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COMMUNICATION

Effect of Polysorbates on Atenolol Release from Film-Coated Tablets

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ABSTRACT

The effects of different concentrations of various polysorbates on the release rate of atenolol from film-coated tablets were evaluated. The release profile of atenolol showed that increasing the concentration of polysorbate resulted in an increase in the release rate of atenolol. The type of polysorbate had less effect on the release rate of atenolol. This study revealed that the release kinetic of atenolol from these film-coated tablets was a function of polysorbate concentration. Correlation coefficients of kinetic models could not solely determine the suitability of the models; the sum of the least square of differences also should be calculated when different kinetic models have similar correlation coefficients.

INTRODUCTION

Over the last few decades, much attention has been focused on fabricating oral controlled-release dosage forms. The polymeric film-coating technique often has been utilized for achieving sustained release of the active substance from pharmaceutical preparations (1,2).

Ethylcellulose (EC) is probably the most widely used water-insoluble polymer in film coating (3,4) due to its good film-forming properties, which produce tough and flexible coatings.

Recently, Narisawa et al. found that EC could spontaneously form a porous film when an EC, ethanol, and water ternary mixture was cast (5). The pore-forming mechanism was found to be based on the phase separation of the polymer, and the density of the resultant film could be modified by altering the ethanol/water ratios of the polymer solution.

In the coating process, surfactants could facilitate spreading of the coating mixtures on the surface of the tablets (6). Small amounts of nonionic surfactants have been used to wet and homogenize the coating mixtures (7,8). Lindholm et al. previously have shown that the release rates of salicylic acid and sodium salicylate from the coated tablet depend on the concentration of the surfactants (polysorbates 20, 80) added to the EC coating (6).

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In the present study, three different types of polysorbates (i.e., polysorbates 20, 40, 80) were used as permeability modifiers in atenolol film-coated tablets, for which EC was used as the film former. The effect of surfactant concentrations on the rate and kinetic of drug release from the film-coated tablets was evaluated.

MATERIALS AND METHODS

Materials

Atenolol (Daru pakhsh, Iran); lactose (Merck); polyvinylpyrrolidone (PVP) with a molecular weight of 25,000–30,000 (Merck); magnesium stearate (Merck); polysorbates 20, 40, and 80 (Merck); EC, viscosity grade 100 cps (Hercules); dichloromethane (Merck); and ethanol (Daru pakhsh, Iran) were used.

Methods

Atenolol film-coated tablets were produced by mixing atenolol, lactose, and PVP, granulating them with the ethanol, then passing the mixture through a No. 16 sieve. The sieved fractions were dried in an oven at 50°C. The granules were mixed with magnesium stearate for 2 min. The granules were compressed into tablets on a 12-mm concave punches using an Erweka single-punch machine. The tablets were then coated using the dip-coating technique. Dichloromethane was used as the polymer solvent, and the polymer concentration in the coating formulation was kept constant (2% w/w). The dip-coating process of the tablets was performed in six steps, and between the each step, the coated layers were dried. In the final product, the weight of the polymeric layers was 2% of the initial weight of the core. The amount of surfactant in each formulation was calculated as the percentage of dry polymer weight. The amount of atenolol was 100 mg in each formulation.

Dissolution Studies

The release rate of atenolol from coated tablets was studied using USP dissolution apparatus 1 (Caleva tablet dissolution tester 8st). In this method, distilled water is used as the dissolution medium. The rate of stirring was 100 rpm. The tablets were placed in 900 ml of dissolution medium, and the temperature was maintained at 37°C. At appropriate intervals, 5 ml of each sample were taken and filtered through a 0.45-mm Millipore filter. Then 5 ml of fresh dissolution fluid was added to the dissolution medium to maintain a constant volume. The samples were then analyzed at 273 nm by an ultraviolet (UV)–visible spectrophotometer (Shimadzu 160). The mean of six determinations was used to calculate the drug release from each formulation.

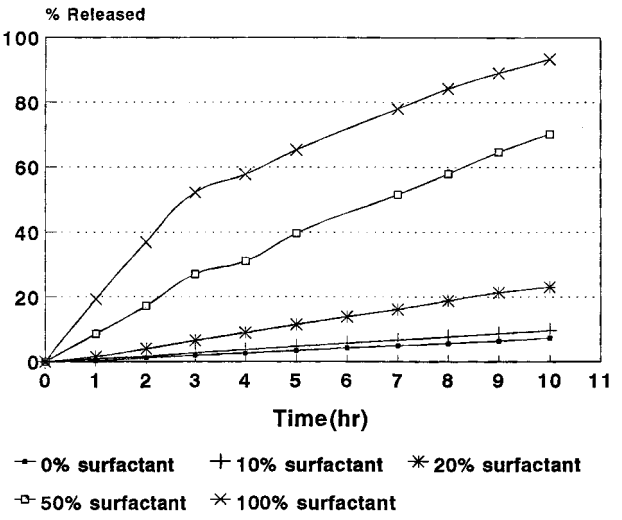

Figure 1. Effect of various concentrations of Tween 80 on the release rate of atenolol from the film-coated tablets.

RESULTS AND DISCUSSION

Figure 1 represents the release pattern of atenolol from the different film-coated tablets containing Tween 80. Different kinetic models (zero order, first order, Higuchi equation, and Weibull equation) were applied to interpret the release rate from the film-coated tablets. The results showed that there were many cases in which the correlation coefficients for kinetic models were similar, but the sums of the least squares of differences were significantly different. To overcome this discrepancy, the sums of the least square of differences were calculated for each set of data. For instance, when the ratio of EC to surfactant was 10:0 (formulation 1) or when the ratio of EC to Tween 80 was 10:2 (formulation 3), the correlation coefficients were equal to 1.000, but these formulations had different sums of the least square of differences (Table 1). Therefore, it can be concluded that the correlation coefficient alone could not be used as the suitable criterion to find the best kinetic model.

Another interesting finding of this research was the effect of polysorbates on the release rate of atenolol from

Table 1

Values of the Sum of the Least Squares of Differences for Various Formulations and Kinetic Models

No.	Zero-Order Model	First-Order Model	Higuchi Model	Weibull Model	Korsemeyer Model
1	1375.9	0.9	37271.7	1690.2	2835.0
2	239.6	0.8	10872.3	155.1	127.8
3	65.2	0.7	14028.9	205.7	281.3
4	922.9	142.4	1314.7	132.4	150.6
5	3525.9	1051.7	501.7	103.2	526.5
6	936.2	2.1	26812.6	146.7	167.7
7	2029.8	14.9	13250.2	1169.4	932.4
8	2327.1	1885.7	159.7	97.7	282.2
9	2041.4	1983.0	194.5	92.3	235.6
10	1556.7	0.9	39362.2	154.9	322.0
11	3677.5	7.4	24996.2	635.0	504.2
12	339.3	640.0	1510.0	255.1	31.2
13	922.9	1296.7	138.2	284.8	68.0

these tablets. Figure 1 shows that an increase in polysorbate (Tween 80) concentration resulted in an increase in the release rate of atenolol. The same pattern was observed for Tween 40 and Tween 20. The type of polysorbate had less effect on the release rate of atenolol. Korosmeyer et al. (8) used a simple empirical equation to describe general solute behavior 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 incorporating 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 (9). When n approximates 0.5, a Fickian diffusion-controlled release is implied, where $0.5 < n < 1.0$; non-Fickian transport could be obtained, and when n equals 1, the release mechanism becomes zero order. When the value of n approaches 1.0 phenomenologically, one can conclude that the release mechanism approaches zero order (8).

The result of this study showed that when the concentration of polysorbate gradually was increased, the n decreased (Table 2). In other words, the presence of polysorbates could control the release mechanism of atenolol from film-coated tablets. It can be concluded that the presence of polysorbates in the film formulations containing EC not only increases the rate of drug release across the membrane, but also changes the release mechanism, making it possible to have zero-order release with higher concentrations. Table 2 also shows that the type of polysorbate has less effect on the n values.

In conclusion, the results obtained in this study confirmed that the concentration of polysorbates had a great

Table 2

The Values of K *and* n *Based on Equation 1*

Polysorbate Type	Concentration Part	*K*	*n*	*r*
No Tween	—	0.362	1.353	0.986
Tween 20	1	0.836	1.064	0.999
	2	1.690	1.165	0.998
	5	9.120	0.897	0.998
	10	22.131	0.653	0.987
Tween 40	1	1.183	1.213	0.999
	2	2.958	1.034	0.991
	5	21.330	0.663	0.993
	10	23.878	0.615	0.994
Tween 80	1	0.634	1.301	0.998
	2	1.656	1.173	0.996
	5	10.715	0.856	1.000
	10	17.179	0.709	0.999

effect on the mechanism of drug release, and by change of the concentration of polysorbate, zero-order release can be produced.

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