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COMMUNICATION

An Approach to Controlled-Release Dosage Form of Propranolol Hydrochloride

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ABSTRACT

It is possible to release a drug with only limited diffusion from a membrane-coated system using osmotic pumping. In this study, a propranolol osmotic pump was produced by coating the core tablets with cellulose acetate. The effects of membrane thickness, pore size, and stirring rate on the release rate of propranolol hydrochloride were studied. It was found that the thickness of cellulose acetate membrane had a profound effect on the release rate of propranolol hydrochloride from the membrane-coated tablets. The results showed that, when the membrane thickness increased, the release rate of propranolol decreased. The drug release follows a zero-order release when the delivery orifice is between 200 and 800 μm, but when the delivery orifice size is increased to 1000 μm, the release kinetic is abnormal. Fluid dynamics have an important effect on the delivery rate of propranolol from this device; the delivery rate increases as a function of the fluid flow. The drug release is higher under a turbulent condition with high rate of stirring.

INTRODUCTION

Significant advances have been made in the development of drug delivery devices in which the controlled amount of drug can be released in a defined period. Membrane coating is a very convenient way of regulating the release rate of oral formulations. Membrane coatings are in general considered to release the drug by diffusion of the drug through the membrane material or through the pores.

There are formulations for which osmotic pumping is the major release mechanism, the most common being

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the elementary osmotic pump (1). In these therapeutic systems, osmotic pressure was used as the energy source to induce drug release in a predictable and uniform manner (1–3). This system consists of a solid core containing active ingredient, alone or with an osmotic agent, surrounded by a semipermeable membrane, which has a delivery pore. When this device is placed in water, the water is imbibed osmotically into the core, thereby pushing a volume of saturated drug solution through the delivery orifice in a programmed manner.

There are also osmotic devices in which no attempts have been made to create pores (2). For example, Lindstedt and coworkers used an appropriate mixture of ethylcellulose and hydroxypropylmethylcellulose as the membrane coating materials; in dissolution medium, the hydroxypropylmethylcellulose portion of the membrane was dissolved in water, and a porous membrane was produced.

Until the solid phase of the osmotic delivery system is exhausted, drug delivery from the device is constant. Once the solution no longer is saturated, the rate of drug delivery declines parabolically (1).

The aim of this report is to show the existence and importance of osmotic pumping in a membrane-coated propranolol hydrochloride formulation; it outlines some aspects of the design of two daily systems for propranolol hydrochloride.

EXPERIMENTAL

Materials

Propranolol hydrochloride (Merck, Darmstadt, Germany), lactose (Merck), polyvinylpyrrolidone with a molecular weight of 25,000–30,000 (Merck), magnesium stearate (Merck), tricalcium phosphate (Merck), cellulose acetate with 38% substitution (Carlo Erba, Milan, Italy), dichloromethane (Merck), and ethanol (Daru-pakhsh, Tehran, Iran) were used.

Methods

Preparation of Osmotic Pumps

A propranolol hydrochloride osmotic pump was produced by mixing propranolol, lactose, or tricalcium phosphate and polyvinylpyrolidone, granulating with ethanol, then passing the mixture through a number 16 sieve. The sieved fraction was dried in an oven at 50°C. The resulting granules were then mixed with magnesium stearate for 2 min and compressed into tablets on 12-mm concave punches using an Erweka single-punch machine (Erweka, Heusenstamm, Germany). The weight of each tablet was determined to be within the range of 700 ± 20 mg. Each tablet theoretically contained 80 mg propranolol, and the compression pressure was adjusted so that the average hardness of the tablets after compression was 7–8 kgf.

The tablets were then coated using the dip-coating technique. The mixture of dichloromethane and ethanol with the ratio of 90/10 was used as the polymer solvent, and the polymer concentration in the coating formulation was kept constant (2% w/w). The coating process was performed as required so that the weights of the polymeric layers after drying were about 1.1–2.2% of the initial weight of the core depending on the aim of the formulation. The coated tablets were dried at room temperature for 24 hr, and then the film-coated tablets were drilled using a microdrill to produce the delivery orifice in the size range 200–1000 μm, depending on the aim of the study.

Two different types of cores were designed to study the mechanism of propranolol release from film-coated tablets; release is a function of the osmotic pressure produced in the inside of the devices. Group 1 cores contained propranolol hydrochloride as the model drug and lactose as the soluble filler, whereas group 2 cores contained propranolol hydrochloride as the model drug and tricalcium phosphate as the insoluble filler. These cores were then coated separately with cellulose acetate solution, and the weights of coated layers were evaluated after the drying period as about 1.7% of the initial weight of the core.

Dissolution Studies

The release rate of propranolol from the coated tablets was determined using the USP dissolution apparatus 1 (Caleva tablet dissolution tester 8st). Distilled water was used as the dissolution medium. The stirring rate of the media was 100 rpm. To evaluate the effect of stirring rate on the release rate of the drug, different stirring rates (i.e., 100, 200, or 300 rpm) were used. The tablets were placed in 900 ml of dissolution media, and the temperature was maintained at 37°C ± 0.1°C. At appropriate intervals, 5 ml of each sample were taken and filtered through a 0.45-μm Millipore filter. The samples were then analyzed at 289 nm using an ultraviolet-visible (UV-Vis) spectrophotometer (Shimadzu 160A, Kyoto, Japan). The mean of six determinations was used to calculate the drug released from the samples.

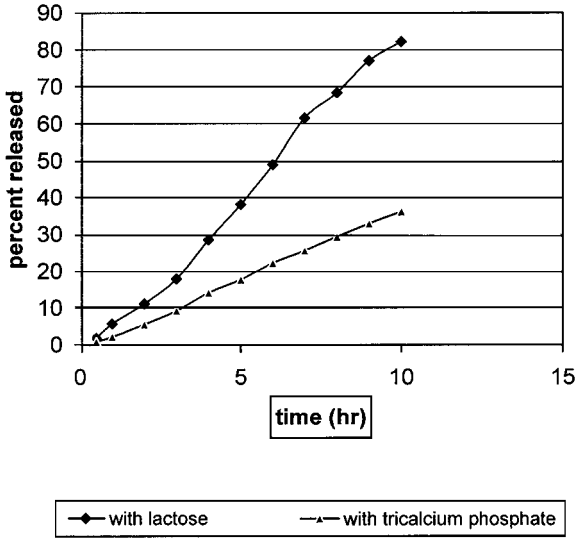

Figure 1. The effect of filler on the release rate of propranolol from film-coated tablets.

RESULTS AND DISCUSSION

The release rates of propranolol from each group of coated tablets are shown in Fig. 1. The results showed that, with lactose as the filler, the rate of drug release was considerably higher than for the tablets containing tricalcium phosphate (Fig. 1). The reason is the higher water solubility of lactose (about 2 g/ml at 37°C) in comparison with tricalcium phosphate (about 0.2 g/ml at 37°C). It is obvious that the differences in solubility produce these different release rates. This finding confirms that the propranolol hydrochloride release from these film-coated tablets is a function of the osmotic pressure produced inside the system. Each group of these tablets was drilled to produce an orifice with a diameter of 500 μm. When undrilled film-coated tablets were studied, the hydrodynamic pressure of the inside of the cores ruptured the membrane. That was the reason why it was not possible to determine the role of diffusion in the propranolol release rate.

Table 1

Release Parameter for Different Orifice Sizes

Orifice Size (μm)	Correlation Coefficient	Zero-Order Rate Constant (mg/hr)	Release Exponent
200	0.995	8.88	1.092
500	0.997	8.98	1.085
800	0.996	9.11	1.101
1000	0.963	10.7	1.225

To evaluate the role of membrane thickness on the release rate of propranolol, three different thicknesses were prepared and studied (the membrane thickness was evaluated as the weight increase in the tablet after finishing the coating process and drying the tablets). The results showed that, when the film thickness was increased, the rate of drug release was considerably decreased (Fig. 2).

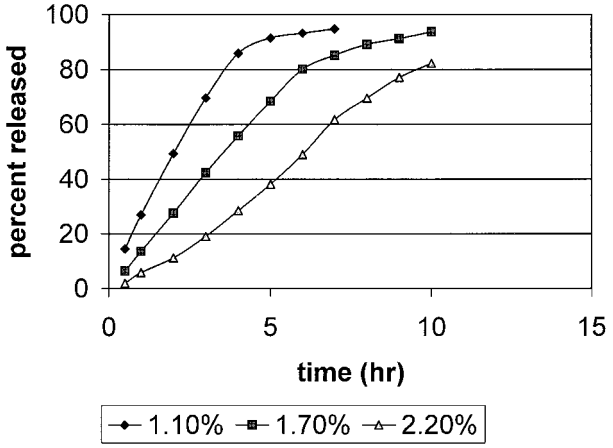

Figure 2. The effect of cellulose acetate concentration on the release rate of propranolol from film-coated tablets.

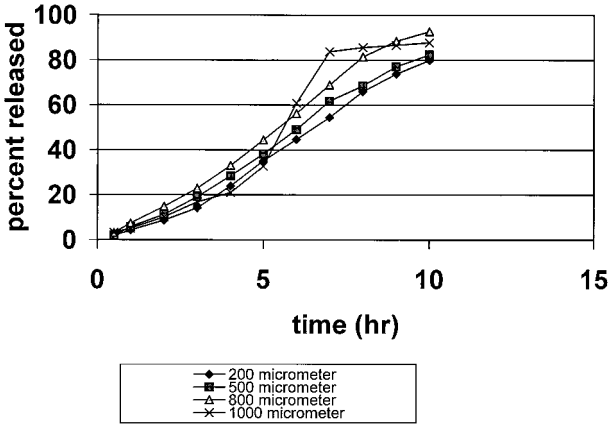

Figure 3. The effect of orifice size on the release rate of propranolol from film-coated tablets.

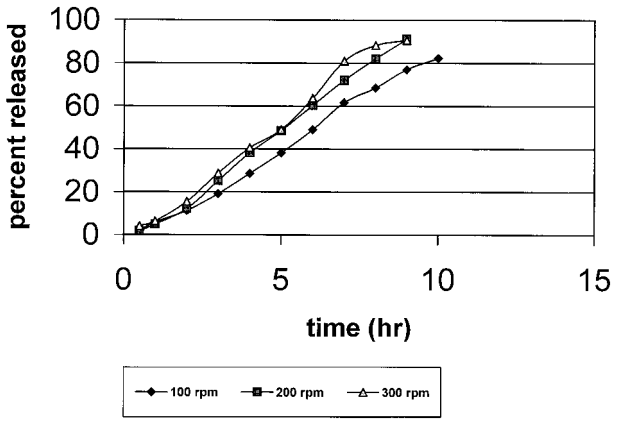

Figure 4. The effect of stirring rate on the release rate of propranolol from film-coated tablets.

To evaluate the deviation from zero-order kinetics, two different parameters (i.e., correlation coefficient and the release exponent *n*) were used (Table 1). Krosemeyer et al. (4) used a simple empirical equation to describe the general behavior of solute release from controlled-release polymeric tablets:

$$Q = Kt^n \quad (1)$$

where *Q* is the percentage of drug released, *t* is the release time, *K* is a constant that incorporates structural and geometric characteristics of the release device, and *n* is the release exponent that indicates the mechanism of release. Equation 1 assumes that release occurs as soon as the tablet is placed in contact with dissolution media and thus predicts an intercept at the origin. When *n* is equal to 1, the release mechanism approaches zero order (4).

Figure 3 represents the effect of delivery orifice size on the rate of drug release. Four different opening sizes (i.e., 200, 500, 800, or 1000 μm) were studied. Table 1 shows the effect of orifice size on the release rate and release exponent *n* of propranolol. The table shows an increase in the orifice size resulted in an increase in release rate and release exponent. The release data showed that, in the delivery orifice size between 200 and 800 μm, the release mechanism follows zero-order release, but when the delivery orifice size increases to 1000 μm, the release rate of propranolol becomes abnormal (see Fig. 1). This finding could be attributed mainly to the increase of water influx through the delivery orifice at the 1000-μm opening size (5).

Table 2

Release Parameter for Different Stirring Rates

Stirring Rate (rpm)	Correlation Coefficient	Zero-Order Rate Constant (mg/hr)	Release Exponent
100	0.994	8.98	1.092
200	0.999	11.00	1.121
300	0.994	11.2	1.132

The effect of stirring rate on the release rate of propranolol hydrochloride from EOPs (elementary osmotic pumps) that had an orifice with about a 500-μm diameter was also studied. Three different stirring rates (i.e., 100, 200, or 300 rpm) were examined (Fig. 4). An increase in the rate of stirring resulted in an increase in the release rate of the drug (Table 2). Increment in drug delivery as a function of fluid velocity was explained by the fact that agitation increased water influx into the core of EOPs by forcing water through the pores of the membrane or through the delivery orifice (5).

In conclusion, the study showed that the type of filler, orifice size, concentration of the polymer, and stirring rate can influence the release rate and release kinetic of propranolol hydrochloride from film-coated tablets. Therefore, using the correct parameters mentioned above, zero-order release formulations of propranolol hydrochloride can be achieved.

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