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International Journal of Pharmaceutics 158 (1997) 91–97

international journal of pharmaceutics

Design of a controlled release osmotic pump system of ibuprofen

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Received 5 May 1997; received in revised form 21 July 1997; accepted 30 July 1997

Abstract

Elementary osmotic pumps releasing solutions of active materials at a controlled rate have increased in popularity during the last two decades. In this study, the effect of the delivery orifices and the concentration of osmotic agents on the rate of release of the active material was investigated. For this purpose, ibuprofen tablets were prepared and sodium chloride and polyethylene glycol 6000 were used as osmotic agents. The tablets were coated with a mixture of cellulose acetate and polyethylene glycol 400 by the use of a modified fluidized bed apparatus. Delivery orifices on the coated tablets are produced using a microdrill. The tablets were tested for dissolution rate using the USP paddle method. Finally, it was observed that the release rate of ibuprofen was influenced by the concentration of osmotic agents sodium chloride and polyethylene glycol 6000. © 1997 Elsevier Science B.V.

Keywords: Osmotic pump; Ibuprofen; Controlled release; Osmotic pressure

1. Introduction:

Elementary osmotic pumps are systems for the delivery of a drug in the form of a solution that release the active material at controlled rates. These systems work with the principle of osmosis; osmotic pressure is produced by active material in itself and/or an accompanying osmotic agent. The preparation consists of the core that contains the active material and a semipermeable membrane that coats the core, having an orifice produced by a microdrill in order to release the active material. When the system is in the gastrointestinal tract, fluid enters into the preparation and dissolves the active material in the core. Thus, the pressure formed in the preparation induces a release of the solution at a slow but continuous rate (Theeuwes, 1975).

The rate-limiting step in the absorption of active materials that are poorly soluble in water is

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PII S0378-5173(97)00250-0

their solubility in the fluids of the gastrointestinal tract (GI) which reduces the bioavailability of active material. Furthermore, it is known that irritation in the gastrointestinal tract occurs due to long-term exposure to such materials. These features are the most important characteristic problems encountered in active anti-inflammatory materials.

This study was designed to create a preparation of ibuprofen, an anti-inflammatory substance which has the previously described problems, to be delivered by a controlled release osmotic pump. Thus, by releasing the active material at a desired rate, and in a solution, it was thought that not only the irritation in the gastrointestinal tract may be prevented but also the bioavailability problem would be solved owing to the controlled release. Also, the effect of orifice size, as well as the type and concentration of the osmotic agent, on the release of active material has been examined in this study.

2. Materials and methods

2.1. Chemicals

Ibuprofen (Eczacibapi, Turkey), sodium chloride (NaCl), polyethylene glycol 6000 (PEG 6000) and polyethylene glycol (PEG 400) (Merck, Germany), and cellulose acetate (BDH, UK) have been employed in the study.

2.2. Design parameters

By using the pharmacokinetic parameters of ibuprofen that were previously determined in several studies, a dose structure was designated for the preparation of ibuprofen for controlled release (Özdemir and Özateş, 1996). The values proposed were: (1) sustaining dose, 145 mg; (2) zero-order release rate, 20.7 mg/h; (3) dosage interval, 7 h.

These values have been determined assuming an administration of 2 units at a time.

2.3. Preparation of the formulations

A constant dose (145 mg) of the active material and increasing concentrations of the osmotic agent (NaCl or PEG 6000) were used in all formulations. The formulation shown in Table 1 coded IP was prepared as a control formulation for pure ibuprofen. The effects of NaCl and PEG 6000 on the release were examined by comparison with this formulation.

Formulations that contain ibuprofen in a predetermined dose were compressed in a press using a 9-mm diameter punch at a compression force of 267.3 MPa. A solution of cellulose acetate in acetone at a concentration of 4% (w/w) was used to coat the tablets. Since this covering was fragile, PEG 400 at a concentration of 2% (w/w) was added to the coating solution as a plasticizer. The tablets were coated and then dried using a fluidized bed apparatus. The orifices for the delivery of active material were created by a microdrill (Özdemir and Ordu, 1990).

2.4. Dissolution rate tests

The USP paddle method was used in the dissolution rate studies at 37 ± 0.5°C (US Pharmacopeia XX, 1980). The dissolution rate test was performed at 50 rpm in 900 ml phosphate buffer at pH 7.2. All formulations were tested for 3 h.

Table 1
The formulations used in the study

Formulations	Ibuprofen (mg)	NaCl (%)	PEG 6000 (%)
IP	145	—	—
N5	145	5	—
N10	145	10	—
N15	145	15	—
N30	145	30	—
N50	145	50	—
N70	145	70	—
P5	145	—	5
P10	145	—	10
P15	145	—	15
P30	145	—	30
P50	145	—	50
P70	145	—	70

Samples taken at predetermined time intervals were measured spectrophotometrically at a wavelength of 264 nm. Sink conditions were maintained during all measurements. If no significant differences existed statistically between the results obtained, the mean of three dissolution tests results were taken and their fit to different kinetic models was evaluated.

2.5. Measurements of osmotic pressure

Osmotic pressures of both dissolution medium and solution in the tablet rendered by cutting the preparation were measured using a Wescor Osmometer at various times during the dissolution rate studies. The results obtained were used in the explanation of the mechanism of the release of active material from preparations.

3. Results and discussion

In the present study, the controlled release dosage form was designed on the basis of pharmacokinetic data on ibuprofen. With a maintenance dose of 290 mg, the release of active material at a rate of 41.4 mg/h for 7 h was found to be ideal (Özdemir and Özateş, 1996). As the dosage form was considered to be inconveniently large due to the additional substances, it was reduced by half by changing the regime of administration to two tablets per dose.

Firstly, an estimated amount of active material was compressed without any additional substance and coated with a solution of cellulose acetate in acetone (4% w/w). Since the coating material was too hard and fragile, however, PEG 400 (2% w/w) was added as a plasticizer. Scanning electron microscope (SEM) photographs demonstrate the structures of both coating materials after contact with water (Fig. 1). As seen in these pictures, the structure seems to have a more elastic and porous condition with the addition of PEG. Therefore, the solution of cellulose acetate containing PEG 400 was used to coating all tablets in the study. The coated tablets with the IP code, that contain no orifice, were subjected to a dissolution rate test in order to detect whether the active material passes through the film by diffusion. Since no active material was released through the tablets during first 150 min, and it was determined that only 1.66% of the active material was released by the end of 180 min, it was concluded that diffusion from the membrane did not influence the release of active material and was not shown in the figures.

To investigate the effect of orifice size on the release of active material, orifices with diameters of 150, 250 and 350 μm, respectively, were formed using a microdrill on the tablets coded IP, and subjected to the dissolution rate test (Fig. 2). Since active material in the tablets does not induce an osmotic effect due to its property of poorly solubility in water, an initial lag-time of 60 min is necessary to moisten of the system, allow penetration of water into the core, and for dissolving active material. The time, during which it is necessary to moisten the tablets, may be reduced by the addition of a surface-active agent to the coating material (Özdemir et al., 1995). Statistical analyses of the data from the dissolution rate test did not reveal a significant difference between the release rates of active material from tablets with different size of orifices. Quantities of active material released were examined and it was found that zero-order kinetics rather than diffusion predominates. Therefore, it was decided that an orifice diameter of 350 μm should be used for all the other formulations to minimize the gradient of hydrostatic pressure inside and outside the tablets.

Release of active material from IP tablets with an orifice of 350 μm was observed for 3 h. and it was determined that 2.7, 5.95 and 14% was released at 60, 150 and 180 min, respectively. The onset of release of active material takes place at the end of a certain time (lag-time); it apparently begins after an osmotic pressure builds up in the tablet. This event demonstrates that the mechanism influencing the release of active material is osmotic pressure instead of diffusion. In an attempt to approximate the delivery of active material to the target profile, osmotically active agents, NaCl and PEG 6000, were added to the tablets in different concentrations. The release of active material was enhanced owing to the osmotic effect,

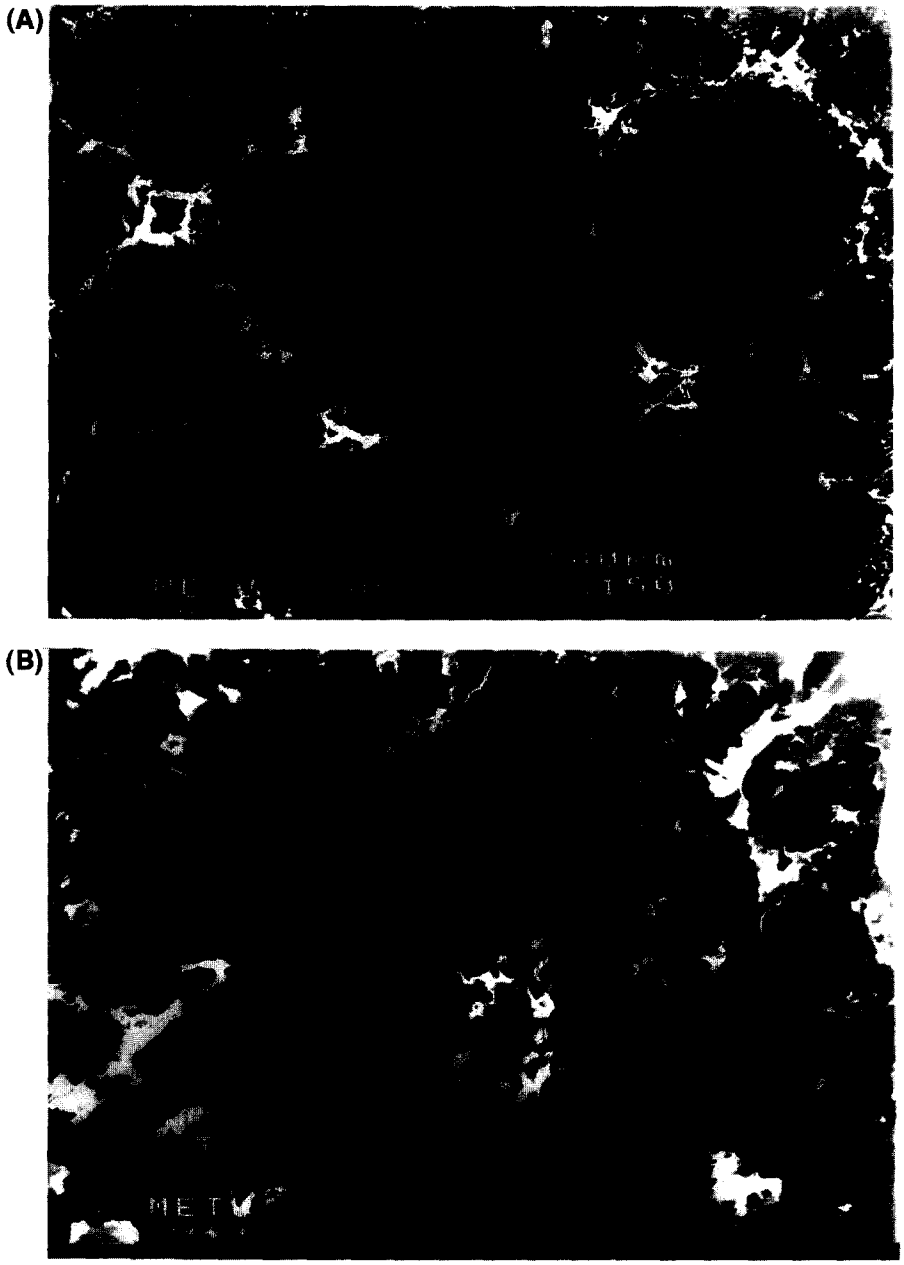

Fig. 1. The scanning electron micrographs of the coating materials after exposure to water. (A) pure cellulose acetate films; (B) cellulose acetate films containing PEG 400 as a plasticizer.

as the concentrations of NaCl and PEG 6000 were increased (Figs. 3 and 4). A significant increase in delivery in all tablets was observed after 120 min. The relationship between the rate constant of zero-order release from the tablets and the concentrations of NaCl and PEG 6000 is shown in Fig. 5.

The steady-state zero-order release rate (dm/dt) of a drug from an osmotic delivery device can be calculated using Eq. (1)

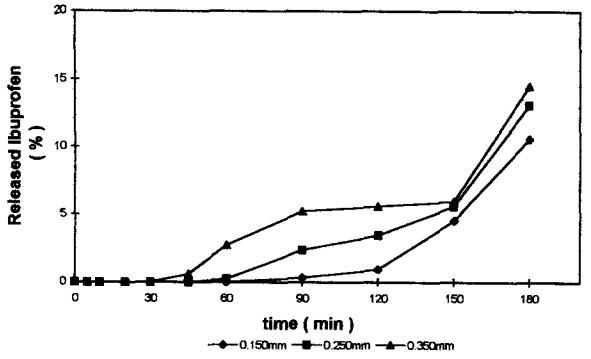

Fig. 2. Effect of orifice diameter on the release of ibuprofen.

$$dm/dt = AS/hLp\sigma\Delta\Pi + PAS/h$$
$$= \text{osmotic pumping} + \text{diffusion} \quad (1)$$

where A is the device surface area, h is the coating thickness, S is the drug solubility, $Lp\sigma$ is the fluid permeability of the coat, P is the permeability coefficient of the drug through the coat, and $\Delta\Pi$ is the osmotic pressure difference across the coat. The first term represents the osmotic pumping component and the second term is the contribution from simple Fickian diffusion (assuming sink conditions).

As mentioned previously, the mechanism that conducts the release of active material from the formulations is the osmotic pressure gradient, and the osmotic pressures of both dissolution medium and solution in the tablet were measured at various points during the dissolution rate tests for the formulations coded N15, P15, P70 and IP. Fig. 6

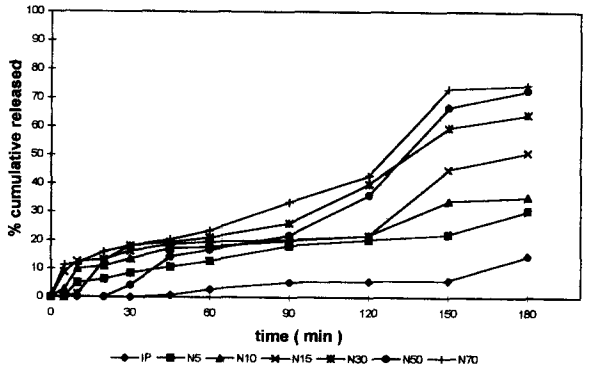

Fig. 3. Influence of the amount of NaCl on the release of ibuprofen.

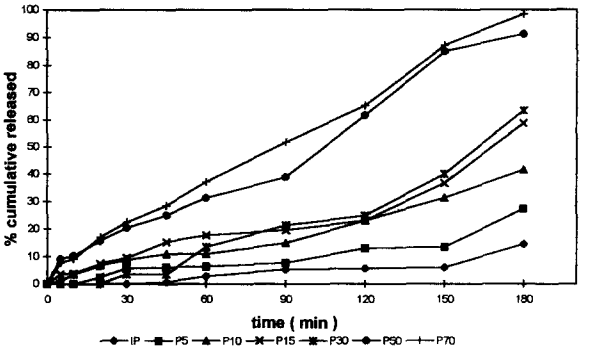

Fig. 4. Influence of the amount of PEG 6000 on the release of ibuprofen.

shows steady-state zero-order release rates of ibuprofen into pH 7.2 buffer solution plotted versus the calculated osmotic pressure difference across the coat. The linear relationship between release rate and $\Delta\Pi$ confirms that osmotic pressure is the driving mechanism that controls the release of ibuprofen. When the least-squares method was applied to the obtained data for the formulations, when their deliveries were considered to be proper to the target profile, the slopes for the formulations coded N15 and P15 were determined to be 1.39 and 1.69 mg/h/MPa, respectively. Additionally, a y intercept of 1.11 mg/h ($r^2 = 0.977$) for N15 and of 1.92 mg/h ($r^2 = 0.922$) for P15 was obtained. The y intercept ($\Delta\Pi = 0$) is indicative of the contribution of the diffusive component to the overall release, which was small relative to the osmotic pumping component. Therefore, it was concluded that the release

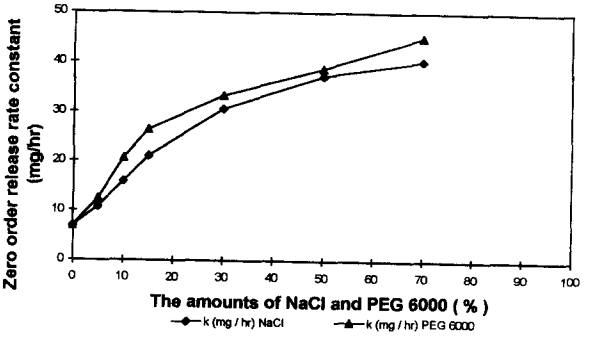

Fig. 5. The relationship between the amount of NaCl and PEG 6000 and zero-order release rate constant of iburofen.

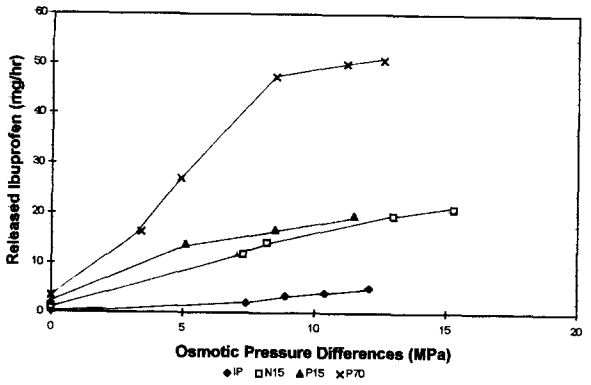

Fig. 6. The relationship between of the release rate of P15, N15, P70 and IP and the differences in osmotic pressure.

was primarily driven by an osmotic pumping mechanism. (Theeuwes, 1975; Zentner et al., 1985; Appel and Zentner, 1991).

In order to explain the mechanism of release of the active material, m and n values were also studied for the tablets coded IP, containing active material only, and P70, containing 70% PEG 6000 (Fig. 6). The slope value for the tablets coded IP was determined to be 0.412 mg/h/MPa, and for the P70 tablets it was found to be 4.21 mg/h/MPa. Again, the estimated values of the y intercept of IP and P70 were found to be 0.276 ($r^2 = 0.947$) and 3.34 mg/h ($r^2 = 0.945$), respectively. The fact that the n values in both formulations were small indicates that the osmotic pressure is the effectual mechanism for release of active material. The values of slopes for the tablets coded IP (containing no PEG), P15 (containing 15% PEG 6000) and P70 (containing 70% PEG 6000) were found to be 0.412, 1.69 and 4.21, respectively, these values indicate that the release of active material was significantly enhanced with increasing amounts of PEG 6000, the water-soluble and water-imbibing agent, situated in the core of tablet (Figs. 4 and 6).

Considering the probability that PEG 6000 forms a solid dispersion with active material, it was supposed that enhancing the solubility of the active material may increase the release rate. Thus, DSC measurements were performed in samples of PEG 6000, pure ibuprofen and mixtures of both, and it was determined that the peaks of ibuprofen seen at 76°C did not disappear and that a solid dispersion did not occur (Fig. 7). Thus, it was concluded that the effective mechanism in release of active material was osmotic pressure. It was also determined that, in the presence of water-soluble and water-imbibing agents in the core (e.g. PEG 6000), the amount of water penetrating into the core increased in proportion to the amounts of these substances. From this fact it is inferred that the quantities of dissolved active material and, hence, the pumped volume of fluid containing dissolved active material increase, and ultimately enhance the release rate of active material.

The desired release rate was accomplished in the formulations containing 15% NaCl and both

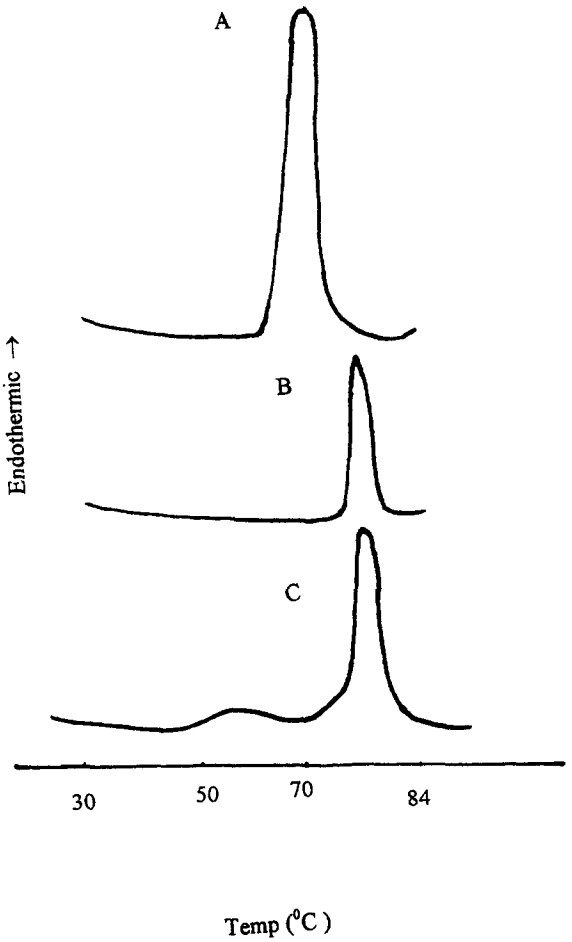

Fig. 7. DSC thermograms of (A) PEG 6000, (B) ibuprofen, (C) the physical mixture of PEG 6000 and ibuprofen.

10 and 15% PEG 6000. In the formulation containing 10% PEG 6000, a release rate of 20.7 mg/h was achieved.

4. Conclusion

In this study, it has been shown that release of active material increased as the concentrations of NaCl and PEG 6000 added to ibuprofen tablet formulations increased. An ibuprofen preparation that allows the controlled release by osmosis was prepared.

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