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Research paper

The effect of various surfactants on the release rate of propranolol hydrochloride from hydroxypropylmethylcellulose (HPMC)-Eudragit matrices

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Abstract

Hydrophilic and lipophilic polymers are widely used excipients to control the release rate of drugs from matrices. Researchers found that surfactants are able to control the release rate of drugs. The aim of the present investigation is to determine the effects of surfactant type, its concentration and the different ratios of surfactants on the release rate of highly soluble drug (propranolol HCl). In this study, sodium lauryl sulphate (SLS) as an anionic surfactant, cetyl trimethyl ammonium bromide (CTAB) as a cationic surfactant, Tween 65 and Arlacel 60 as non-ionic surfactants were selected. The different concentrations of surfactants were incorporated into hydroxypropylmethylcellulose-Eudragit matrices and then dissolution rate of the drug from the matrices were evaluated at pH 1.2 or 6.8. The results showed that the release rate of propranolol decreased as the concentration of SLS increased. This is due to that SLS is able to form complex with propranolol. In contrast Tween 65 caused an increase in the release rate of the drug. Cationic surfactant (CTAB) had little effect on the release rate of the drug. It was shown that as the ratio of CTAB:SLS increased the release rate of propranolol increased from matrices. This indicated that as CTAB is able to interact with SLS molecules, therefore number of the interacting anionic molecules with the cationic drug was decreased. It can be concluded that, the type and ionization of surfactant, hydrophilicity and lipophilicity of surface active agent and various ratios of surfactants are important factors in controlling the release rate of propranolol.

Keywords: Release rate; Surfactants; Propranolol HCl; Hydroxypropylmethylcellulose matrix

1. Introduction

A method of obtaining a sustained-release product is to embed or disperse the solid medicinal compound in an insoluble matrix by compression of a physical mixture of the compound and a polymeric material. Sustained release matrices liberate the drugs with slower rate than that of the conventional dosage forms. Since the frequency of drug administration is reduced, patient compliance can be improved, and drug administration can be made more convenient as well. A less obvious advantage, implicit in the design of sustained release matrices, is that the total amount of drug administered can be reduced, thus maximizing availability with a minimum dose. In addition, better control of drug absorption can be attained. Overall, administration of sustained release forms enables increased reliability of therapy. Generally, the release of highly water-soluble medicinal compounds is of special interest. Matrix tablets have long been used to obtain sustained drug delivery and it was Higuchi who first presented a detailed mathematical analysis of this release [1]. Bamba et al. further developed the mechanisms of release from matrix systems that swell at the tablet periphery to form a gel which then acts as a barrier to drug diffusion [2,3]. The use of hydroxypropylmethylcellulose (HPMC) in the preparation of controlled release dosage form has been documented [4]. The principal advantage of HPMC matrix formulation is that drug release rates are generally independent of processing variables such as compaction pressure, drug particle size, and the incorporation of a lubricant [5]. Drug is liberated by a combination of diffusion through and attrition of this gel layer [6].

Various studies [7–10] of the release from matrices in

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which a surfactant had been incorporated showed a faster release with the addition of the surfactant. Choulis and Papadopoulos [11] noted that the release of quinine sulfate from a nylon matrix containing sodium lauryl sulfate (SLS) was slower than from a matrix containing polyoxyl 40 stearate. Daly et al. [12] found that the incorporation of 15% SLS in modified HPMC matrices produced a zero-order release of chlorpheniramine maleate. Feely and Davis [13] reported that the rate of release of chlorpheniramine maleate from a HPMC matrix was reduced as more SLS was incorporated into the matrix. Gaylord and Schor [14] have patented a cellulose-based controlled system, which utilizes an anionic surfactant (diocetyl sodium sulphosuccinate) to retard the release of ascorbic acid. The surfactant, however, decreased the amount of drug released only during the 1st h. The effect of surfactants on the swelling properties of polymeric materials has also been evaluated [15]. They found that surfactants are able to alter the swelling properties of polymeric materials resulting in considerable changes in release rate of the drug [15].

It is important to ascertain which surfactants and in what concentrations should be employed to regulate the release of drugs. This report is concerned with the effects of surfactant type, its concentration and the different ratios of binary mixtures of surfactants on the release of a cationic medicinal compound, propranolol HCl.

2. Materials and methods

Propranolol hydrochloride (Darou Pakhsh, Iran), HPMC K4M (Methocel K4M, Colorcon Ltd, UK), ammonia methacrylate copolymer (Eudragit RSPO, Rohm Pharma, Germany), magnesium stearate (BDH Chemicals Ltd, Poole, Dorset, UK), polysorbate (Tween 65, Merck, Germany), sorbitan stearate (Arlacel 60, Merck, Germany), sodium lauryl sulfate (SLS, BDH Chemicals Ltd, Poole, Dorset, UK) and cetyltrimethylammonium bromide (Cetrimide, Merck, Germany) were used as obtained.

2.1. Methods

2.1.1. Preparations of tablets

Propranolol HCl matrices were produced by mixing the drug with HPMC K4M, Eudragit and surfactant with different concentrations ranging from 0 to 10% w/w for a period of 10 min. The mixture was mixed with magnesium stearate for 2 min. The mixtures were compressed on an 11-mm punch and die using a single-punch machine (Table 1).

Table 1
Different formulations of propranolol HCl matrices and their composition (mg)

Code	Propranolol	HPMC	Eudragit	SLS	CTAB	Arlacel 60	Tween 80
F1	80	60	60	–	–	–	–
F2	80	60	60	5	–	–	–
F3	80	60	60	10	–	–	–
F4	80	60	60	20	–	–	–
F5	80	60	60	–	5	–	–
F6	80	60	60	–	10	–	–
F7	80	60	60	–	20	–	–
F8	80	60	60	–	–	5	–
F9	80	60	60	–	–	10	–
F10	80	60	60	–	–	20	–
F11	80	60	60	–	–	–	2
F12	80	60	60	–	–	–	5
F13	80	60	60	–	–	–	10
F14	80	60	60	15	5	–	–
F15	80	60	60	10	10	–	–
F16	80	60	60	5	15	–	–
F17	80	60	60	15	–	5	–
F18	80	60	60	10	–	10	–
F19	80	60	60	5	–	15	–
F20	80	60	60	18	–	–	2
F21	80	60	60	15	–	–	5
F22	80	60	60	10	–	–	10
F23	80	60	60	–	15	5	–
F24	80	60	60	–	10	10	–
F25	80	60	60	–	5	15	–
F26	80	60	60	–	18	–	2
F27	80	60	60	–	15	–	5
F28	80	60	60	–	10	–	10
F29	80	60	60	–	–	18	2
F30	80	60	60	–	–	15	5
F31	80	60	60	–	–	10	10

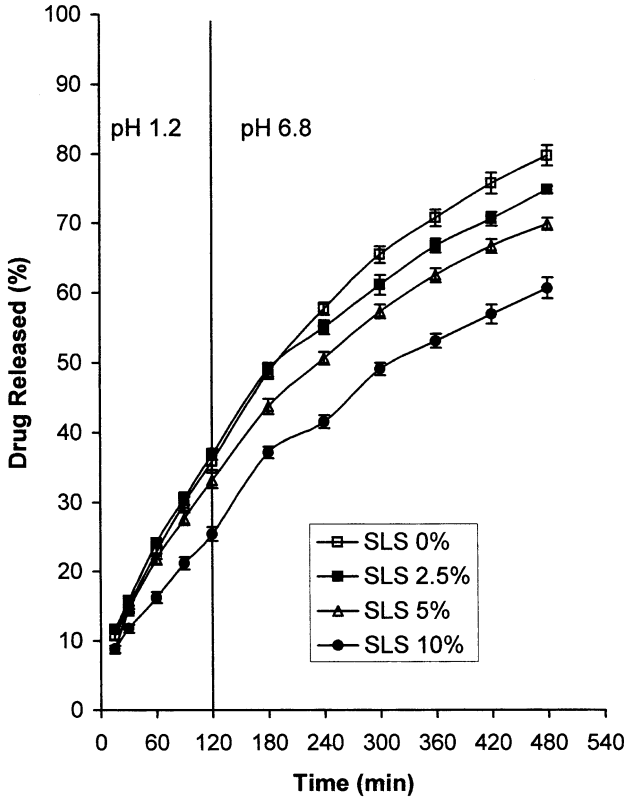

Fig. 1. The effect of SLS on the release of propranolol hydrochloride from HPMC-Eudragit matrices.

To investigate the effect of binary mixtures of surfactants on the release rate of the drug from HPMC-eudragit matrices homogeneous binary mixtures of SLS:cetyl trimethyl ammonium bromide (CTAB) (3:1, 1:1 and 1:3), SLS:Tween 80 (9:1, 3:1 and 1:1), SLS:Arlacel 60 (3:1, 1:1 and 1:3) Arlacel 60:Tween 80 (9:1, 3:1 and 1:1), CTAB:Arlacel 60 (3:1, 1:1 and 1:3), CTAB:Tween 80 (9:1, 3:1 and 1:1) were used. The amount of binary mixtures of surfactants used in formulations was 10% w/w.

2.1.2. Dissolution studies

The United State Pharmacopoeia (USP) basket method was used for all the in vitro dissolution studies. In this method, distilled water which simulated gastric fluid (pH 1.2), and intestinal fluid (pH 6.8) without enzyme, were used as dissolution media. The rate of stirring was 100 ± 2 rpm. The amount of propranolol was 80 mg in all formulations. The matrices were placed in 900 ml of gastric fluid and maintained at 37 ± 0.1°C for 2 h. At appropriate intervals, 5 ml of the samples were taken and filtered through a 0.45 mm Millipore filter. The dissolution media was then replaced by 5 ml of fresh dissolution fluid to maintain a constant volume. After 2 h the dissolution medium pH was changed from 1.2 to 6.8 using phosphate buffer to simulate intestinal fluid. The samples were then analyzed at 289 and 288.5 nm at pH 1.2 and 6.8, respectively, by ultraviolet/visible spectrophotometer. The mean of three determinations was used to calculate the drug release from each of the formulations.

3. Results and discussion

Fig. 1 shows the dissolution characteristics of matrices prepared with different percentages of SLS. In vitro release profiles of propranolol showed that an increase in the percentage of SLS from 2.5% (formulation F2) to 10% w/w resulted in a decrease in the release rate of propranolol (Fig. 1). For example, the percentage of drug released from basic formulation without any surfactant, after 8 h was 79.86 ± 1.5, whereas the percentages of drug released from matrices containing 2.5, 5 or 10% w/w SLS, were 74.90 ± 0.8, 69.97 ± 0.9 or 60.73 ± 1.7, respectively, indicating a remarkable effect of SLS on the decrease of release rate of propranolol from HPMC-Eudragit matrices. This is probably due to the fact that SLS with negative charge is able to form a complex with a cationic drug. The propranolol-SLS complex, presumably, has a less solubility than the free propranolol resulting in a noticeable decrease in the release rate of propranolol. In addition, retardation effect of SLS is could be due to enhanced viscosity of gel layer surrounding the matrix which leads to a reduction in the release rate of drugs [16]. Walderhsaug and coworkers studied the nature of the interaction between SLS and cellu-

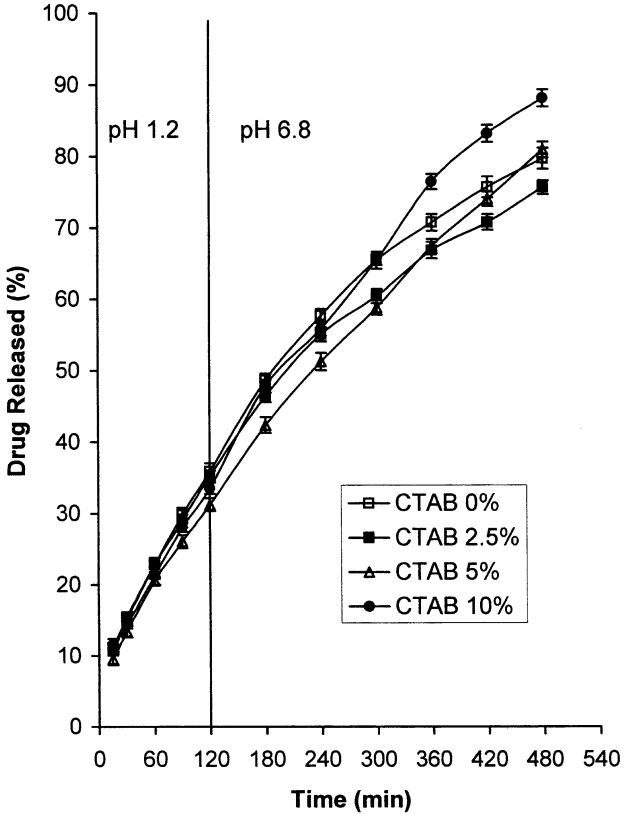

Fig. 2. The effect of CTAB on the release of propranolol hydrochloride from HPMC-Eudragit matrices.

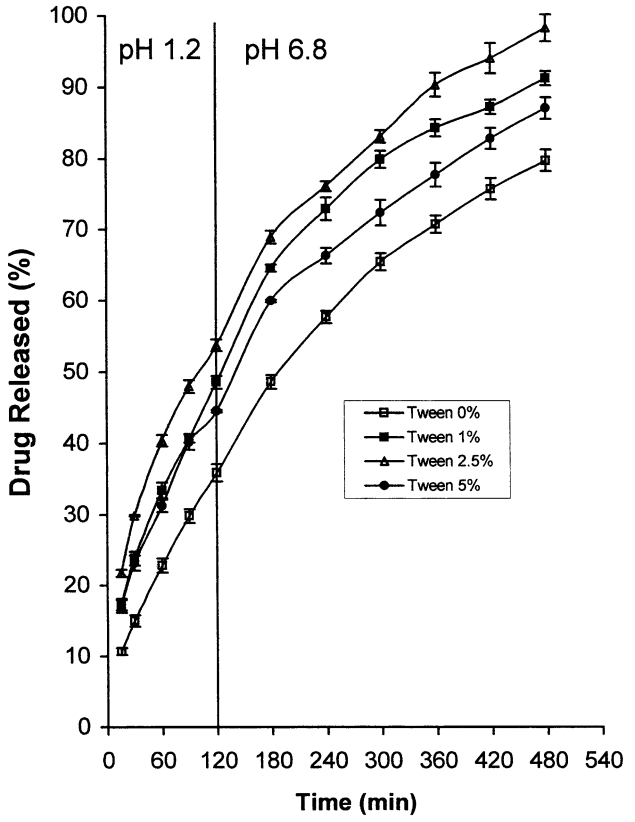

Fig. 3. The effect of Tween 80 on the release of propranolol hydrochloride from HPMC-Eudragit matrices.

lose ethers [17]. They concluded that the anionic surfactant could bind to the non-ionic cellulose to form a stronger gel network [5,17]. Furthermore, complexation and subsequent precipitation provide a more tortouse pathway and less porous matrix through which the dissolved medicinal compound must diffuse [18].

Fig. 1 also shows that the release rate in acidic media was faster than at pH 6.8. This can be attributed to an increase in viscosity of gel layer in pH 6.8 [13]. In other word the viscosity of HPMC-Eudragit in pH 6.8 is greater than that of pH 1.2. The figure shows that the rate of drug release was reduced as more surfactant was added to the formulation. In the case of SLS the percentage of drug released was linearly related to the square root of time. These findings agree with the results obtained by other researchers [13,14]. A plot of the release rate constant (obtained by calculating the gradient of the percentage release versus root time curve) against the weight percentage of the surfactant in the matrix, shows that the release rate changes linearly with the amount of surfactant present. The slope ($-0.094\ \text{min}^{-0.5}$) with correlation coefficient of 0.985 provides a value which characterizes the effect of SLS on propranolol hydrochloride release from HPMC-Eudragit matrices.

In order to investigate the effect of cationic surfactant on the release rate of the drug, CTAB was chosen. The release of propranolol from HPMC matrices containing 2.5 to 10% w/w was measured. It can be seen that CTAB had no considerable effect in release profiles at pH 1.2. An increase in the amount of CTAB from 2.5 to 10% w/w only could slightly increase ($P < 0.05$) the release rate of the drug at pH 6.8 (Fig. 2). It is probably due to this fact that surfactant lowers the interfacial tension between the product and the dissolution fluid; hence it will increase the release rate of drug from matrix. Similar results were reported on the effect of CTAB on the release of procaine hydrochloride from HPMC matrices, in which CTAB decreased the interfacial tension between the product and the dissolution fluid and consequently increased the drug release rate [18].

The release rate of propranolol from matrices containing Tween 65 as a non-ionic surfactant at concentrations of 1–5% w/w is shown in Fig. 3. It is expected that non-ionic surfactant would not affect the release rate of propranolol, however, it can be seen that when the concentration of Tween 65 was increased even to 1% w/w, the release rate of propranolol both in acidic and phosphate buffer was increased considerably ($P < 0.05$). By decreasing the surface tension of the dissolution medium, Tween 65 allowed a more rapid and possibly more complete penetration into matrix [19].

The release data for matrices incorporating 0, 2.5, 5 and

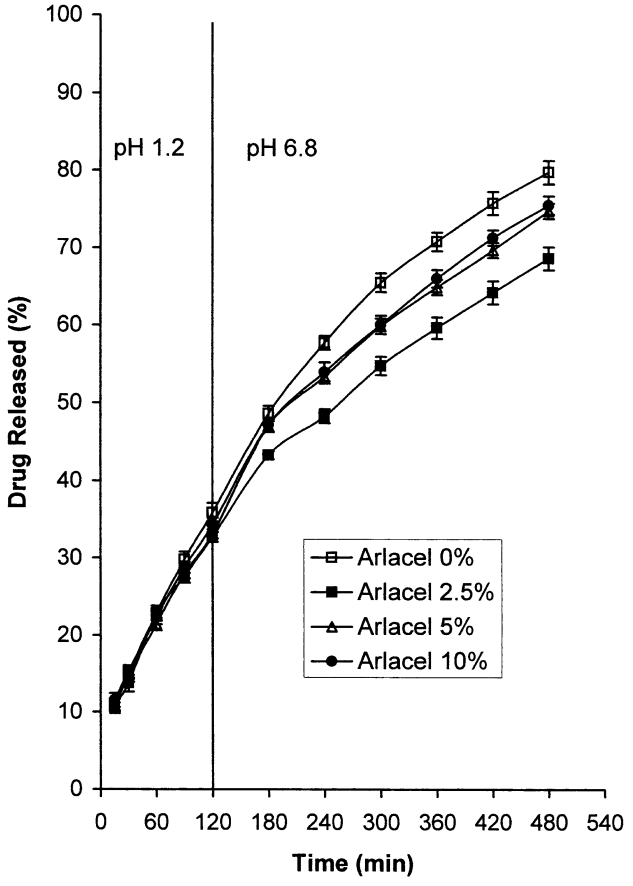

Fig. 4. The effect of Arlacel 60 on the release of propranolol hydrochloride from HPMC-Eudragit matrices.

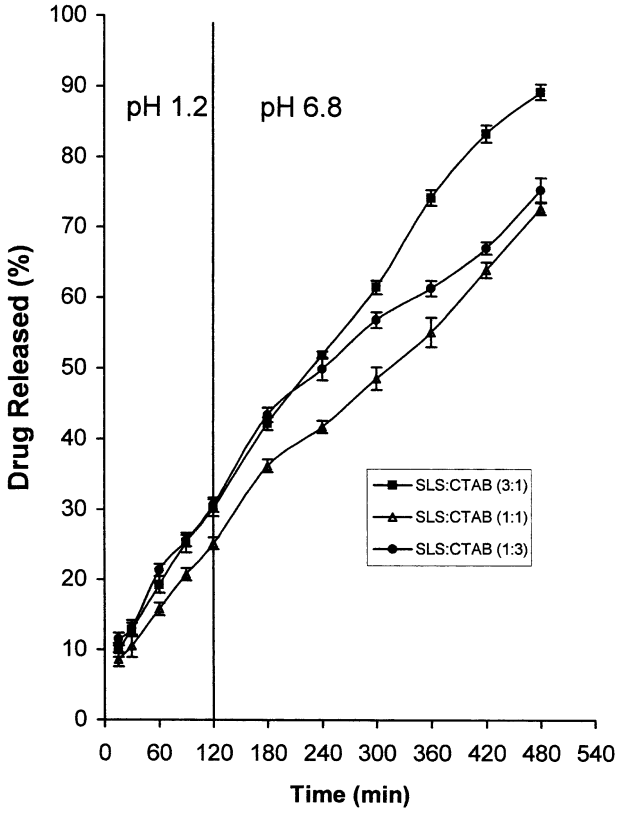

Fig. 5. The effect of ratio of SLS:CTAB on the release rate of propranolol hydrochloride from HPMC-Eudragit matrices.

10% w/w Arlacel 60 are presented in Fig. 4. The dissolution with 5% w/w was similar to that seen with 10% w/w incorporated surfactant. When the surfactant concentration was increased from 0 to 2.5% the release rate was decreased. In general, Fig. 4 shows that an increase in the concentration of Arlacel 60 resulted in a decrease in the release rate of propranolol. It can be seen that when Tween 65 with hydrophilic lipophilic balance (HLB) equal 10.5 was replaced to another non-ionic surfactant with less HLB (4.7), the release profile was reversed. This indicates that lipophilicity and hydrophilicity of surfactant has a main role in release rate of propranolol. This role is clearer in phosphate buffer than acidic medium. This decrease in the release rate could be explained by being insolubility and lipophilicity of surfactant in dissolution medium. This effect would decrease the penetration rate of water into the matrices and consequently rate of dissolution of drug was reduced.

This study also determines the effect of binary surfactants with different chemical structures on the release rate of propranolol from matrices. Fig. 5 shows the effect of binary mixtures (total concentration of surfactants in matrix is 10% w/w) of SLS:CTAB with different ratios (3:1, 1:1 and 1:3) on the release rate of propranolol HCl from HPMC-Eudragit matrices. It is interesting to note that the slowest release rate was obtained for the matrices which the ratio of SLS:CTAB was 1:1. The faster release rate was observed for matrices containing SLS:CTAB (1:3) especially in pH 6.8.

Fig. 6 shows the release profile of propranolol matrices containing the different ratios of SLS:Arlacel (1:3, 1:1 and 3:1). As previously described, SLS (see Fig. 1) and Arlacel (see Fig. 4) are able to decrease the release rate of the drug from HPMC-Eudragit matrices. It is expected that when both surfactants were incorporated within the matrix the release rate should considerably decrease. The results showed that not only the ratio of SLS:Arlacel had little effect on the release rate but also the presence of the binary surfactants increased the release rate of the drug. This indicated that Arlacel is able to suppress the retardation effect of SLS on the propranolol release from HPMC-Eudragit matrices. Similar results were obtained for the matrices containing the different ratios of SLS:Tween (Fig. 7). The figure shows that in all matrices retardation effect of SLS was significantly decrease by the presence of Tween 65 with different ratios due to enhancement effect of Tween on the release rate. It is interesting to note that there was no significant difference between the release rate of propranolol containing SLS:Tween; 9:1 and 3:1 at pH 1.2. When the pH of the dissolution media was increased to 6.8, the difference between the release profiles was quit clear. Similar results were obtained for matrices containing CTAB:Tween 80 (Fig. 8). It can be concluded that the presence of Tween 80 overcome to the retardation effect of the second surfactant. Figs. 9 and 10 show the release profiles of propranolol

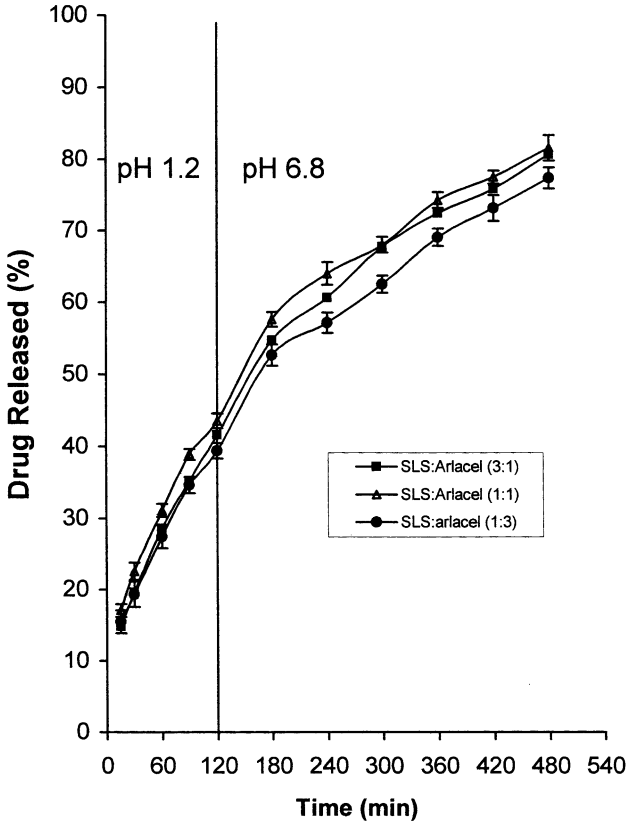

Fig. 6. The effect of ratio of SLS:Arlacel 60 on the release rate of propranolol hydrochloride from HPMC-Eudragit matrices.

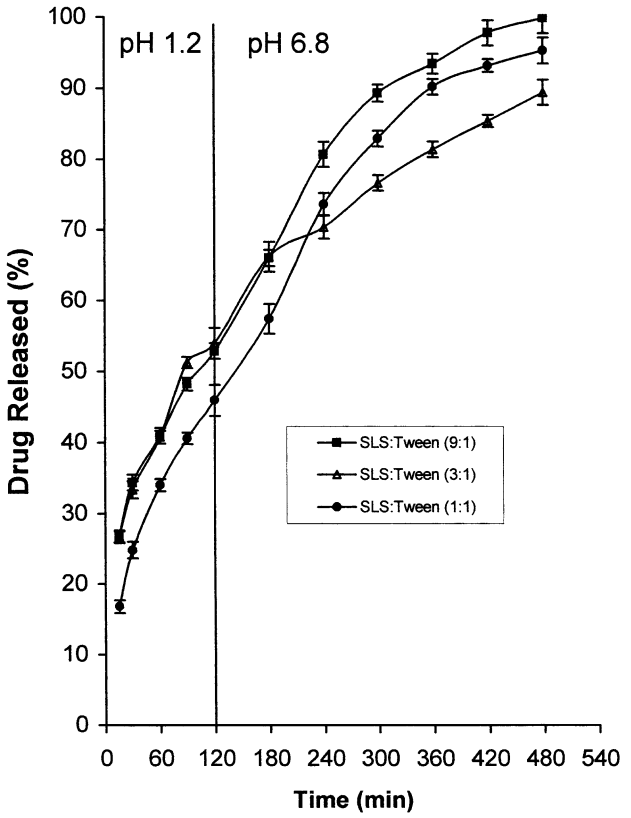

Fig. 7. The effect of ratio of SLS:Tween 80 on the release rate of propranolol hydrochloride from HPMC-Edudragitit matrices.

matrices containing binary surfactants of CTAB:Arlacel and Arlacel:Tween, respectively. These figures showed that it is difficult to interpret the release data according to lipophilicity or lowering effect of surfactant on the surface tension. It might be other factors such as complexation between surfactants and solubilization of propranolol by forming surfactant micelle would involve in release of propranolol from HPMC-Eudragit matrices.

The figures clearly show that in some cases (see Figs. 1, 3–6, 9 and 10) the release profiles become biphasic, i.e. it consists of two phases, an initial rather fast release phase and a terminal slower release phase. The initial phase is faster in all cases as can be seen from the slopes and it is the combined effect of drug released from the surface of the matrix increased due to better wetting caused by the presence of surfactant and of the change of the matrix structure, i.e. the start of disintegration of the tablet resulting in a rapid increase in dissolution area. The slower terminal phase describes the dissolution of the amount of the drug entrapped in the interior of the matrix. Similar results were reported by Efentakis on the effects of surfactants on the release of flurbiprofen [20]. He showed that the biphasic profile at higher concentration might be attributed to increased drug release caused by the greater amount of surfactant incorporated, which results in greater wetting and solubilization of the drug [20]. The results indicate that surface-active agents may produce more channels available for the dissolution fluid to leach out the drug at concentrations over 1%. At such high concentrations the surfactants are above their critical micelle concentration (CMC) and the solubilization effect could enhance further the release of the drug, since when surfactant is present at concentration above CMC dissolution may also be favoured by the increased solubility resulting from micellar solubilization [16,21,22].

The mechanism of drug release naturally is influenced by the presence and the location of drug and surfactant molecules in the tablet. The possible sites of location of the surfactant molecules could be either on the surface of the tablet, within the tablet matrix isolated from the interior environment or within the tablet but connected with its outer surface by means of channels. A similar model was proposed by Cupta et al., in their work concerning the release of adriamycin from albumin microsphere [23]. Thus, the rate of release of the drug from one site will differ from the other sites and will depend on several factors. In particular, the release of the drug from the surface of the tablet will depend on drug solubility, its physical state, its affinity for the excipients and the ability of the surfactant to facilitate wetting, while the release of incorporated drug is mainly due to diffusion of the drug through the existing or created channels. The release rate is further affected on dissolution medium penetration and the wetting effect of

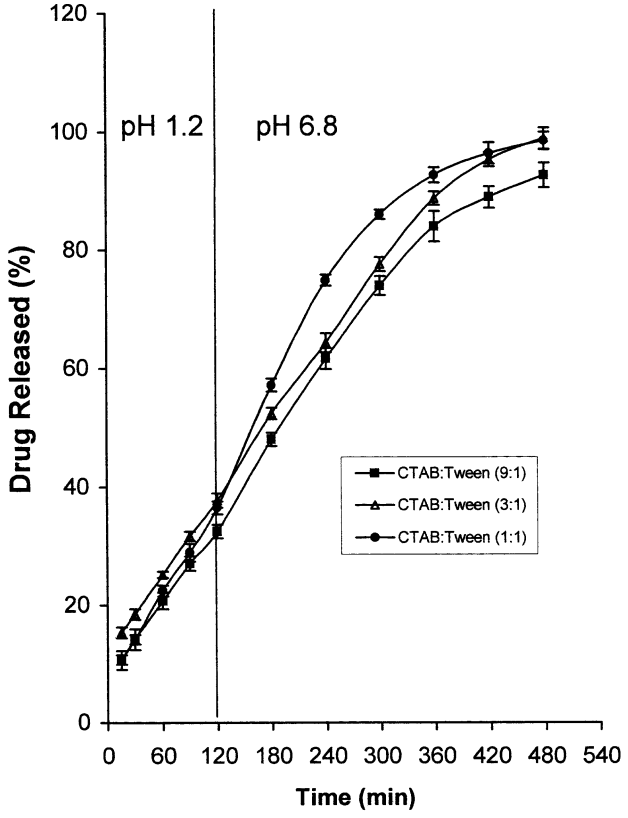

Fig. 8. The effect of ratio of CTAB:Tween 80 on the release rate of propranolol hydrochloride from HPMC-Eudragit matrices.

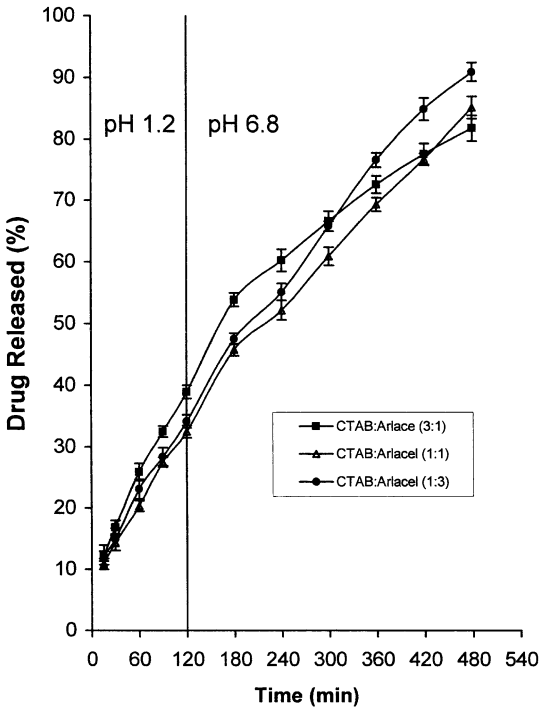

Fig. 9. The effect of ratio of CTAB:Arlacel 60 on the release rate of propranolol hydrochloride from HPMC-Edudragit matrices.

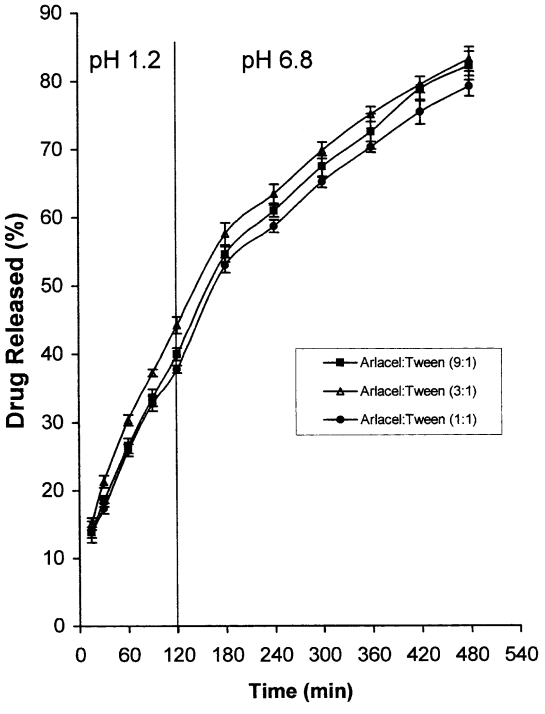

Fig. 10. The effect of ratio of Arlacel 60:Tween 80 on the release rate of propranolol hydrochloride from HPMC-Edudragit matrices.

the surfactant. Consequently, the release of the drug appears rather complex and differs from location to location.

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