 300	HPMC/PVA	42/42

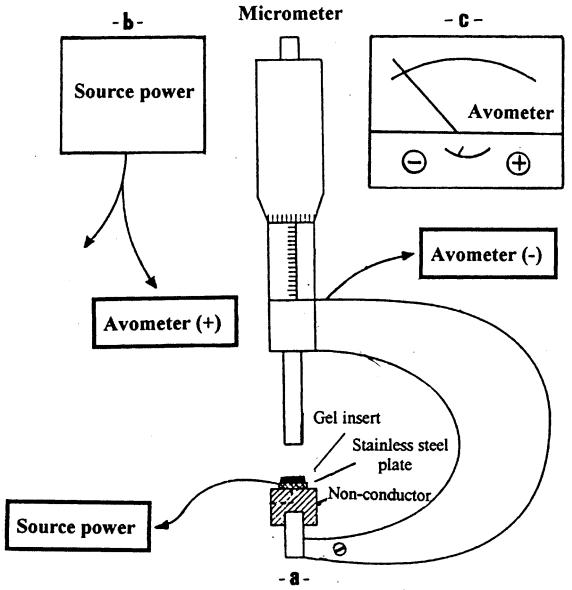

Fig. 1. Side view of the electrical device used to measure the thickness of hydrated inserts.

Table 2
Analysis of release data from swellable insert using Eq. (1)

Polymer	Kinetic constant $k \times 10^{-2}$ (m^{-n})	Diffusion exponent n ($\pm$ SD)
HPC-L	0.891	0,83 $\pm$ 0.067
HPC-M	2.69	0.69 $\pm$ 0.031
HPC-L/HPC-M	1.41	0.72 $\pm$ 0.045
MC	4.79	0.64 $\pm$ 0.15
HPC-L/MC	1.76	0.76 $\pm$ 0.02
MC/HPC-L	0.758	0.85 $\pm$ 0.006
HPMC	0.724	0.92 $\pm$ 0.045
PVA	1.66	0.89 $\pm$ 0.077
HPMC/PVA	5.62	0.53 $\pm$ 0.01

2.2.3. In vitro release studies

The release of indomethacin from inserts was studied in pH 7.4 phosphate buffer. The insert was carefully pressed onto the glass microscope slide without lubricant. The slide was then immersed in 5 ml pH 7.4 phosphate buffer at 35°C. The slide was removed from the buffer solution at the selected time intervals and the buffer solution was analysed spectrophotometrically at 266 nm for indomethacin. The slide was then placed in another beaker containing a fresh solution of buffer at 35°C [9]. The procedure was carried out repeatedly. Each set of release data was obtained using three inserts.

3. Results and discussion

The kinetic of drug release was evaluated by using the well known exponential release equation [10,11].

$$M_t/M_\infty = kt^n \quad (1)$$

In this equation, M_t/M_∞ is the fraction of drug released, k is the kinetic constant, t is the release time and n is the diffusional exponent that depends on the release mechanism and the shape of the swelling device tested. For thin slabs, values of $n = 0.5$ indicate Fickian release (case-I transport), values of $0.5 < n < 1.0$ indicate anomalous (non-Fickian or coupled diffusion/relaxation) drug release, whereas values of $n = 1.0$ indicate case-II or zero-order release kinetics. Table 2 summarises the values of n for all the samples tested.

Comparing the mechanistic information obtained from different samples using this equation, the calculated exponent n of Eq. (1) (Table 2) indicates that the release mechanism is anomalous for all cases except for HPMC and HPMC/PVA, as would be expected for swellable matrices [12]. The HPMC insert exhibits a value of the exponent n (0.92) which indicates anomalous transport very close to case-II transport (Table 2). The Fickian diffusion mechanism of release from the HPMC/PVA insert is apparent from the n value (0.53) which approximates to the value of 0.5 characteristic of this release mechanism (Table 2).

A more reliable and informative analysis can be obtained by considering that drug release in swellable matrices depends on two processes: (i) drug diffusion into the swollen polymer, and (ii) matrix swelling due to the penetrant. Calculation of the approximate contribution of the diffusional and relaxational mechanism to the anomalous release process is carried out by fitting the data to the heuristic model proposed by Peppas and Sahlin [13] for quantifying the two phenomena controlling the release from a swellable matrix.

The equation of the model is:

$$M_t/M_\infty = k_1 t^m + k_2 t^{2m} \quad (2)$$

Where the first term of the right-hand side represents the Fickian contribution, and the second term is the case-II relaxational contribution. In this model, drug release from swellable matrices is described as the result of two transport mechanisms, i.e diffusion across the gel layer (F) and relaxation of the polymeric chains (R). F is linked to the coefficient of the diffusional contribution (square-root dependence on time) and R to the coefficient of the relaxational contribution (linear dependence on time) of the binomial equation describing the time dependence of fractional drug release. The ratio of relaxational (R) and Fickian (F) contributions can be calculated as:

$$R/F = k_2/k_1 t^m \quad (3)$$

The release curves of all the inserts were analysed according to Eqs. (2) and (3). The values of the ratio of R/F versus released fraction are presented in Fig. 2.

With increasing amount and moleculer weight of HPC, drug release apparently approaches a purely diffusion controlled mechanism (Table 2, Fig. 2).This finding confirms the results of Urtti et al. [7]. For the HPC-M insert the ratio R/F is very low ($n = 0.69$), indicating that drug release is almost diffusive. The release from the HPC-L insert is characterised by higher values of R/F, very close to the value of unity ($n = 0.83$). This might reflect increased resistance of drug diffusion by the hyrated layers of the insert. The increased resistance could be due to the decreased diffusivity of the drug or to the increased swelling of the matrix.

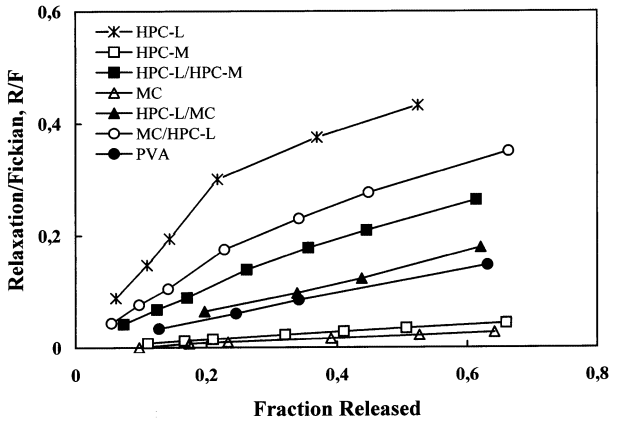

Fig. 2. R/F ratio values versus fraction released for inserts.

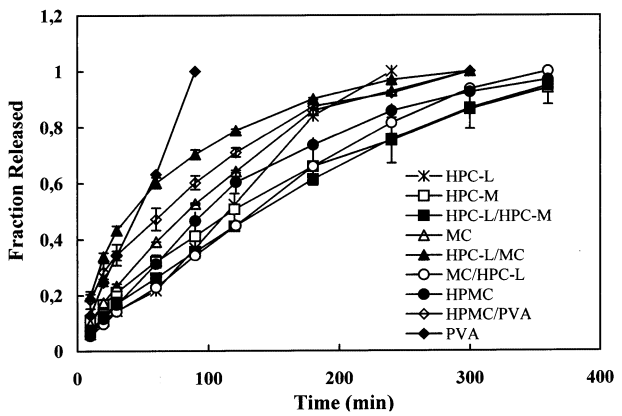

Fig. 3. Drug release profiles of inserts (each point represents the mean ± SE of three experiments).

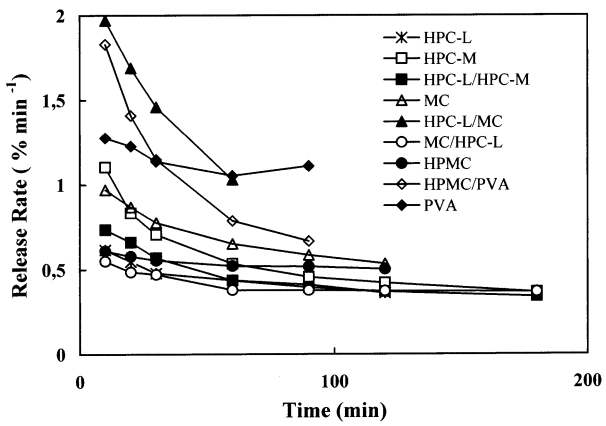

Fig. 4. Instantaneous release rates of inserts measured from drug release profiles.

Decreasing the amount of MC in the inserts resulted in the R/F curve showing a shift from Fickian diffusion towards a swelling controlled mechanism. In fact, drug release approaches a diffusion-controlled mechanism ($n = 0.64$) when the amount of MC increases (Fig. 2).

Fig. 2 shows the R/F ratio plotted versus fraction released for only a PVA insert. This figure indicates that release was affected both by relaxation of the polymeric chains and diffusion of drug ($n = 0.89$). The HPMC insert shows case-II transport ($n = 0.92$) which identifies zero-order release, because the rate of erosion remains constant provided the surface area of the insert does not change dramatically. The HPMC/PVA insert shows case-I transport ($n = 0.53$) which identifies Fickian transport.

The results of Fig. 3 indicate that drug release can be influenced by low moleculer weight HPC. The release of drug from HPC inserts was increased by the use of lower molecular weight HPC. This increase of drug release was due to the increased rate of drug diffusion from the insert. Relaxation of the polymer structure increased the diffusion coefficient of the drug and thus accelerated drug release, whereas at the high molecular weight the polymer was entangled and the effective molecular diffusion area was reduced.

The differences in release of the drug from inserts are more clearly represented in Fig. 4 where the release rates of drug versus time are shown. Drug release rates could be calculated from the slopes of the curves of Fig. 3, multiplied by M_∞. Catellani et al. [14] reported that the amount of swellable polymer is inversely related to the initial release rate. However, as shown in Fig. 4, there was an early increase in the release of drug from inserts containing a high molecular weight of HPC (HPC-M, HPC-L/HPC-M). When the molecular weight of HPC increased in inserts, the penetration rate of solvent into the inserts was reduced. This reduction in solvent penetration was probably due to increased entanglement of the macromolecules. Since the gelling rate of the insert (HPC-M) was initially slower, the indomethacin fraction present at the surface of the insert was rapidly released [15].

The volume of equilibrium swelling of the inserts was affected by the molecular weight of the HPC. In general, polymer erosion was also found to be inversely related to the polymer molecular weight. Therefore HPC-M inserts are more swellable and less erodable than HPC-L inserts (Fig. 5). Gel layer thickness is defined as the difference between erosion and swelling

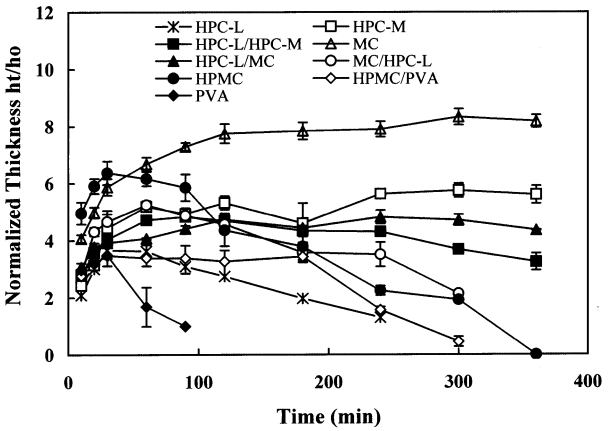

Fig. 5. Increase of normalised thickness of inserts during drug release experiments (each point represents the mean ± SE of four experiments).

front position. As shown in Fig. 5, the gel layer thickness increased early and then slowed down. It is also interesting to note that the initial patterns of change of drug release rate (see Fig. 4) follow inversely the dynamics of gel layer thickness (see Fig. 5).

The release of drug from MC and HPC-L/MC inserts was faster than that of MC/HPC-L inserts (Fig. 3). As the amount of MC increased, release rate of drug from the insert increased (Fig. 4). This may be explained by the normalised thickness of MC insert being higher than that of MC/HPC-L and HPC-L/MC inserts (Fig. 5). Intact normalised thickness of MC and HPC-L/MC inserts (containing high amount of MC) was maintained over the period of time. If an intact hyrated layer can establish over the period of study, diffusion may be the most important factor controlling the rate of drug release from the system diffusion [16]. Therefore, diffusion was a more important factor in these inserts than in MC/HPC-L inserts (containing low MC amount) in controlling the rate of drug release.

PVA and HPMC possess different weight equilibrium swelling degrees. When more swellable polymers are introduced into the formulations, the release of drug decreases with time. This may be due to an increase in diffusional path lengths for the drug which in turn may be due to a slower erosion rate of the rubbery layer and faster advancement of the swelling front into the glassy polymer [17]. The release proves to be a function of the type and amount of more swellable material used. As shown in Fig. 3, the release of drug from HPMC and HPMC/PVA inserts was lower than that of PVA inserts.

The control of the initial rate of the insert is linked to the weight equilibrium swelling degree of the polymer. HPMC controls the release rate sooner than PVA. This is shown by comparing initial rate values of PVA (1.27 μg/min) to that of HPMC (0.608 μg/min) (Fig. 4). The initial rate of the more swellable polymer (HPMC) is lower than that of the less swellable polymer (PVA). The initial rate of HPMC/PVA is expected to be between these values. However, it was found to be 1.83 μg/min. This can be interpreted by considering that undissolved drug is present at the high concentration close to the polymer transition region, i.e. near the swelling front.

It was also found that the normalised thickness showed the greatest increase with the use of the more swellable polymer (HPMC) in the insert (Fig. 5).

4. Conclusions

In the prepared inserts, as the ratio of R/F decreased, which indicates that drug release is mainly diffusive, drug release deviated from linearity. This phenomen was explained in terms of an increase of the importance for drug release of the polymer relaxation.

Drug release from polymeric inserts could occur both by diffusion and swelling controlled mechanism. The HPMC insert showed zero-order release ($n = 0.92$), whereas the HPMC/PVA insert exhibited a purely Fickian diffusion mechanism ($n = 0.53$).

Increasing the amount of HPC-M and MC in the inserts resulted in a reduction in the drug release rate, leading to the shift from swelling controlled towards a Fickian diffusion mechanism.

As the weight equilibrium swelling degree of the polymer decreased, normalised thickness of the insert decreased. However, the release rate of the drug from the insert increased.

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