

## Effect of various surfactants and their concentration on controlled release of captopril from polymeric matrices

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Various methods are available to formulate water soluble drugs into sustained release dosage forms by retarding the dissolution rate. One of the methods used to control drug release and thereby prolong therapeutic activity is to use hydrophilic and lipophilic polymers. In this study, the effects of various polymers such as hydroxypropyl methylcellulose (HPMC), ethylcellulose (EC) and sodium carboxymethylcellulose (CMC) and surfactants (sodium lauryl sulphate, cetyltrimethylammonium bromide and Arlacel 60) on the release rate of captopril were investigated. The results showed that an increase in the amount of HPMC K15M resulted in reduction of the release rate of captopril from these matrices. When HPMC was partly replaced by NaCMC (the ratio of HPMC/NaCMC was 5:1), the release rate of the drug significantly decreased. However, there was no significant difference in release rate of captopril from matrices produced with ratios of 5:1 and 2:1 of HPMC/NaCMC. The presence of lactose in matrices containing HPMC and NaCMC increased the release rate of captopril. It was interesting to note that although partial replacement of HPMC by EC reduced the release rate of the drug (ratio of HPMC/EC 2:1), the release rate was increased when the ratio of HPMC/EC was reduced to 1:1. The effects of various surfactants on the release rate of captopril from HPMC/EC (1:1) matrices were also investigated. The results showed that the surfactants did not significantly change the release rate of the drug. Release data were examined kinetically and the ideal kinetic models were estimated for the drug release. The kinetic analysis of drug release data from various formulations showed that incorporation of surfactants in HPMC/EC matrices did not produce a zero-order release pattern.

*Keywords:* captopril, polymers, controlled release, surfactant, release kinetic

Accepted February 14, 2008

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Captopril is freely water-soluble and has an elimination half-life of 1.7 h after an oral dose (1). It is usually prescribed to patients who are chronically ill and require long-term use for therapeutic benefit. Development of a once daily captopril oral formulation would be a significant advantage for patient compliance accompanied by minimization of the drug side effects as a result of reduction in the drug blood concentration fluctuations, especially in long-term therapy (2).

The release of highly water-soluble medicinal compounds having fast rates of dissolution is of special interest. Matrix tablets have long been used to obtain sustained drug delivery and it was Higuchi (3) who first presented a detailed mathematical analysis of such release. Bomba *et al.* (4) further developed the mechanisms of release from matrix systems that swell at the tablet periphery to form a gel which acts as a barrier to drug diffusion.

Various studies of the release from matrices in which a surfactant had been incorporated showed a faster release with the addition of surfactant (5, 6). According to the importance of captopril sustained release formulation in clinical use, different attempts have been made to design long acting devices for captopril delivery in the form of sustained or controlled release formulations (7–9). The effect of surfactants was not studied in controlled or sustained-release formulations for captopril delivery. Therefore, the present study firstly concerns the release of captopril from hydroxypropylmethylcellulose (HPMC K15M), sodium carboxymethylcellulose (NaCMC), ethylcellulose (EC) and their mixtures matrices and secondly the effect of anionic, cationic, and nonionic surfactants incorporated in an inert, heterogeneous HPMC matrix in order to obtain zero-order release formulations. This study also examines the effect of surfactants on the mechanism of drug release from HPMC-EC matrices.

## EXPERIMENTAL

### *Materials*

Captopril (Iran Darou, Iran), Methocel K15M (Colorcon, UK), NaCMC (Aqualon, France), ethylcellulose (Merck, Germany), lactose (BDH Chemicals, UK), magnesium stearate (BDH Chemicals), Tween 80 (Merck), Arlcel 60 (BDH Chemicals), sodium lauryl sulphate SLS (BDH Chemicals) and cetytrimethyl ammonium bromide (CTAB) (Merck) were used as obtained.

### *Preparation of tablets*

Captopril matrices were produced by mixing captopril with HPMC K15M, ethylcellulose, NaCMC or their mixture for a period of 15 min in a double cone mixer. After completed mixing, magnesium stearate was added and mixed for 2 min. The mixtures were compressed on a 9-mm punch at a pressure of 150 MPa (Table I).

In case of formulations F8 and F9, 25% and 50% of HPMC was mixed with drug-lactose (ratio 1:1), respectively, and granulated with distilled water. The moist granules were passed through a sieve (aperture size 1.4 mm). The granules were dried in an oven at 60 °C for a period of 24 h. The dried granules were mixed with the remainder of HPMC

Table I. Different formulations of captopril matrices and their compositions

Code	Lactose (mg)	HPMC (mg)	NaCMC (mg)	EC (mg)	CTAB (mg)	Arlacel 60 (mg)	SLS (mg)
F1	–	50	–	–	–	–	–
F2	–	100	–	–	–	–	–
F3	–	150	–	–	–	–	–
F4	–	125	25	–	–	–	–
F5	–	100	50	–	–	–	–
F6	25	100	25	–	–	–	–
F7 <sup>b</sup>	50	75	25	–	–	–	–
F8 <sup>c</sup>	50	75	25	–	–	–	–
F9 <sup>d</sup>	50	75	25	–	–	–	–
F10	–	100	–	50	–	–	–
F11	–	75	–	75	–	–	–
F12	–	75	–	75	–	–	4.5 (3%)
F13	–	75	–	75	–	–	9.5 (6%)
F14	–	75	–	75	–	–	20.5 (12%)
F15	–	75	–	75	4.5 (3%)	–	–
F16	–	75	–	75	9.5 (6%)	–	–
F17	–	75	–	75	20.5 (12%)	–	–
F18	–	75	–	75	–	4.5 (3%)	–
F19	–	75	–	75	–	9.5 (6%)	–
F20	–	75	–	75	–	20.5 (12%)	–

<sup>a</sup> Amount of captopril in all formulation is 50 mg.

<sup>b</sup> Simple mixture.

<sup>c</sup> 25% of HPMC was granulated with water.

<sup>d</sup> 50% of HPMC was granulated with water.

and NaCMC for 10 min. After completed mixing, magnesium stearate was added and mixed for 2 min. The mixtures were compressed on a 9-mm punch at a pressure of 150 MPa (Table I).

A mixture of HPMC and ethylcellulose (1:1) was chosen to investigate the effect of surfactant on the release rate of captopril from matrices (see Table I). Captopril (25 g) was mixed well with the mixture of HPMC (75 g) and ethylcellulose (75 g) for a period of 15 min in a double cone mixer. Then the mixture was transferred to mortar with pestle and surfactant was added (3, 6 or 12%, *m/m*) to the mixture and mixed for an additional period of 15–20 min. After completed mixing, magnesium stearate was added and mixed for 2 min. The mixtures were compressed on a 9-mm punch at a pressure of 150 MPa (Table I). The amount of captopril was 50 mg in all formulations.

### Dissolution studies

The USP basket method (10) was used for all *in vitro* dissolution studies. In this method, distilled water containing HCl 0.1 mol L<sup>-1</sup>, which simulated gastric fluid (pH 1.2), and intestinal fluid (pH 6.8) containing phosphate buffer without enzyme were used as dissolution media. Phosphate buffer was prepared according to USP (10) from 0.2 mol L<sup>-1</sup> monobasic potassium phosphate and 0.2 mol L<sup>-1</sup> sodium hydroxide. The stirring rate was 100 ± 2 rpm. 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 samples were taken and filtered through a 0.45-µm Millipore filter. The dissolution medium was then replaced by 5 mL of fresh dissolution fluid to maintain a constant volume. After 2 hours, 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 205 and 206 nm at pH 1.2 and 6.8, respectively, using a UV/Vis spectrophotometer (Shimadzu, Japan) (10). The mean of three determinations was used to calculate the drug release from each formulation.

### Release parameters

To investigate the mode of drug release from matrices, Eq. (1) was applied to interpret the release rate from matrices (11):

$$Q = K_1 t^n \quad (1)$$

where  $Q$  is the percent of drug released at time  $t$ ,  $K_1$  is the constant incorporating structural and geometric characteristics of the release device and  $n$  is the release exponent indicative of the mechanism of release. When  $n$  approximates 0.5, a Fickian/diffusion-controlled release is implied, where  $0.5 < n < 1.0$  non-Fickian transport and  $n = 1$  for zero-order (case II transport). When the value of  $n$  approaches 1.0, one may phenomenologically conclude that the release is approaching zero-order.

To compare the effects of polymer or surfactant type or concentration on the drug release, different criteria were used, such as mean dissolution time ( $MDT$ ) and dissolution efficiency ( $DE$ ). Mean dissolution time is described below (12):

$$MDT = \frac{\sum_{j=1}^n t \Delta M_j}{\sum_{j=1}^n t M_j} \quad (2)$$

where  $j$  is the sample number,  $n$  is the number of dissolution times,  $t$  is the time at midpoint between  $t$  and  $t-1$  (easily calculated with  $(t + t-1)/2$ ) and  $\Delta M_j$  is the additional amount of drug dissolved between  $t$  and  $t-1$ . Dissolution efficiency ( $DE$ ) was used as the criterion for comparing the effect of polymer and surfactant concentration on the release rate. The dissolution efficiency ( $DE$ ) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time,  $t$ , expressed as percentage of the

area of the rectangle described by 100% dissolution in the same time. *DE* is described below (13):

$$DE = \frac{\int_0^T Y \times dt}{Y_{100} \times T} \times 100\% \quad (3)$$

where *Y* is the percent drug release as the function of time, *t*, *T* is the total time of drug release and *Y*<sub>100</sub> is 100% drug release.

### Statistical analysis

All data were statistically analyzed by the analysis of variance or Tukey's multiple comparison test.

## RESULTS AND DISCUSSION

All formulations were relatively robust in terms of friability and hardness (Table II). Table I shows the formulation compositions analyzed in this study. The effect of HPMC K15M concentration on the release rate of captopril is shown in Fig. 1a. The results showed that an increase in the concentration of HPMC (F1–F3) resulted in a reduction of the captopril release rate. *DE* and *MDT* were used to compare the dissolution data. The results of fitting the dissolution data with these dissolution criteria are shown in Table II. *DE* values are consistent with the dissolution data. For example, the *DE* value for the tablets containing 50 mg HPMC is 72.7% whereas this value decreased to 62.2 or 50% for the tablets containing 100 or 150 mg HPMC, respectively. The ANOVA statistical test showed that the reduction in *DE* percentage was significant ( $p < 0.05$ ). However, it seems that the amount of HPMC does not change the release pattern. No positive deviation occurred from the curves, indicating that attrition did not contribute to drug release (14).

Simple examination of Fig. 1a shows that as the polymer fraction increased, the dissolution of the drug decreased. However, a prospective formulator would require a more quantitative rationalisation of these trends. The slopes (% min<sup>-1/2</sup>) of Eq. (1) are given in Table II. When these slopes were plotted as a function of the reciprocal of the HPMC concentration at which they were obtained, a straight line plot was obtained (correlation coefficient 0.999). The general relationship for the line can be expressed by Eq. (4).

$$R = M (1/W) + C \quad (4)$$

where *R* is the Higuchian release rate (% min<sup>-1/2</sup>), *M* is the slope of derived line (% min<sup>-1/2</sup> mg), *W* is the mass of HPMC (mg), *C* is the constant (% min<sup>-1/2</sup>) representing the captopril release rate at a theoretically infinitely high HPMC level.

The derived values of *M* and *C* were 756 and 0.364, respectively. The data mentioned above permit the dissolution rate to be estimated from a limited number of data

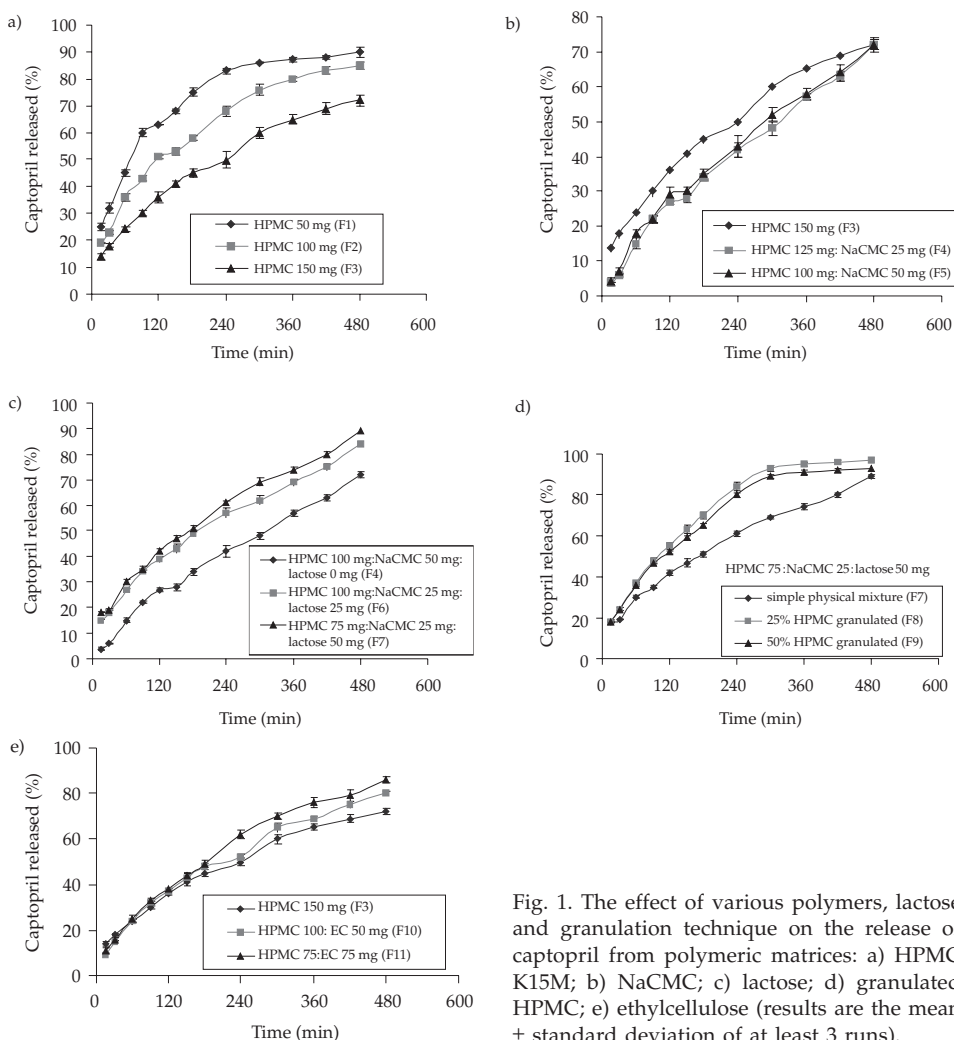


Fig. 1. The effect of various polymers, lactose and granulation technique on the release of captopril from polymeric matrices: a) HPMC K15M; b) NaCMC; c) lactose; d) granulated HPMC; e) ethylcellulose (results are the mean  $\pm$  standard deviation of at least 3 runs).

points. Such a relationship was also obtained for promethazine hydrochloride with varying concentrations of HPMC of different viscosity grade (15).

Fig. 1b shows the effect of incorporated NaCMC on the release rate of captopril from HPMC matrices. The results indicate that replacement of HPMC with NaCMC caused a considerable reduction ( $p < 0.05$ ) in drug release (compare release profiles of F3 and F4 in Fig. 1b and also *DE* and *MDT* in Table II). *DE* and *MDT* values significantly changed from 40% and 178.9 min to 53% and 144.6 min for F4 and F6 formulations, respectively. However, there was no significant difference between formulations F4 the

(HPMC/NaCMC ratio was 5:1) and F5 (the HPMC/NaCMC ratio was 2:1). For example, after 4 h, the amounts of drug released from formulations F3, F4 and F5 were 50, 42 and 43%, respectively.

Fig. 1c shows the dissolution characteristics of matrices prepared with different ratios of HPMC/lactose. Addition of lactose led to a significant increase ( $p < 0.05$ ) in the release rate of captopril (compare F4 and F6 in Fig. 1c). An increase in the amount of lactose from 25 (formulation F6) to 50 mg (formulation F7) resulted in an increase in the release rate of captopril (Fig. 1c). For example, after 4 h, the percentages of drug released were 42, 57 and 61% from matrices containing 0, 25 and 50 mg lactose, respectively. This could be due to a reduction in the tortuosity of the diffusion path of the drug caused by lactose and/or the gel layer became thinner because of smaller amount of HPMC in these formulations. It was interesting to note that the granulating of HPMC with water had a significant effect on drug release. For instance in Fig. 1d, F7 was a simple mixture of components, in F8 and F9, 25 and 50% of HPMC was granulated with water and then mixed with other ingredients. The figure shows that when 25% of granulated HPMC was incorporated into the matrix formulation, the amount of drug released increased from 61 to 84% after 4 h (compare F7 and F8). As more granulated HPMC was incorporated, there was no significant increase in the release rate of captopril.

Fig. 1e shows the effect of ethylcellulose on the release rate of captopril from HPMC matrices. Although partial replacement of HPMC by EC increased the release rate of the drug (F3 and F11 in Fig. 1e), when the ratio of HPMC/EC was reduced to 1:1 (F11), the amount of captopril released increased from 52 to 62%. It can be seen that the difference in release profiles of F3, F10 and F11 is more significant at pH 6.8 than it is at pH 1.2.

To investigate the effects of surfactants on the release rate of captopril, HPMC K15M/EC (1:1) was chosen as the inert matrix. The release of captopril from matrices containing different percentages of SLS (formulations F11–F14) was measured. The release rate of captopril from Methocel K15M-EC matrices was generally decreased by the anionic surfactant (Fig. 2a). The rate of drug release slightly decreased as more surfactant was added to the formulation. ANOVA and Tukey's multiple comparison tests showed that the presence of SLS did not cause any significant changes in the amount of drug released from these matrices, with the exception of high SLS concentration (12%). The presence of high SLS concentration (12%) caused a significant decrease in drug release ( $p < 0.05$ ). For instance, the amount of captopril released decreased from 65 to 55% after 4 h.

As captopril has two  $pK_a$ s 3.7 (weak acid) and 9.8 (very weak acid), the drug will be in cationic form (about 99%) at pH 1.2 possessing the ability of complex formation with the anionic surfactant SLS. Thus SLS is expected to retard the release rate of captopril at pH 1.2. The data showed that SLS retarded the release of captopril at pH 6.8. At higher SLS concentration (12%), the release rate of captopril was higher than in SLS 6%, *m/m*. At pH 6.8, captopril has a negative charge on the carboxyl group and a positive charge on nitrogen. Therefore, SLS is still able to interact with the cationic group to make a complex. In addition, the retardation effect of SLS could be due to enhanced viscosity of the gel layer surrounding the matrix, which leads to reduction in the release rate of drugs (16). Walderhasug *et al.* (17) studied the nature of the interaction between SLS and cellulose ethers. They concluded that the anionic surfactant could bind to the non-ionic cellulose to form a strong gel network. Furthermore, complexation and subsequent precipita-

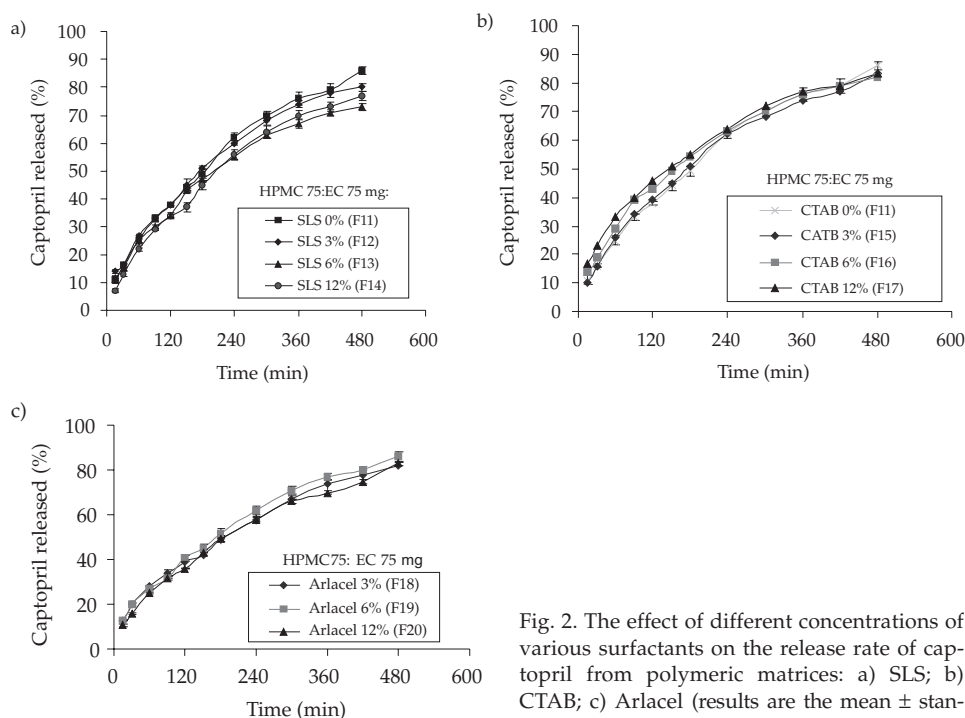


Fig. 2. The effect of different concentrations of various surfactants on the release rate of captopril from polymeric matrices: a) SLS; b) CTAB; c) Arlancel (results are the mean  $\pm$  standard deviation of 3 determinations).

tion provide a more tortuous pathway and less porous matrix through which the dissolved medicinal compound must diffuse (18). Daly *et al.* (19) found that the incorporation of 15% SLS in modified hydroxypropyl methylcellulose matrices produced a zero-order release of chlorpheniramine maleate. Feely and Davis (20) reported that the release rate of chlorpheniramine maleate from a HPMC matrix was reduced as more SLS was incorporated into the matrix.

The release of captopril from matrices containing CTAB as cationic surfactant 0–12% (*m/m*) (formulations F3, F13–F15) is shown in Fig. 2b. The release of the drug from the matrices was increased by the cationic surfactant CTAB at pH 1.2. As the concentration of CTAB increased from 0 to 12% (*m/m*), the amount of the drug released increased from 38 to 45% after 2 hours. As captopril has a positive charge at pH 1.2, CTAB is not able to interact with captopril.

The release of captopril from matrices containing 0–12% *m/m* Arlancel 60 as non-ionic surfactant (formulations F11, F18–F20) is illustrated in Fig. 2c. It can be seen that the release rate was not affected significantly as the concentration of Arlancel 60 was increased from 0 to 12%. Similar results were obtained when *DE* and *MDT* were compared for matrices with different concentrations of Arlancel. The results (Table II) showed that the presence of Arlancel in concentrations of 3–12% had no significant effect on *DE* and *MDT*.



Table II. Hardness,  $K_1$ ,  $n$  and  $R$  based on Eq. (1) for controlled release formulations of captopril

Formulation code	Hardness (kg)	$K_1$	$n$	$R$	DE (%) <sup>a</sup>	MDT (min) <sup>a</sup>
F1	10 ± 2	9.50	0.38	0.966	72.7 ± 5.2	84.2 ± 9.8
F2	12 ± 2	5.38	0.46	0.994	62.2 ± 2.4	120.2 ± 12.1
F3	11 ± 3	3.14	0.52	0.988	50.0 ± 2.1	133.5 ± 11.9
F4	9 ± 2	0.41	0.85	0.985	40.1 ± 2.4	178.9 ± 13.5
F5	11 ± 2	0.49	0.82	0.983	41.6 ± 2.5	172.2 ± 12.3
F6	10 ± 3	3.65	0.50	0.994	53.0 ± 3.5	144.6 ± 13.4
F7	12 ± 3	4.17	0.49	0.988	56.9 ± 4.2	141.8 ± 8.6
F8	14 ± 2	3.83	0.56	0.995	73.0 ± 5.2	115.3 ± 12.0
F9	15 ± 3	4.07	0.54	0.997	69.7 ± 4.0	116.6 ± 8.9
F10	9 ± 1	1.69	0.62	0.983	52.1 ± 2.1	163.2 ± 14.2
F11	11 ± 2	2.27	0.59	0.993	55.5 ± 2.9	145.1 ± 11.2
F12	12 ± 1	2.91	0.55	0.994	54.9 ± 4.0	142.9 ± 10.8
F13	13 ± 2	2.38	0.57	0.997	50.3 ± 2.9	141.0 ± 10.6
F14	9 ± 2	1.46	0.66	0.993	50.4 ± 3.5	150.5 ± 11.0
F15	11 ± 1	2.13	0.60	0.991	55.2 ± 2.1	138.5 ± 11.3
F16	12 ± 2	3.30	0.53	0.995	57.5 ± 1.9	131.7 ± 8.9
F17	11 ± 2	4.90	0.46	0.998	59.1 ± 3.5	122.6 ± 8.7
F18	9 ± 3	3.11	0.53	0.998	54.6 ± 2.9	145.4 ± 11.2
F19	9 ± 3	2.96	0.55	0.995	56.9 ± 3.1	140.8 ± 11.9
F20	10 ± 2	2.21	0.59	0.998	53.0 ± 2.6	144.0 ± 9.9

<sup>a</sup> Mean ± SD,  $n = 3$ .

It can be concluded for these surfactants that wetting does not play a significant role in the dissolution process and that the minor acceleration or retardation observed with the incorporation of CTAB and SLS might be due to the surfactant dissolving and forming pores/channels, which increases the effective surface area by a method other than wetting.

Two possible mechanisms have been postulated as to why surfactants increase the rate of drug release from matrix formulations (21, 22). Firstly, it is possible that the surfactant lowers the interfacial tension between the product and the dissolution fluid; secondly, it is possible that the surfactant acts as a wicking agent, causing the fluid to enter the dosage form; the surfactant may then dissolve and form pores (or other disruptions) from which the drug release may be affected (21). The same results were reported on the effect of surfactants on the dissolution profiles of flurbiprofen (22). Efentakis *et al.* (18) showed that in most cases, wetting plays a small role in aiding dissolution. They concluded that the major mechanism by which surfactants increase the dissolution rate is the

formation of pores to aid the access of the dissolution fluid and egress of the dissolved drug. It is also possible that the presence of the relatively concentrated surfactant solution in the wetted tablet would reduce interparticle adhesion and thereby enhance the drug release rate as a result of increased disintegration.

As captopril is a highly soluble drug, the release will be predominantly controlled by diffusion. The release kinetics from matrices composed of varying ratios of polymer(s) and surfactants were analyzed using Eq. (1); the results are shown in Table II. It can be observed that increasing HPMC concentration leads to higher  $n$  values. It is clearly seen that the  $n$  values for matrices containing HPMC or the mixtures of HPMC and lactose are around 0.5 because of the high solubility of captopril in dissolution media, indicating the diffusion release mechanism. Table II shows that incorporating NaCMC in HPMC matrices leads to a significant increase in  $n$  values. This indicates that the presence of NaCMC in HPMC matrices increases the contribution of erosion in the captopril release.

The presence of higher concentration (12%,  $m/m$ ) of the anionic surfactant (SLS) slightly increased the  $n$  value. The values of  $n$  were between 0.55 and 0.66 for matrices containing different concentrations of SLS, ranging from 0–12% ( $m/m$ ). In other words, there is a slightly higher contribution of diffusion in the presence of 3 or 6% SLS compared to with the matrices with 12% surfactant. A similar result was obtained for matrices containing Arlacel 60, in which the contribution of diffusion was predominant at lower concentration of surfactants (3 and 6%,  $m/m$ ). Table II also shows that an increase in the concentration of CTAB results in a reduction in the value of  $n$ . For example, when the concentration of CTAB is increased from 3 to 6 and 12% ( $m/m$ ), the value of  $n$  was reduced from 0.60 to 0.53 and 0.46, respectively. This shows that a low concentration of CTAB has no significant effect on the mechanism of release, whereas the contribution of diffusion increases with higher CTAB concentrations compared to with matrices without the surfactant (F11).

## CONCLUSIONS

The present work has showed that surfactants can be used to control the release rate of captopril from HPMC-EC matrices. However, they are not able to produce the zero-order release pattern for captopril matrices. The magnitude of the increase or decrease of release rate remarkably depends on the type of surfactant and on concentration. The results also show that the surfactants are able to change the mechanism of captopril release from the matrices. The principal mechanism by which surfactants retard drug release from HPMC-EC matrices is the drug/surfactant ionic interaction.

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#### S A Ž E T A K

### Utjecaj različitih površinski aktivnih tvari i njihovih koncentracija na kontrolirano oslobađanje kaptoprila iz polimernih matriksa

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Postoje različite metode formuliranja vodotopljivih lijekova u dozirane ljevakovite oblike s polaganim oslobađanjem. Jedan od načina postizanja kontroliranog otpuštanja, a prema tome i produljenog učinka je upotreba hidrofilnih i lipofilnih polimera. U ovom radu proučavan je utjecaj različitih polimera poput hidroksipropil metilceluloze (HPMC), etilceluloze (EC) i natrijeve soli karboksimetilceluloze (NaCMC) i površinski aktivnih tvari (natrijevog lauril-sulfata, cetiltrimetilamonijevog bromida i Arlacela 60) na oslobađanje kaptoprila. Rezultati pokazuju da povećanje količine HPMC K15M ima za posljedicu smanjenje oslobađanja kaptoprila iz matriksa. Ako se HPMC djelomično zamijeni s NaCMC (omjer HPMC/NaCMC 5:1), oslobađanje ljevakovite tvari značajno se smanjuje. Međutim, nema značajne razlike u oslobađanju kaptoprila iz matriksa s omjerom HPMC/NaCMC 5:1 i 2:1. Prisutnost laktoze u matriksu koji sadrži HPMC i NaCMC povećalo je oslobađanje kaptoprila. Iako djelomična zamjena HPMC s EC smanjuje oslobađanje ljevakovite tvari (omjer HPMC/EC 2:1), oslobađanje se povećava uz omjer HPMC/EC 1:1. Nadalje, ispitan je utjecaj površinski aktivnih tvari na oslobađanje kaptoprila iz matriksa u kojima je omjer HPMC/EC (1:1). Može se zaključiti da površinski aktivne tvari ne utječu značajno na oslobađanje ljevakovite tvari. U sklopu istraživanja određen je i kinetički model oslobađanja kaptoprila. Analiza kinetičkih podataka ukazuje da dodatak površinski aktivnih tvari u HPMC/EC matrikse ne slijedi kinetiku nultog reda.

*Cljučne riječi:* kaptopril, polimeri, kontrolirano oslobađanje, površinski aktivna tvar, kinetika oslobađanja

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