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Original Article

The Effect of HLB on the Release Profile of Atenolol from Ethyl Cellulose-coated Tablets

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Abstract

It is possible to alter the permeability of ethyl cellulose membrane with certain materials such as surfactants. In this study the effect of surfactant concentration and different HLB values on the release rate of atenolol from ethyl cellulose-coated tablets was evaluated. The results showed that when the concentration of surfactant increased, the rate of drug release also increased. The kinetics of atenolol release from these tablets also depended on surfactant concentration and their total HLB value. The data showed that there was an optimum HLB for an optimum rate of drug release. When the HLB value was increased to 9, the release rate increased and the kinetics of drug release approached a zero order model. But, further increase in HLB value up to 15 did not have any additional significant effect on the release rate of atenolol from these film-coated tablets.

Keywords: Atenolol; Surfactant; HLB; Film-coating; Release kinetics.

Introduction

Over the last few decades, much attention has been focused on designing oral controlled release dosage forms. The polymeric film-coating technique has been used for controlling the release rate of active ingredients from the solid pharmaceutical dosage forms (1-5). Ethyl cellulose is probably the most widely used water- insoluble polymer in film-coating (6-10). Because of its good film forming properties, much attention has been focused on the control of the permeability of ethyl cellulose (2, 9, 11,). There are several approaches to correct the permeability characteristics of water insoluble polymers, which are used in film-coating. In the coating process, surfactants could facilitate spreading of the coating solution on the surface of the tablets (13). Small amounts of non-ionic surfactants have also been used to wet and homogenize the coating mixtures (14-16). Several researchers previously showed that the release rate of active ingredients from the film-coated tablets depended on the surfactants concentration, which was added in the ethyl cellulose coating solution (1, 13).

Atenolol, a model drug, is a polar cardioselective β-blocker widely used alone or in combination to treat essential hypertension. The administration of atenolol conventional tablets, with doses of 100 mg/day may cause fluctuations in plasma concentration, resulting in side effects or a reduction in drug concentration at receptor sites. Therefore, the objective of the present work was to apply a film-coating technique for the controlled drug delivery of atenolol (17).

In the present study the effects of different HLB values of surfactants and their concentration have been evaluated as release modulator moieties.

Experimental

Materials

Atenolol and ethanol (99%) were purchased

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Table 1. The proportion of tween 80 and span 60 in different polymeric solutions with different HLB values (th e total amount of surfactants was 50 % of ethyl cellulose in these formulations)

HLB	4.7	7	9	12	15
Parts of tween 80	0	2.3	4.3	7.3	10.3
Parts of span 60	10.3	8	6	4	0

from Darou-Pakhsh (Iran), sodium phosphate dibasic, polyvinyl pyrrolidone with molecular weight of 25000-30000, magnesium stearate, dichloromethane and tween 80 were obtained from Merck (Germany), span 60 was from Sigma and ethyl cellulose with a viscosity grade of 1000 mPas was obtained from Hercules.

Methods

Formulation of core tablets

Atenolol core tablets were produced by mixing atenolol, dicalcium phosphate and polyvinyl pyrolidone, granulated with ethanol, and then passed through a No. 20 sieve. Sieved fraction was dried in an oven at 50°C for a period of 1 h. The granules were mixed with magnesium stearate for 2 min and then compressed into tablets on 12-mm concave punches, using an Erweka single punch machine (Germany). The weight of each tablet was within a range of 700±14 mg. Each tablet theoretically contained 100 mg atenolol and the compression pressure was adjusted so that the average hardness of the tablets after compression was 5-6 kgf. Content uniformity test was performed according to BP 1999 protocol for atenolol tablets and the samples met the specified requirement of the atenolol tablets mentioned in its monograph.

Preparation of polymeric solution with different HLB values

Tween 80 (HLB 15) and span 60 (HLB 4.7) were used to prepare different polymeric solutions with different HLB values. The ratios of these surfactants in each formulation have been presented in Table 1.

Table 3. The correlation coefficients and zero order release constant (K_o) for different formulations with various HLB values

HLB value of the Polymeric solution	zero order model	first order model	Higuc hi model	K_o(m g/h)
no surfactant	0.998	0.997	0.971	6.16
4.7	0.991	0.996	0.973	7.25
7	0.993	0.980	0.995	7.93
9	0.995	0.984	0.993	8.59
12	0.987	0.990	0.999	8.45
15	0.999	0.985	0.994	8.49

Table 2.The release rate correlation coefficients of different formulations with var ious proportions of polymer: tween 80

Ratio of polymer: tween 80	UT*	10:10	10:8	10:5	10:2	10 :0
Correlation coefficient	0.972	0.991	0.995	0.999	0.998	0.9 98

* Uncoated tablets

Coating of tablet cores

The tablets were coated using the pan coating technique. A conventional 25-inch diameter Erweka pan (model AR 401) was used. In each experiment 200 g core materials were coated. Dichloromethane and ethanol with a ratio of 50:50 were used as the polymer and surfactant solvents, and the polymer concentration in coating formulation was kept constant (2% w/w). The coating process was performed until the thickness of the polymeric layers became 40±5 □m. The coated tablets were dried first in the pan and finally at room temperature for 24 h and then the film-coated tablets were used to evaluate the release profiles.

The thickness of polymeric layer was evaluated by means of a digital micrometer (Mitutoyo, Japan). For this purpose, dried-coated tablets were moistened with water for 1 h and then free film was prepared and after drying the film, its diameter was measured and the mean value of three samples calculated.

Dissolution Studies

The release rate of atenolol from coated tablet was investigated using the USP dissolution apparatus No. 1 (Erweka tablet dissolution tester DT70, Germany). Distilled water was used as the dissolution media. The stirring rate of the media was kept at 100 rpm. Coated tablets were placed in 900 ml of dissolution media and the temperature was maintained at 37±0.1°C. At appropriate time intervals, 5 ml samples were taken and filtered through a 0.45 □m Millipore filter. Then the samples were analyzed at 223 nm by means of an UV- visible spectrophotometer (Cecil 9000, U.K.). After each sampling, the same amount of the dissolution medium was replaced. A dilution

factor was calculated and the observed release data corrected based on the calculated dilution factor. The mean of 6 determinations was used to calculate the drug release profile from the samples obtained from each formulation.

Results and discussion

The release profiles of atenolol from uncoated tablets and each group of coated tablets with ethyl cellulose solution having different ratios of ethyl cellulose:tween 80 are shown in figure 1. The results show that when the ratio of polymer:surfactant decreases, the rate of atenolol release increases. According to this figure (Fig. 1) and based on the kinetic analysis data which presented in table 2 it seems that when the polymer:surfactant ratio is 10:5 the release profile is optimum for releasing at least 80 % of atenolol during 10 h and in this ratio the release kinetics approaches a zero order model and becomes more uniform (18).

The release profiles of atenolol from tablets, which have been coated with polymeric solutions with different HLB values, have been presented in figure 2. According to this figure (Fig. 2) and based on table 3, it is obvious that there is an optimum HLB value for a suitable release of active ingredient. Based on figure 2 and table 3, when the HLB value increased from 4.7 to 7 and then to 9, the rate of atenolol release increased ($P<0.01$), but when the HLB value was increased from 9 to 12 or 15, no significant difference in the release rates was obtained ($P<0.35$). In this regard the zero order release rate constant of each formulation has been compared with the next formulation, with a higher HLB value and the ANOVA test was performed to compare the release rate constants. Based on the release data, an HLB value of 9 is found to be the best value for obtaining an optimum release rate (releasing at least 80% of atenolol during 10 h and because of zero order release profile).

Conclusion

Surfactants have a profound effect on the release rate and profile of atenolol from ethyl Cellulose-coated tablets. Using proper amounts

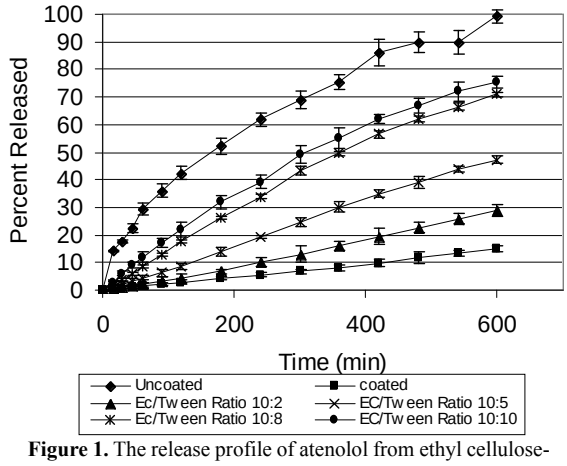

Figure 1. The release profile of atenolol from ethyl cellulose-coated tablets with various proportions of polymer/ surfactant.

of surfactant and a suitable HLB value, the release rate and kinetic of drug release could be controlled. In the lower HLB values the rate of drug release is low, because these surfactants are more lipophilic and have lower water solubility. But with higher HLB values, hydrophilicity of surfactants was increased. Due to increase in the ratio of tween 80 at higher HLB values, water solubility and hydrophilicity of surfactant mixtures were increased. An increase in water solubility of surfactant mixtures could produce a microporous matrix within the tablet coat for water diffusion and increases the rate of atenolol dissolution and diffusion to the dissolution medium. According to Narisawa et al.,(8). the release of drugs from ethyl cellulose-coated tablets is independent on their physicochemical

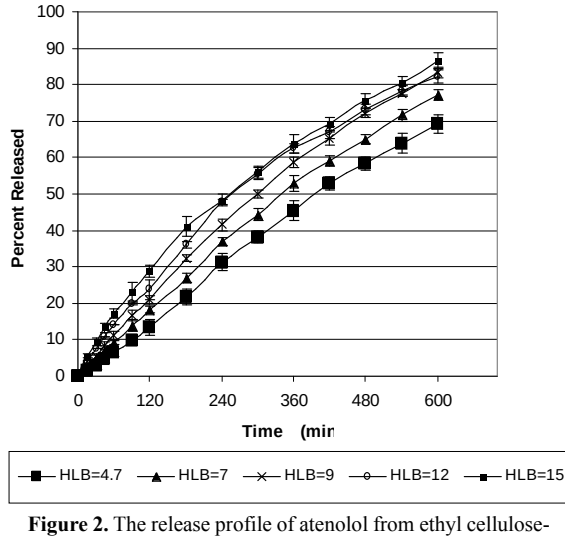

Figure 2. The release profile of atenolol from ethyl cellulose-coated tablets in the presence of surfactants having various HLB values.

characteristics and therefore, similar release pattern may be obtained for other drugs (9).

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