

The Effect of Various Surfactants on Release Behavior of Procainamide HCl from Ethylcellulose Based Matrices

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Abstract

The effect of different kinds of surfactants in various concentrations incorporated in an inert matrix, on the release of procainamide hydrochloride, as a cationic model compound, was investigated in this study. Sodium lauryl sulfate and sodium stearate as anionic surfactants, cetyl pyridinium chloride and cetyltrimethyl ammonium bromide as cationic and span 60 and tween 80 as non-ionic surfactants were selected. Hydrophobic matrices were prepared using procainamide HCl, ethyl cellulose, dicalcium phosphate and different percentages of each surfactant and the dissolution rate of drug from various matrices was determined in pH values 1.2 (for 2 h) and 7.2 (up to 10 h). The results showed that incorporation of anionic surfactants in matrix preparations resulted in a remarkable decrease in the release rate of procainamide HCl ($P < 0.05$), which was attributed to the formation of a poorly soluble complex between the cationic drug and the anionic surfactant. The formation of complex was confirmed by the precipitation titration test. On the other hand, presence of cationic surfactants considerably increased the drug release rate and it was noted that by raising the percentage of surfactant, a faster drug release rate was achieved. With span 60 there was no change in drug release rate, probably due to its lower wetting capability. While in the case of tween 80, as a hydrophilic non-ionic surfactant, the drug release rate was increased, although statistically not significant. In general, it seems that the influence of cationic and non-ionic surfactants on drug release rate was in accordance with the ability of each surfactant in wetting the matrices and producing a greater number of channels for the dissolution fluid to leach out the drug. Kinetics evaluation of the release profiles showed that the Higuchi equation is the main model, fitting the data.

Keywords: Surfactant; Procainamide HCl; Matrix tablet; Release behavior.

Introduction

Matrix tablets have long been used to obtain sustained drug delivery. Embedding or dispersing a drug within hydrophobic matrices by compression of a physical mixture of polymeric materials and the medicinal compound is often

applied to prepare a sustained release formulation of a highly water soluble drug (1).

The effect of various surfactants incorporated in matrix systems on the release rate of various drugs has been investigated in previous studies. The addition of surfactant in matrix formulations has generally resulted in a faster drug release rate (2-4). Also, a distinct change in the release kinetics has been previously reported (5). Efentakis reported that the surfactant concentration could

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change the release profile from linear to biphasic (5). Incorporation of an anionic surfactant in the matrix caused the release of a highly water soluble drug to be linearly related to the square root of time and the release pattern was shown to be dependent on the surfactant concentration (6). Limited studies have been conducted, concerning the reduction of drug release rate in the presence of an oppositely charged surfactant (7-9).

The use of sodium lauryl sulfate (SLS) in modified hydroxypropyl methylcellulose (HPMC) tablets has been shown to retard the release rate of chlorpheniramine and resulted in a zero order release profile (7). Feely and Davis reported that by increasing the amount of SLS incorporated within a HPMC matrix, the release rate of chlorpheniramine maleate was reduced (8). In another study, it was found that the release rate of propranolol decreased as the concentration of anionic surfactant increased. Also, the use of different ratios of various charged surfactants was able to change the release rate of the drug (9). Almost all these studies have used HPMC, a hydrophilic swellable polymer, in the preparation of matrices. Thus, it seemed important to further investigate this phenomenon in tablet matrices containing a non-swellable hydrophobic polymer such as ethyl cellulose.

Hence, the effect of various surfactants and their concentrations on the release behavior of procainamide HCl, as a water-soluble cationic drug, from inert polymeric matrices was investigated in the present study.

Experimental

Materials

Procainamide hydrochloride (Chimidaru, Iran), ethylcellulose (EC, Dow Chemicals), cetyl pyridinium chloride (CPC, Merck), cetyltrimethyl ammonium bromide (CTAB, Merck), sodium lauryl sulfate (SLS, Merck), sodium stearate (SS, Merck), span 60 (Aldrich), polysorbate (Tween 80, Merck), dicalcium phosphate (Fluka), and magnesium stearate (BDH Chemicals) were used in this study.

Methods

Preparation of Tablets

Matrices containing 100 mg procainamide

hydrochloride were prepared using 40% w/w ethylcellulose as an inert hydrophobic polymer. Different percentages of surfactants (lower than CMC), including anionic (sodium lauryl sulfate and sodium stearate), cationic (cetyl pyridinium chloride and cetyltrimethyl ammonium bromide) and non-ionic (span 60 and tween 80) were incorporated within the tablet formulations prepared. Appropriate amounts of dicalcium phosphate, as a diluent, and 1.5% w/w magnesium stearate, as a lubricant, were also used in these tablet formulations (Table 1). Matrices were prepared by the direct compression method, using a single punch machine (Erweka, Germany) with a 9 mm flat-faced punch and die set.

Dissolution Studies

The invitro drug release studies from the various formulations prepared was carried out, using the USP dissolution test apparatus II (Erweka, Germany), paddle method, at 50 ± 1 rpm. The dissolution media were 1000 ml 0.1 N HCl (pH=1.2) and phosphate buffer solution (pH=7.2) at $37 \pm 0.5^\circ\text{C}$. Matrices were placed in simulated gastric fluid (pH=1.2) and maintained for 2 h. After the mentioned time, the dissolution medium was replaced with the phosphate buffer solution to simulate intestinal fluid and the release study was continued up to 10 h. Five ml samples were withdrawn at various time intervals and filtered through 0.45 μm Millipore filter. Samples were then analyzed for drug concentration using a UV spectrophotometer (Shimadzu, Japan) at 224 nm and 275 nm for acidic and buffer medium respectively. The mean of three determinations was used to calculate the drug release from each formulation. The release kinetics was evaluated by three different models including the zero order, first order and the Higuchi equation, (considering the release data up to 60-70%). The selection of the best model was based on the comparison of the relevant correlation coefficients. The release rate constants (k), calculated based on the best model, were compared using ANOVA, with tukey post test.

Precipitation Titration Test

This test was carried out to study the possible

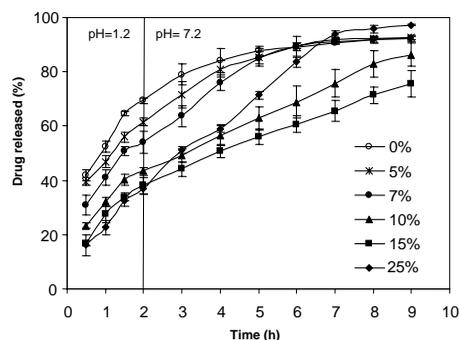


Figure 1. Drug release profiles of procainamide HCl from tablet matrices as a function of sodium lauryl sulfate concentration (mean \pm SD, n=3)

interaction between the cationic drug and anionic surfactants. Ten mg/ml of procainamide hydrochloride aqueous solution was titrated with the same concentration of an anionic surfactant aqueous solution and changes in the solution were observed (6). In addition, an aqueous medium was used as the blank. Each test was carried out in triplicates.

Results and Discussion

Anionic Surfactants:

Procainamide HCl release patterns from tablets containing sodium lauryl sulfate and sodium stearate are presented in Figures 1 and 2 respectively. According to the results, incorporation of 5-15% w/w SLS and 5-25% w/w SS in matrix systems, sustained the release rate of drug in both the acidic and buffer medium. SLS, as an anionic surfactant with good solubility, can improve the wettability of tablets in the dissolution medium. Due to this characteristic, a significant increase in the dissolution rate of lipophilic drugs such as flubiprofen, griseofulvin, carbamazepine

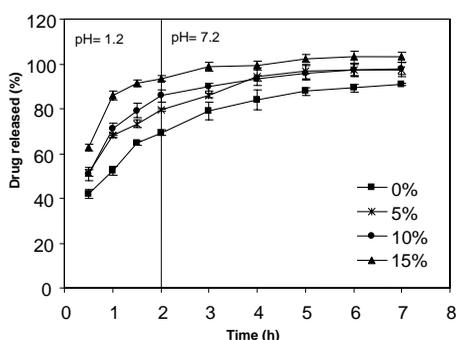


Figure 3. Drug release profiles of procainamide HCl from tablet matrices as a function of cetyl pyridinium chloride concentration (mean \pm SD, n=3)

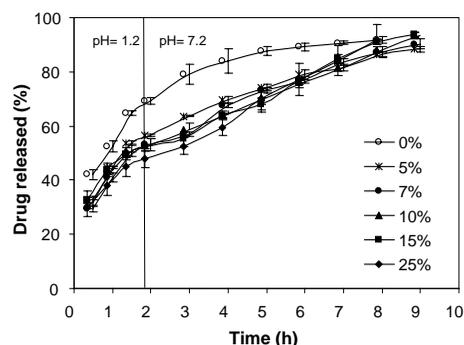


Figure 2. Drug release profiles of procainamide HCl from tablet matrices as a function of sodium stearate concentration (mean \pm SD, n=3)

and clofibrate has been reported (10, 11). The opposite results obtained in this study could be attributed to the formation of a weak complex between the cationic drug and the anionic surfactant. The procainamide-SLS complex presumably, with a lower solubility than the free procainamide, resulted in a noticeable decrease in the dissolution of drug. This complex could even increase the tortuosity and reduce the porosity of the matrix system, which is a useful parameter in drug release into the medium (6). To study the possible interaction between the cationic drug and the anionic surfactant, precipitation titration tests were carried out. No change occurred in the blank solution, but existence of the following three stages were clear within the samples: a primary clear solution, a turbid solution (due to complex formation) and a secondary clear solution probably because of solubilization of the complex in surfactant concentrations higher than CMC (6). On the other hand, there was no change in drug solution titrated with a solution of CPC, the cationic surfactant, indicating that no complex has been formed.

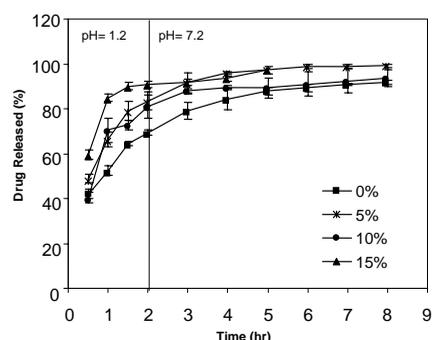


Figure 4. Drug release profiles of procainamide HCl from tablet matrices as a function of cetyltrimethyl ammonium bromide concentration (mean \pm SD, n=3)

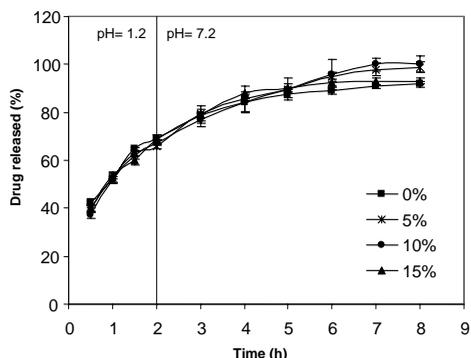


Figure 5. Drug release profiles of procainamide HCl from tablet matrices as a function of span 60 concentration (mean \pm SD, n=3)

Increasing the viscosity of the non-ionic polymer in the presence of anionic surfactants has also been reported earlier (7). In addition, anionic surfactants could bind to the non-ionic cellulose to form a stronger gel network (12). Ethylcellulose, used in this study for matrix preparation, is not soluble and no gel formation occurred around the matrix. Therefore complex formation could be considered as the underlying mechanism for the observed reduction in the release rate of procainamide HCl.

As shown in Figure 1, presence of 25%

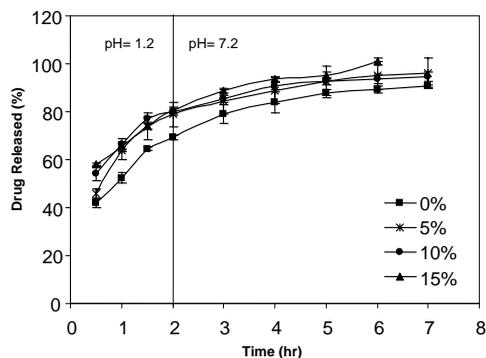


Figure 6. Drug release profiles of procainamide HCl from tablet matrices as a function of tween 80 concentration (mean \pm SD, n=3)

SLS (F5) within the matrix resulted in an ($p < 0.05$) increase in the release rate of drug compared to lower percentages of SLS (F3, F4). It seems that the existence of 25% SLS in tablet formulations along with lower amounts of dicalcium phosphate (as insoluble filler) caused a fast disintegration of tablets after 2-3 h, which was also noticeable in the dissolution medium. These results indicate that the higher concentration of SLS could reduce the release rate only before the occurrence of tablet disintegration.

It appears that drug-surfactant interaction

Table 1. Composition of different matrices prepared in this study

Formulation	Surfactant (%) w/w						Dicalcium phosphate (%)
	SLS	SS	CPC	CTAB	Span 60	Tween 80	
F0	-	-	-	-	-	-	25
F1	5	-	-	-	-	-	20
F2	7	-	-	-	-	-	18
F3	10	-	-	-	-	-	15
F4	15	-	-	-	-	-	10
F5	25	-	-	-	-	-	0
F6	-	5	-	-	-	-	20
F7	-	7	-	-	-	-	18
F8	-	10	-	-	-	-	15
F9	-	15	-	-	-	-	10
F10	-	25	-	-	-	-	0
F11	-	-	5	-	-	-	20
F12	-	-	10	-	-	-	15
F13	-	-	15	-	-	-	10
F14	-	-	-	5	-	-	20
F15	-	-	-	10	-	-	15
F16	-	-	-	15	-	-	10
F17	-	-	-	-	5	-	20
F18	-	-	-	-	10	-	15
F19	-	-	-	-	15	-	10
F20	-	-	-	-	-	5	20
F21	-	-	-	-	-	10	15
F22	-	-	-	-	-	15	10

over a certain range of surfactant concentration was an important factor in decreasing the wetting characteristics of SLS, as well as and the drug release rate.

As shown in Figure 2, incorporation of 5% SS within the matrix significantly decreased ($P < 0.05$) the release rate of procainamide HCl, compared to formulation F0. However, the reduction of drug release rate from matrices containing 7-25% SS was rather low. In contrast to formulation F5 (containing 25% SLS), the unexpected increase in drug release rate was not observed in matrix tablets containing 25% SS (F10). This could be attributed to the lower solubility of SS, compared to SLS, which could prevent early tablet disintegration.

Kinetics evaluation of the related dissolution profiles showed that the release rate constant for most formulations within this group was significantly lower than formulation F0 ($P < 0.05$, Table 2). However, almost all release kinetics were similar to formulation F0 and in accordance to the Higuchi model.

Cationic Surfactants:

The dissolution profiles of procainamide HCl from matrix tablets prepared with 5-15% w/w cetyl pyridinium chloride are presented in Figure 3. It could be seen that drug release from these matrices is higher than tablets with no surfactant at both pHs of 1.2 and 7.2. As more surfactant was added to the formulation, the rate of drug release was increased. The same results were obtained for matrices prepared in the presence of 5-15% CTAB (Figure 4). Two possible mechanisms have been postulated for this finding (13). Firstly, it is possible that the surfactant lowers the interfacial tension between the tablet matrix and the dissolution medium, and as a result the drug release rate increases. Secondly, the surfactant could act as a wicking agent, causing the fluid to enter the dosage form. The surfactant may then dissolve and form pores, through which the drug release rate may be affected.

Similar results were reported by Efentakis et al. (10). They showed that the incorporation of CPC within hydrophobic matrix formulations

Table 2. Correlation coefficient (r^2) of different matrices based on various models and the release rate constant (k)

Formulation	Correlation coefficient (r^2)			k (mg.hr ^{-0.5})	SE	P value ^a
	Zero order	First order	Higuchi equation			
F0	0.928	0.866	0.967	36.81	1.90	-
F1	0.958	0.956	0.972	32.35	1.39	0.130
F2	0.961	0.954	0.972	34.59	1.34	0.392
F3	0.945	0.929	0.965	25.66	0.98	0.006
F4	0.946	0.958	0.977	24.24	0.66	0.003
F5	0.957	0.948	0.952	39.95	1.92	0.309
F6	0.901	0.970	0.967	25.37	1.01	0.006
F7	0.946	0.980	0.983	26.35	0.69	0.007
F8	0.949	0.979	0.981	23.41	0.66	0.003
F9	0.954	0.932	0.960	23.97	0.98	0.004
F10	0.939	0.902	0.937	25.53	1.42	0.009
F11	0.911	0.961	0.953	38.80	2.74	0.582
F12	0.905	0.922	0.934	55.08	5.55	0.036
F13	- ^b	-	-	-	-	-
F14	0.947	0.914	0.954	30.17	2.71	0.115
F15	0.778	0.818	0.838	54.47	6.06	0.049
F16	-	-	-	-	-	-
F17	0.951	0.982	0.981	37.75	1.45	0.714
F18	0.906	0.959	0.965	35.53	1.69	0.641
F19	0.959	0.987	0.988	37.60	1.14	0.739
F20	0.781	0.827	0.860	37.18	4.16	0.939
F21	0.918	0.946	0.950	38.46	2.79	0.651
F22	0.983	0.977	0.977	32.26	1.56	0.137

k was calculated based on the Higuchi model, SE: Standard error of release rate constant.

a: The release rate constant of each formulation was compared to Formulation F0 (without surfactant).

b: Release kinetics was not calculated due to a very fast release of drug.

accelerated the flurbiprofen release rate due to the dissolution of surfactant and formation of pores or channels. The effect of cetyl trimethyl ammonium bromide, as a cationic surfactant, on the enhancement of propranolol HCl release from HPMC-Eudragit RS matrices has also been reported in the literature (9).

Table 2 shows the results obtained from kinetics evaluation of these matrices. The release kinetics from formulation F0 (without surfactant) and matrices containing CPC (F11, F12) and CTAB (F14, F15) had a good correlation with the Higuchi model. The results indicated that the use of higher concentrations of these surfactants (F12, F15), increased the release rate constant significantly ($P < 0.05$), but had no considerable effect on the release kinetics.

Non-ionic Surfactants:

Figure 5 shows the release profiles of procainamide HCl from matrices made with 5-15% w/w span 60 as the non-ionic surfactant. It can be seen that the use of different percentages of span 60 has no effect on release rate in both the acidic and buffer media and the release rate constant (k) for tablet formulations F17-F19 is similar to that of formulation F0 (Table 2). This could be due to the lower solubility and wettability of this surfactant. In another study, incorporation of span 60 within the Methocel based matrices even retarded the release rate of ketoprofen (14). It seems that the higher solubility of procainamide HCl competes with the hydrophobicity of span 60 ($HLB=4.7$) and the net result is no change in the dissolution rate of drug. In order to study the effect of HLB value on the drug release rate, matrices containing 5-15% tween 80 were also investigated. Based on Figure 6, the release rate of procainamide HCl from these matrices is slightly higher than formulation F0 due to the hydrophilicity of tween 80 ($HLB=15$). This is in agreement with the results obtained for propranolol HCl matrices containing tween 65 (9). This indicates that the lipophilicity and hydrophilicity of surfactant has an important role in the release rate of procainamide HCl. No statistically significant difference was noted between the release rate constants of drug from matrices (formulations F20-F22) containing various percentages of

tween 80, (Table 2). It is probable that a higher concentration of tween 80 within the tablet matrix is required to obtain a higher release rate of drug. Similar to the matrix tablets prepared without any surfactant, the best kinetics model for both types of matrices is Higuchi (Table 2).

The effect of various surfactants (anionic, cationic and non-ionic) in different concentrations, incorporated in an inert matrix, on the release of procainamide HCl (as a cationic model compound) was studied in the present investigation. The release rate of drug was distinctly reduced by incorporation of anionic surfactants in matrix formulation. This is because SLS and SS are able of forming poorly water soluble complexes with the drug. The formation of complex was confirmed by the precipitation titration test. In the case of cationic surfactants, the drug release rate was significantly increased ($P < 0.05$). It is probable that these agents have reduced the interfacial tension and could also act as a wicking agent, causing the fluid to enter the dosage form. Non-ionic surfactants had no notable effect on the release rate, but it seems that the release rate was dependent on the HLB values, as found to increase slightly in the presence of the hydrophilic non-ionic surfactant. Kinetics evaluation showed that in almost all matrices the percentage of drug released was linearly related to the square root of time.

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