J Mater Sci: Mater Med (2008) 19:677–682
DOI 10.1007/s10856-007-0168-4

Ketotifen controlled release from cellulose acetate propionate and cellulose acetate butyrate membranes

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Received: 10 May 2006 / Accepted: 12 February 2007 / Published online: 10 July 2007

Abstract Ketotifen was immobilised in cellulose acetate propionate (CAP) membranes and in cellulose acetate butyrate (CAB) membranes. The characteristics of each system were evaluated under a range of experimental conditions. The topography and uniformity of the membranes was assessed using scanning electron microscopy. The release characteristics associated with Ketotifen were monitored spectrophotometrically. The swelling capacity of the membranes was evaluated and attributed to the combined effects of diffusion and of complex dissociation, during swelling. The materials produced were able to provide controlled release of Ketotifen due to their controlled swelling behaviour and adequate release properties. The results showed that the release of Ketotifen from the CAB membranes is higher but the release from the CAP membranes is more uniform.

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Introduction

The application of controlled release systems, in which biologically active substances are released to their environment with controllable rates, has recently grown enormously. The controlled administration of chemicals or drugs is widely publicised in the field of medicine and pharmacy, agriculture, food industry and biotechnology [1–5].

In the preparation of these materials, the biologically active substance is immobilised in/on a carrier, generally a polymeric material. These polymeric systems must have the right balance of hydrophobicity/hydrophilicity, the right charge character and, if used as a biomaterial, they must be biocompatible. Their form (powder, fibre or membrane) is dependent on the application. Membranes can be used as a carrier in which the bioactive compounds can be attached to the surface of the membrane or entrapped within the polymer network. In this area, membrane composites of cellulose are well known controlled release agents for a large number of compounds [6–11].

In this article we report the results obtained when Ketotifen, an important anti-histaminic and anti-anaphylactic drug [12–17], was immobilised by entrapment in cellulose acetate propionate (CAP) and in cellulose acetate butyrate (CAB) membranes, that constitute extremely useful external biocompatible bandages for drug release.

Ketotifen is a widely used prophylactic antiasthmatic drug with pronounced antianaphylactic properties and a specific H1-antihistaminic effect. Asthma, a complex disease with an aetiology characterized by reversible episodes of airflow obstruction, airway hyper responsiveness and a chronic inflammatory process of the airways, affects more than 300 million individuals in world. Almost 90% of the cases have their origins in childhood and the last decades

showed significant increases in asthma prevalence, hospitalization, health care utilization and mortality rates. Despite the availability of several classes of therapeutic agents for asthma, it has been estimated that as many as one-half of asthmatic patients do not respond to treatment with b2-agonists, LT antagonists, or inhaled corticosteroids, presenting a large potential for drug development.

In parallel with this, the development of controlled release systems of antiasthmatic antianaphylactic drugs is expected to grow significantly, to avoid acute over dosage. Ketotifen is a perfect candidate for the development of controlled release systems of antiasthmatic antianaphylactic compounds. Its acute toxicity is rather low, since no serious effects have been reported either in children or in adults after the intake of up to 20 mg of ketotifen, which is 10 times the recommended dose and it is well tolerated specially by the children. Ketotifen also induces a moderate to marked symptom improvement in the majority of patients with atopic dermatitis, seasonal or perennial rhinitis, allergic conjunctivitis, chronic or acute urticaria [18–20].

Experimental section

Cellulose acetate butyrate and cellulose acetate propionate were supplied by Eastman Chemical Co. Ltd., Workington, Cumbria, UK, and Ketotifen (fumarate salt) was obtained from Sigma Chemical Company, Poole, Dorset, UK.

Membrane preparation

Various solutions of cellulose acetate butyrate (CAB) in tetrahydrofuran (THF) and cellulose acetate propionate (CAP) in THF were prepared in the following way: each component of each solution was mixed with THF, on the basis that the ratio polymer/THF should be 20:80 (by weight). These solutions were maintained at room temperature (25 °C) with strong stirring for 48 h, to ensure homogeneity of the solutions. The solutions were then cast on 20 × 20 cm glass plates. The solvent was evaporated at room temperature for 3 h, resulting in 0.3 mm thick membranes. Previous studies (DSC and TGA) [21] showed that such treatments provided membranes that were free of residual solvents.

Ketotifen entrapment in the membranes

Various solutions of Ketotifen in tetrahydrofuran (THF) at the desired concentrations were added to the membrane pre-solutions in THF to obtain the membranes used in the studies.

Determination of the immobilised Ketotifen in the membranes

Portions of the membranes (50 mg), containing the entrapped Ketotifen, were dissolved in THF (5 cm^3). The amount of Ketotifen in the solution was determined by monitoring the absorption at 295 nm, using as a blank a solution containing 50 mg of the membrane without Ketotifen, in THF (5 cm^3). The absorbance values were converted into the equivalent mg of Ketotifen, using a calibration curve for the pure Ketotifen in THF.

Scanning electron microscopy (SEM)

SEM examinations were performed using a Jeol JSM scanning electron microscope fitted with a Mamiya SLR camera and TV recording facility, coupled to an X-ray energy dispersion unit to determine the presence of elemental sulphur, a component of Ketotifen.

In vitro drug release studies

In order to determine the variation of the drug release with time, portions of the membranes (100 mg) that contained Ketotifen were kept in distilled water (20 cm^3) for various intervals of time, at 25 °C. The amount of drug released was determined at 295 nm, using calibration curves for Ketotifen, dissolved in water.

Determination of diffusion coefficient of ketotifen

Known small portions of membranes, with the same amount of immobilised Ketotifen, were placed in distilled water (20 cm^3) at 25 °C, for several time intervals, over a period of 15 days. The absorbance of the Ketotifen was determined at 295 nm.

Swelling capacity

The swelling capacity and the diffusion capacity were determined as follows. The membranes (100 mg) were incubated in distilled water (50 cm^3) for various time intervals, at 25 °C. The water uptake was determined gravimetrically as well as by spectrophotometric evaluation of the solute release, at 295 nm. Diffusion coefficients were determined using the Fick's models as a basis.

Results and discussion

Determination of sulphur distribution

Analysis of CAP-Ketotifen and CAB-Ketotifen membranes by "sulphur mapping", both at the surface and in cross-

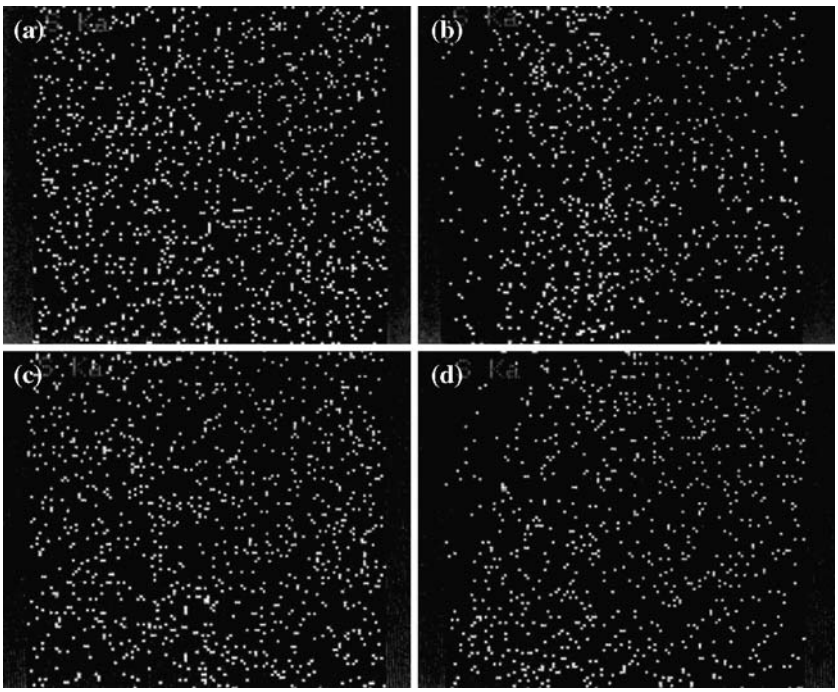

Fig. 1 Sulphur determination (after Ketotifen immobilisation) by X-ray dispersion energy from the surface (**a**) and cross-section (**b**) of cellulose acetate propionate (20% w/w) membranes. Same results for the surface (**c**) and cross-section (**d**) for the cellulose acetate butyrate (20% w/w) membranes

section, present similar results for both membrane systems (Fig. 1). A good uniformity of Ketotifen distribution inside the membranes was found, showing that the physical immobilisation of Ketotifen was achieved by entrapment and not by adsorption.

Determination of membrane structures

In order to relate the release results to the membrane composition and morphology, the membranes were characterised by SEM. Figure 2 show SEM of the CAP membranes, with and without immobilised Ketotifen respectively, and Fig. 3 show SEM of CAB membranes, without and with immobilised Ketotifen respectively. Both CAP and CAB membranes have the same amount of immobilised Ketotifen.

These micrographs show that the CAB membranes have more surface irregularities and are more porous than CAP membranes, probably due to the different size of the butyrate group compared with the propionate group. Also CAB membranes have a more open structure than CAP membranes. The presence of Ketotifen does not imply significant changes in the membrane structure.

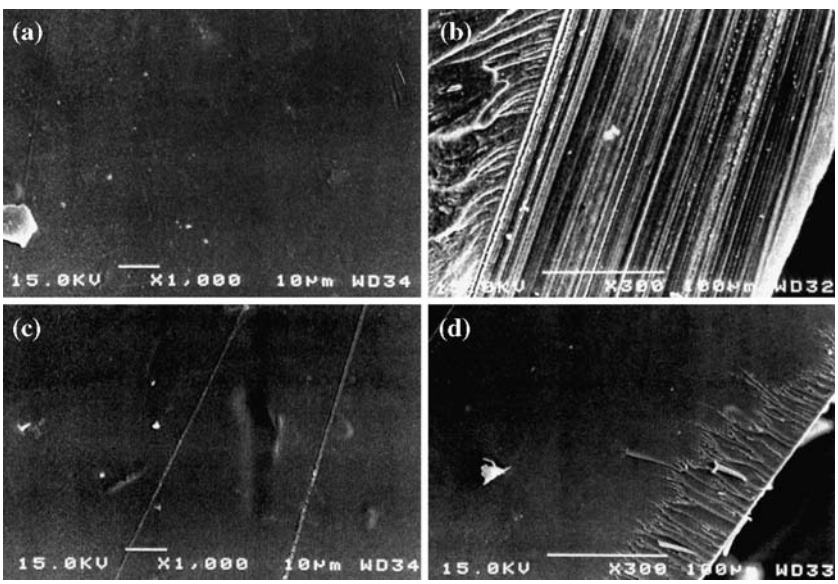

Fig. 2 Scanning electron micrographs of surface (**a**) and cross-section (**b**) of cellulose acetate propionate (20% w/w) membranes without immobilised Ketotifen. Scanning electron micrographs of surface (**c**) and cross-section (**d**) of cellulose acetate propionate (20% w/w) fsmembrane, with immobilised Ketotifen

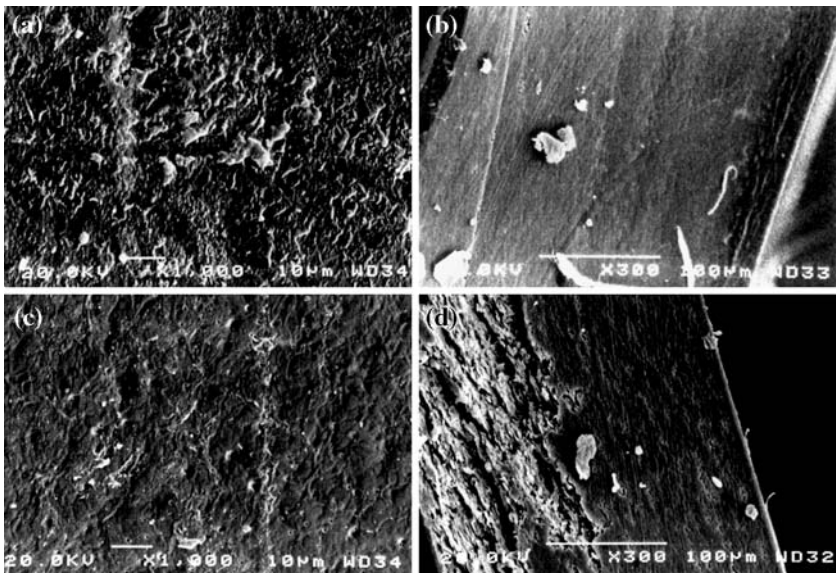

Fig. 3 Scanning electron micrographs of surface (**a**) and cross-section (**b**) of cellulose acetate butyrate (20%) membranes without immobilised Ketotifen. Scanning electron micrographs of surface (**c**) and cross-section (**d**) of cellulose acetate butyrate (20% w/w) membrane with Ketotifen immobilised

Study of the Ketotifen release from CAP and CAB membranes

Figure 4 shows the Ketotifen release profile, for both CAP and CAB systems.

These graphs show that the percentage of drug released is higher for CAB membranes. The total percentage of the drug released is 1.8% (w/w) for the CAB membranes and 0.6% (w/w) for the CAP membranes. These results also show that for the 24–75 h time period the release of Ketotifen is much higher from the CAB membranes. In the interval studied the concentrations of Ketotifen released are 0.1–0.5 mg/g for the CAP membranes and 0.02–3.5 mg/g for the CAB membranes.

The variation of the release of Ketotifen from the membranes shows a slowing down of the Ketotifen release

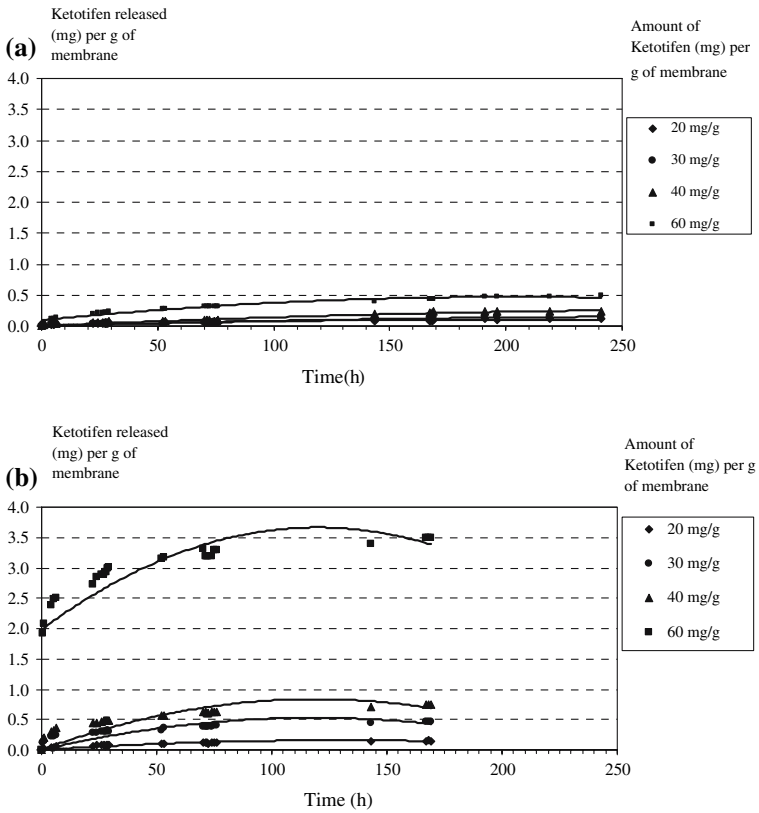

Fig. 4 Ketotifen (mg) released per g of membrane as a function of time, for the (**a**) CAP and (**b**) CAB membrane-Ketotifen systems, using varying amounts of immobilized Ketotifen

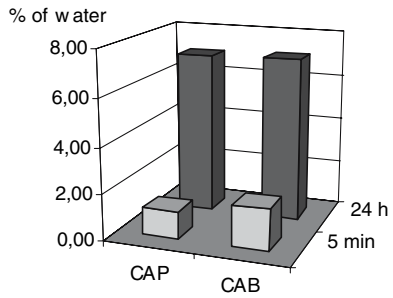

Fig. 5 Water sorption of cellulose acetate propionate and cellulose acetate butyrate membranes at 25 °C

after 50 h. Although the release of Ketotifen from the CAB membranes is higher, the release from the CAP membranes is slightly more uniform.

Determination of water sorption

The percentage of water sorption was calculated as:

$$\% \text{ (w/w) sorption of water} = (M_f - M_i)/M_i \times 100$$

Here M_f is the final membrane mass after water immersion and M_i is the initial membrane mass before water immersion.

In order to relate the results obtained to the hydrophilicity of the membranes, analysis of the water sorption for each membrane at room temperature was carried out. Figure 5 shows the water sorption after 5 min and 24 h. The results show that the water sorption in the both CAP and CAB membranes are quite similar.

Determination of ketotifen release kinetics

To study the kinetics of Ketotifen release, all of the variables were kept constant, except the Ketotifen concentration. Thus, the kinetic profile developed relates to the Ketotifen only. Thus,

$$v = k\ [\text{Ketotifen}]^n$$

and

$$\log\ v_o = \log\ k + n\ \log\ [\text{Ketotifen}]_o$$

The first derivative of the release curves was used to determine log v_o and log k. Figure 6 shows the data used to determinate the kinetic order for the release process relevant to the CAP system and to the CAB system, respectively.

The values for (n), the kinetic orders of the Ketotifen release process are:

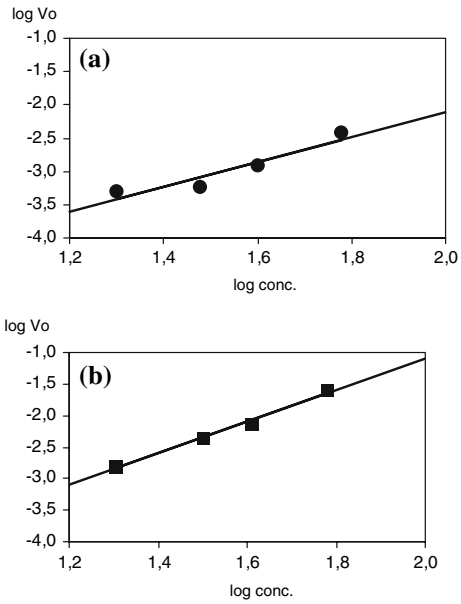

Fig. 6 Variation of log v_o with log [Ketotifen] in the release of Ketotifen from (**a**) cellulose acetate propionate membranes and (**b**) cellulose acetate butyrate membranes

Release from CAP membranes $n = 1.89$

Release from CAB membranes $n = 2.43$

The release characteristics of these systems do not follow a zero order profile, indicating that the diffusion mechanism may be Fickian, mainly due to the membrane morphology.

Diffusion coefficient of ketotifen

Following the kinetic evaluations, the variation in the diffusion coefficient, as a function of the amount of Ketotifen immobilized in the membranes, was established. The diffusion coefficients were obtained by Fick's second law using all of the experimental values. The initial release of Ketotifen is constant. The diffusion coefficient of Ketotifen was determined for several different concentrations of immobilised Ketotifen. As shown in Table 1, it was found that the diffusion coefficient of both membrane systems is not significantly dependent on the initial concentration of Ketotifen.

Swelling behaviour (diffusion coefficients of the solvent)

The dynamic swelling of the CAP (20%) and of the CAB (20%) network was studied in distilled water in the same

Table 1 Diffusion coefficient of Ketotifen in the cellulose acetate propionate and cellulose acetate butyrate membranes

Membrane	Amount of immobilized Ketotifen (mg/g)	Diffusion coefficient of Ketotifen D (cm^2/s)	Linear correlation coefficient *r*
CAP	20	2.26×10^{-8}	0.96
	30	1.52×10^{-8}	0.95
	40	1.67×10^{-8}	0.99
CAB	20	1.84×10^{-8}	0.98
	30	2.65×10^{-8}	0.93
	40	3.03×10^{-8}	0.96

Table 2 Coefficients of the solvent uptake

Membrane	Ketotifen release from the membrane		Solvent uptake coefficient	
	Diffusion coefficient of Ketotifen D (cm^2/s)	Linear correlation coefficient *r*	Diffusion coefficient of solvent D (cm^2/s)	Linear correlation coefficient r
CAP	2.26×10^{-8}	0.96	4.38×10^{-7}	0.98
CAB	1.84×10^{-8}	0.98	5.73×10^{-7}	0.99

conditions. The swelling behaviour of CAP and CAB, in 50 cm^3 of distilled water was measured and the diffusion coefficients were determined, as the normalized average of several experiments, and is presented in Table 2. The data show that there is an initial linear increase in uptake following a levelling of the solution uptake.

Table 2 shows that the uptake coefficients for the solvent and the diffusion coefficient for the Ketotifen release are not similar, the solvent uptake being higher. This may be explained by the relative size of the molecules of solute and solvent. The water molecules are smaller than Ketotifen and so will diffuse faster.

Conclusions

The results obtained indicate that cellulose acetate propionate and cellulose acetate butyrate based membranes show promise for the immobilisation of drugs, namely the important pharmacological Ketotifen, opening the way to biomedical applications due to their relevant, controllable swelling transitions.

Although the release of Ketotifen from cellulose acetate butyrate membranes is higher, the release from the cellulose acetate propionate membranes is slightly more uniform and that may be exploited in future medical applications. The results show also that the sorption of water in the both cellulose acetate propionate and cellulose acetate butyrate membranes is quite similar and that the release characteristics of these systems do not follow a zero order profile, indicating that the diffusion mechanism may be Fickian, controlled mainly by the membrane morphology.

The observed differences between the cellulose acetate propionate and cellulose acetate butyrate systems allow an efficient discrimination of the polymer abilities in terms of drug release, based in small structural factors that affect the morphology and physical properties of these cellulose based polymers, and confirm their potential as medical drug delivery systems.

Acknowledgements A. Sobral thanks Fundação para a Ciência e Tecnologia (POCI/AMB/55281/2004) for financial support.

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