academicJournals

Vol. 8(13), pp. 364-371, 8 April, 2014
DOI 10.5897/AJPP2013. 3890
ISSN 1996-0816

http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Surfactants solubility, concentration and the other formulations effects on the drug release rate from a controlled-release matrix

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Received 17 September, 2013; Accepted 28 March, 2014

Surfactant effects on the drug release from controlled release systems have been widely studied. These effects are dependent on the surfactant physical properties such as structure, charge, solubility and concentration. In addition, presence of excipients in the matrices can modify the surfactants effects. Here we investigated the effects of surfactant solubility and concentration of excipients on the drug release. Two cationic surfactants (cetrimide and cetylpyridinium chloride), two anionic surfactants (sodium lauryl sulfate and sodium taurcholate) and the amphoteric surfactant betaine were used. The used dissolution medium was simulated gastric fluid pH 1.2. The results revealed that surfactants of the same charge with the drug showed increase of drug release rate in concentration below the surfactant critical micelle concentration (CMC), while the increase in the drug release was to a less extent in surfactant concentration above its CMC. On the other hand, drug release rate was increased with surfactant solubility and vice versa. Surfactants of different charges with that of the drug resulted in a decrease in the drug release rate, depending on surfactant solubility and the excipients. The amphoteric surfactant increased the drug release rate depending on surfactant solubility and concentrations.

Key words: Propranolol hydrochloride, surfactant solubility, controlled-release, surfactant concentration, drug release rate.

INTRODUCTION

The effects of surfactant on the drug release rate have been widely studied. Many of the studies concerned with the surfactant effects on drug release rate from different types of matrices including hydrophilic polymers matrices (Daly et al., 1984; Feely and Davis, 1988; Bolourtchian et al., 2005; Nokhodchi et al., 2008), hydrophobic polymer

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(Efentakis et al.,1990; Bucton et al., 1991; Effentakis et al.,1991; Effentakis et al.,1992) and hydrophilic–hydrophobic polymers (Al- Hmoud et al., 1991; Wells and Parrott, 1992; Al-Hmoud, 2002; Nokhodochi et al., 2002). In a study on the effect of branching on surfactant properties of sulfosuccinates, it was reported that if the micelles are small enough the materials are still considered soluble because the structures are below the size that affects clarity (Olenek and O'lenick, 2007).

It was also reported that deflocculating is one of the mechanisms that accelerate the release rate of the slightly soluble drugs (Schott et al., 1982). It was found that low concentration of the surfactant decrease the surface tension and increase the rate of dissolution, whereas higher surfactant concentration tend to form micelles with the drug and thus reduce the dissolution (Shargel and Yu, 1999). Surfactants are known to solubilize poorly soluble drugs at a concentration above the critical micelle concentration (CMC) as reported before (Mall et al., 1996; Rangel-Yagui et al., 2005). Non-ionic surfactant tween 80 was found to be not a good solvent for the amphoteric poorly soluble drug enrofoxacin, whereas ionic surfactants sodium dodacyl sulfate (SDS) was found to be much better solvent as compared to the cationic surfactant cetyl trimethyl ammonium bromide (CTAB) (Seeder and Agwal, 2009). Very high solubility drug in SDS shows that the non-polar part of the molecule solubilizes into the micellar interior, while the positive charged groups are in the outer core, decreasing the repulsive forces of the head groups of the surfactant molecules, thereby decreasing CMC, increasing the aggregation number and volume of micelles and increasing solubilization.

Much lower solubility in CTAB showed that the orientation of solubilized molecules is such that the negatively charged groups do not take part in solubilization. It was reported in an assessment of solubilization characteristics of different surfactants for carvedilol phosphate (CP) at different pH, it was found that cationic surfactant CTAB and non-ionic surfactant tween 80 were suitable for enhancing the solubility of CP, while the anionic surfactants SDS and sodium taurcholate (ST) were found as solubility retardants (Chacraborty et al., 2009).

Here we aimed to study the effects of surfactant solubility and concentration and the presence of excipients on the drug release. Two cationic surfactants (cetrimide and cetylpyridinium chloride), two anionic surfactants (sodium lauryl sulfate and sodium taurcholate) and the amphoteric surfactant betaine were used.

MATERIALS AND METHODS

Propranolol hydrochloride and sodium lauryl sulphate were kindly donated from Arab Pharmaceutical Manufacturing Co. Ltd. (APM) Jordan. Eudragit RL100 was purchased from Rhom Pharma and cetrimide was kindly donated by the Arab Center for Pharmaceuticals, Jordan. Sodium taurocholate and cetylpyridinium chloride were purchased from Fluka. Betaine was purchased from TCI and magnesium stearate was purchased from BDH chemicals Ltd. NaCMC was purchased from FMC.

Preparation of the tablets

The acrylic resin Eudragit RL100 was powdered and sieved through a 300 µm sieves. Formulations, as listed in Table 1, were prepared to evaluate the release rate of propranolol hydrochloride. The ingredients of each formulation were blended for five minutes in a blender and tablets weighing 400 mg were compressed using a direct compression technique, with a single punch tablet machine (Korch-Erweka). The diameter and the thickness of the tablets were 1 and 0.4 cm, respectively. Tablets were compressed to a hardness level of about 9 kg.

Dissolution study

The United State Pharmacopoeia (USP) basket method (Erweka, DT 6R, Heusenstamm, Germany) was used for all the *in vitro* dissolution studies. Matrices were placed in 900 ml of the dissolution medium and maintained at 37 ± 0.1°C for 8 h at pH 1.2. The rate of stirring was 50 rpm. At appropriate intervals (1, 2, 3, 4, 5, 6, 7 and 8 h), 5 ml of samples was taken and filtered through a 0.45 µm Millipore filter. The dissolution media was then replaced by 5 ml of fresh dissolution fluid to maintain a constant volume. The samples were then analyzed by ultraviolet/visible spectrophotometer at wavelengths 289 nm. The mean of three determinations was used to calculate the drug release rate from each of the formulations.

Determination of the critical micelle concentration (CMC) of the surfactants

For the determination the CMC of the different surfactants used in the study, different concentrations of the surfactants were prepared by dissolving these surfactants in distilled water and measuring their surface tension by the DuNoüy ring method using KR-SS Tensiometer.

Data analysis

A model-dependent technique was used to compare the dissolution profiles of the products. The model, based on drug dissolution from dosage forms that do not disaggregate and release the drug slowly, can be represented by the equation:

$$Q/_{Q\infty} = kt^n \quad (1)$$

Where Q is the amount of drug dissolved in time *t,* Q_∞ is the overall released amount of drug in the solution and *k* is the release constant expressed in units of concentration/time and n = 1 in zero order kinetics. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released versus time (Costa and Lobo, 2001; Narashimhan et al., 1999; Hadjiioannou et al., 1993). To characterize the drug release rate in different experimental conditions, $T_{50\%}$ and mean dissolution time (MDT) were calculated from dissolution data

Table 1. Composition of the different formulations matrices used in the study.

Formulation Matrices/Surfactant									
Form.	**Cet.**	**Form.**	**CPC**	**Form.**	**SLS**	**Form.**	**ST**	**Form.**	**Bet.**
F1	0.25	F7	0.25	F13	0.25	F19	0.25	F25	0.25
F2	0.50	F8	0.50	F14	0.50	F20	0.50	F26	0.50
F3	0.75	F9	0.75	F15	0.75	F21	0.75	F27	0.75
F4	1.0	F10	1.0	F16	1.0	F22	1.0	F28	1.0
F5	2.0	F11	2.0	F17	2.0	F23	2.0	F29	2.0
F6	4.0	F12	4.0	F18	4.0	F24	4.0	F30	4.0

Form: Formulations, Cet: Cetrimide, CPC: cetylpyridinium chloride, SLS: sodium lauryl sulfate, ST: sodium taurcholate, Bet: betaine. Each tablet contains 10% RL100, 69% Namco, and 1% MgO, 80 mg of Propranolol HCl and different conc. of surfactants, except for F0 which has no surfactants).

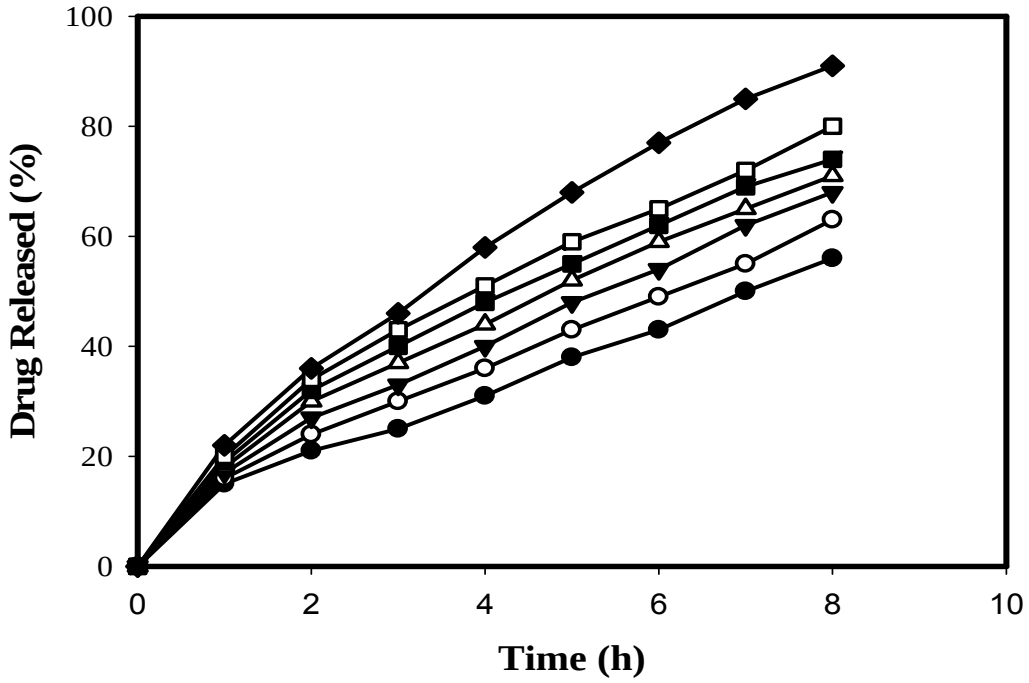

Figure 1. Cetrimide effect on the propranolol-HCl release rate. Cetrimide effect, at different concentrations, on propranolol-HCl release rate (solid line with symbols as follow, F1:○, F2:▼, F3: Δ, F4:■, F5:□, F6 :♦) was compared to matrix without surfactant (F0 :●).

according to equations 2 and 3, respectively (Mockel and Lippold, 1993).

$$T_{50\%} = \left(\frac{0.5}{k}\right)^{\frac{1}{n}} \quad (2)$$

$$MT = \frac{n}{n+1} k^{-1/n} \quad (3)$$

The mean dissolution time (MT) is applied to compare the drug release rates. MT is the amount of the drug in the matrix at a given time (n) divide by the initial amount of the drug.

RESULTS AND DISCUSSION

The purpose of the study was to increase the dissolution rate of the poor water soluble drugs by studying the effects of surfactant solubility and concentration and the presence of excipients. Figures 1 and 2 show the increase of the drug release with the increase of cationic surfactants cetrimide and cetylpyridinium chloride, respectively. Increasing cetrimide concentration from 0.25% in F1 to 4% in F6 increased the drug release rate from 1.12 to 1.62%, respectively (Figure 1). Similarly, with cetylpyridinium chloride, increasing its concentration

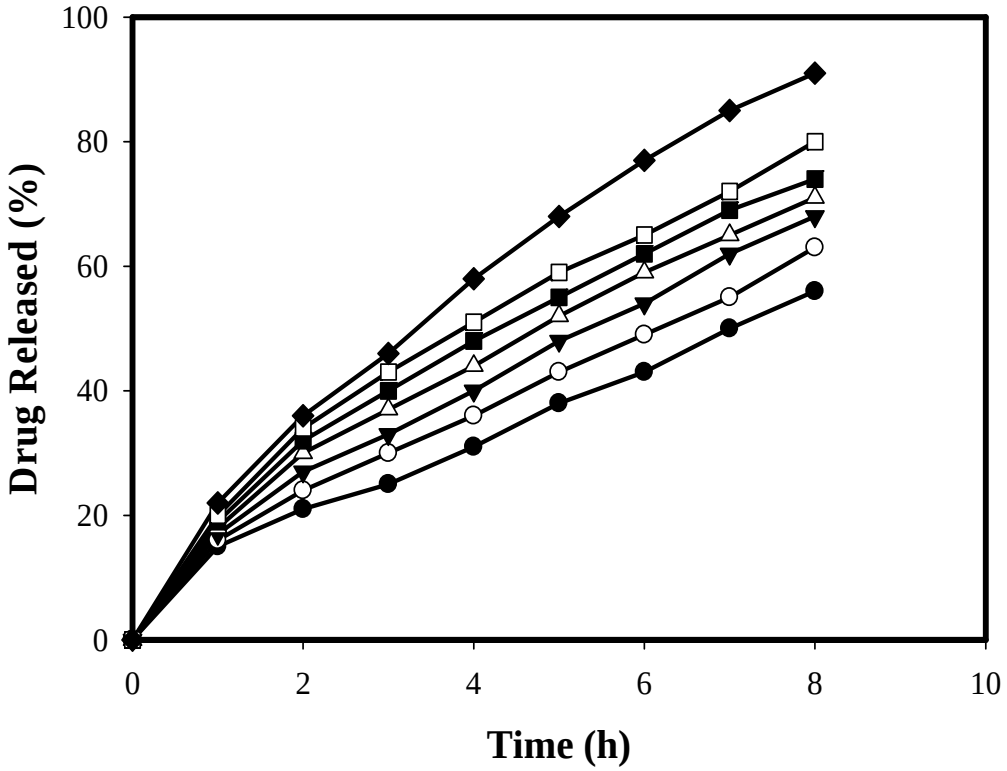

Figure 2. Cetylpyridinium chloride effect on the propranolol-HCl release rate. Acetyl pyridinium chloride effect, at different concentrations, on propranolol-HCl release rate (solid line with symbols as follow, F7:○, F8:▼, F9: Δ, F10:■, F11:□, F12 :♦) was compared to matrix without surfactant (F0 :●).

from 0.25% in F7 to 4% in F12 increased the drug release rate from 1.03 to 1.57%, respectively (Figure 2).

This increase can be attributed to many mechanisms. One mechanism relay on the high solubility of cetrimide (Martindale et al., 1996) that forms pores within the matrix resulted in increasing the drug release (Effentakis et al., 1992). Other mechanism explains this increase in the drug release rate due to the repulsive forces between the cationic matrix and cationic drug (Daly et al., 1984; Feely and Davis, 1988; Nokhodochi et al., 2002; Chacraborty et al., 2009). Or, surfactant lowers the interfacial tension between the product and the dissolution medium which increased the release of the drug (Nokhodochi et al., 2002). Increasing the drug release rate with cetrimide was higher than that with cetylpyridinium chloride, at the same concentration, and this can be attributed to the difference of solubility between cetrimide and the solubility of cetylpyridinium chloride (Martindale et al., 1996).

Similarly, Figures 3 and 4 show the fluctuated drug release with the increasing of anionic surfactants sodium taurcholate and sodium lauryl sulfate, respectively. With increasing sodium taurcholate concentration from 0.25 to 0.75% in F13-F15 (below its CMC), there is a decrease in the drug release rate (Figure 3). However, increasing sodium taurcholate concentration from 1.0% in F16 to 4.0% in F18 (above its CMC) increased the drug release rate (Figure 3). In the same manner, sodium lauryl sulfate behave similarly (Figure 4). The decreasing in the drug release rate can be attributed to the formation of complex between the opposite charges of cationic drug and anionic surfactant as reported before (Daly et al., 1984; Feely and Davis, 1988; Noushin et al., 2005; Nokhodchi et al., 2008), or it can be due to increasing the drug entrapment in the colloidal formulated emulsion (Chacraborty et al., 2009). On the contrary, when the concentrations of the surfactant were above the CMC, the formation of surfactant micelles in the dissolution medium helped in increasing the drug release rate (Olenek and O'lenick, 2007; Mall et al., 1996; Rangel-Yagui et al., 2005). The differences in result values between sodium lauryl sulfate and sodium taurcholate was attributed to solubility differences between them (Effentakis et al., 1992; Martindale et al., 1996).

With amphoteric surfactant, betaine, increasing surfactant concentration from 0.25% in F25 to 4.0% in F30 increased the drug release rate (Figure 5). This increase in the drug release rate can be attributed to it;

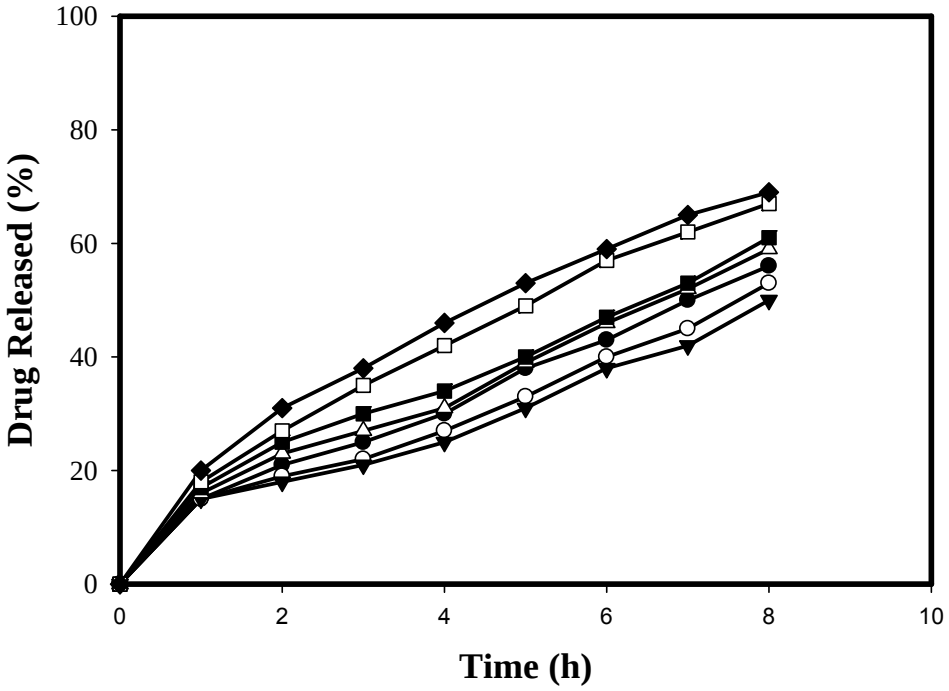

Figure 3. Sodium lauryl sulfate effect on the propranolol-HCl release rate. Sodium Laurayl sulfateeffect, at different concentrations, on propranolol-HCl release rate (solid line with symbols as follow, F13:○, F14:▼, F15: Δ, F16:■, F17:□, F18 :♦) was compared to matrix without surfactant (F0 :●).

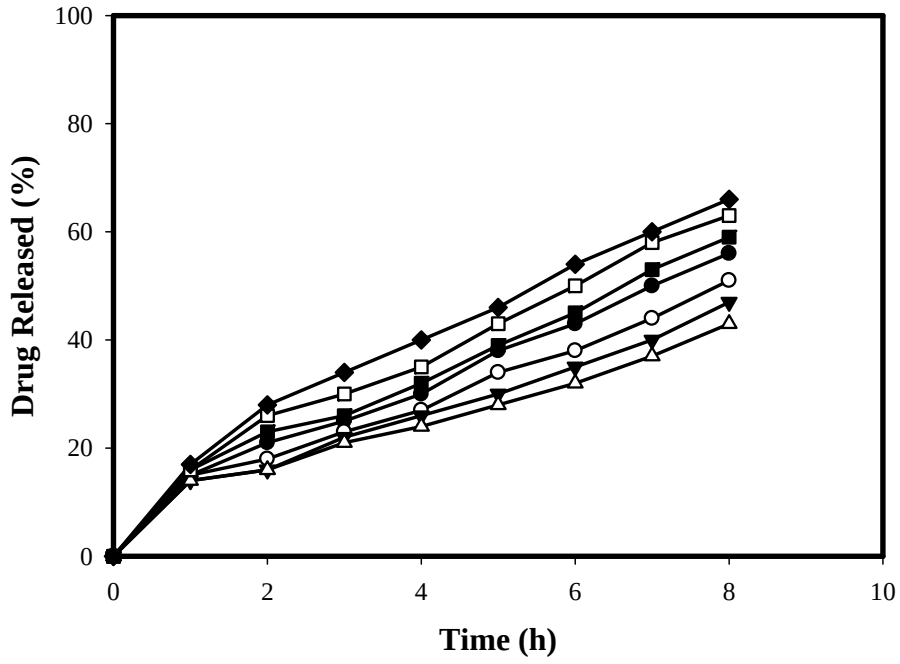

Figure 4. Sodium taurcholate effect on the propranolol-HCl release rate. Sodium taurcholateeffect, at different concentrations, on propranolol-HCl release rate (solid line with symbols as follow, F19:○, F20:▼, F21: Δ, F22:■, F23:□, F24 :♦) was compared to matrix without surfactant (F0 :●).

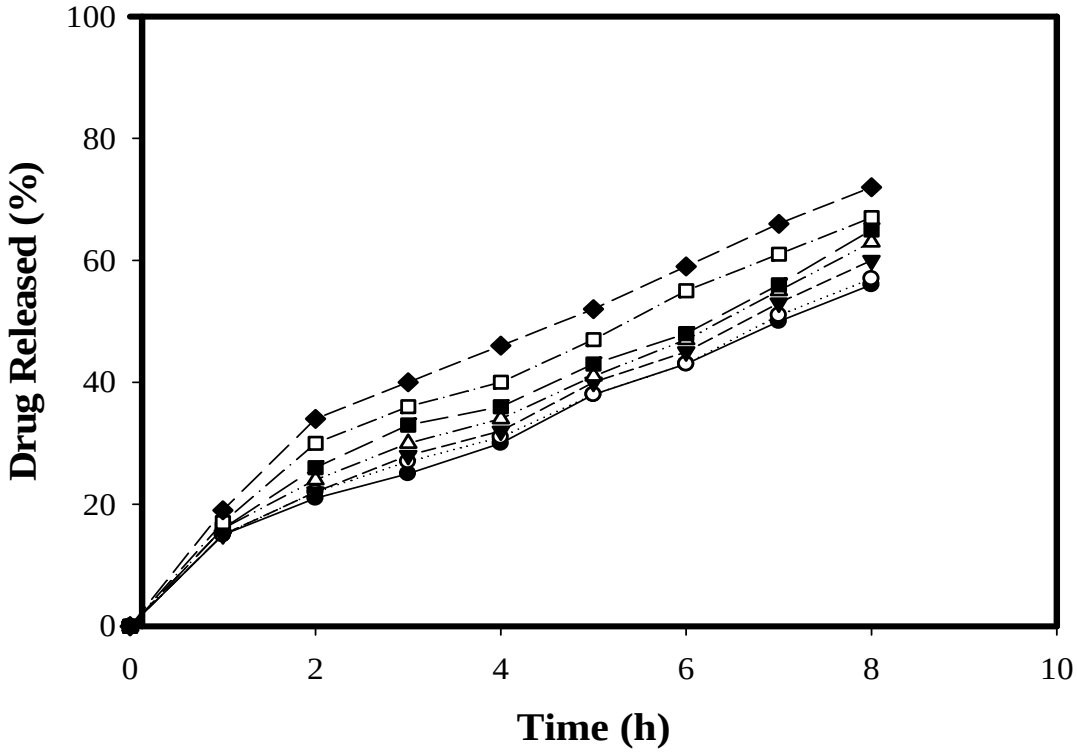

Figure 5. Betaine effect on the propranolol-HCl release rate. Betaine effect, at different concentrations, on propranolol-HCl release rate (solid line with symbols as follow, F25:○, F26:▼, F27: Δ, F28:■, F29:□, F30 :♦) was compared to matrix without surfactant (F0 :●).

Table 2. Surface tension values of surfactants at different concentrations.

Conc.	Formulation matrices/surfactant									
	Cet.	±SD	CPC	±SD	SLS	±SD	ST	±SD	Bet.	±SD
0.25	47	2.12	47	1.01	56	1.1	54	1.64	55	1.95
0.5	43	1.10	43.5	0.95	52	0.9	50	1.15	52	0.92
0.75	40	0.95	39	1.1	47	1.2	42	0.09	48	1.35
1.0	40	0.09	36	0.91	44	0.51	42	0.01	43	0.77
2.0	40	0.01	36	0.03	45	0.6	42	0	36	0.43
4.0	40	0	36	0	44	0	42	0	36	0

Cet: Cetrimide, CPC: cetylpyridinium chloride, SLS: sodium lauryl sulfate, ST: sodium taurcholate, Bet: betaine. Surfactants (Cetrimide, Cetylpyridinium, Sod. Lauryl sulfate, Sod. Taurcholate and betaine) used at concentrations (0.1, 0.25, 0.50, 0.75, 1.0 and 2.0). CMC of the surfactant were approximately at the concentrations as follows: SLS = 0.75%, ST =0.5%, Cet. = 0.5%, CPC = 0.75% and Bet. = 1%.

increasing surfactant concentration leads to increasing the aggregation number and volume of the micelles and increasing solublisation (Seedher and Agwal, 2009). All results were conducted to the regression analysis as shown in Table 2. All the r^2 values were higher than 0.985, indicating that the drug release rate followed zero order kinetics (Table 3).

Time required for 50% drug release ($T_{50\%}$) and mean dissolution time (MDT) were calculated from dissolution data and presented in Table 4. The MDT value was found

Table 3. Kinetics of the drug release rates.

Formulation	Correlation coefficient	Slope	Intercept	Formulation	Correlation coefficient	Slope	Intercept
F0	0.998567	0.169897	8.464286	F16	0.994129	0.240628	8.392857
F1	0.999643	0.161113	8.964286	F17	0,993455	0.241649	7.035714
F2	0.999308	0.153073	10.14286	F18	0.993652	0.262458	7.071429
F3	0.998397	0.141199	11.60714	F19	0.99529	0.172636	7.678571
F4	0.996053	0.139361	12.71429	F20	0.992102	0.181312	7.321429
F5	0.992785	0.138217	14.03571	F21	0.986849	0.190688	7.142857
F6	0.9919	0.137741	15.35714	F22	0.989363	0.208686	7.392857
F7	0.999462	0.168832	9.75	F23	0.988574	0.212672	6.571429
F8	0.999387	0.16134	0.16134	F24	0.989342	0.233577	6.892857
F9	0.999472	0.153966	11.17857	F25	0.996456	0.168496	8.607143
F10	0.9937	0.149182	13.46429	F26	0.998885	0.1721	8.785714
F11	0.990853	0.145194	14.57143	F27	0.998189	0.167392	8.964286
F12	0.990325	0.139395	14.71429	F28	0.99449	0.164509	8.821429
F13	0.994673	0.178726	7.964286	F29	0.998103	0.165052	9.464286
F14	0.995423	0.191781	8.0	F30	0.998538	0.162315	9.607143
F15	0.994911	0.211034	7.642857	-	-	-	-

Correlation coefficient (r^2) for the formulation from F0 to F30, the values of (r^2) for these formulations were greater than 0.985, indicating drug release follows zero- order kinetics.

Table 4. $T_{50\%}$ and MDT for different formulations.

Formulation	$T_{50\%}$ (h)	MDT	Formulation	$T_{50\%}$ (h)	MDT
F0	5.49	6.38	F16	6.47	10.58
F1	6.11	7.11	F17	5.17	7.55
F2	5.38	5.94	F18	4.46	6.73
F3	4.70	4.99	F19	5.56	6.42
F4	3.27	3.19	F20	6.58	7.23
F5	3.90	3.96	F21	6.92	9.23
F6	3.33	3.29	F22	7.81	11.93
F7	6.22	7.46	F23	8.51	13.80
F8	5.37	6.01	F24	9.01	17.09
F9	4.71	5.13	F25	6.88	8.47
F10	4.38	4.59	F26	6.55	8.02
F11	3.86	3.93	F27	6.42	7.76
F12	3.34	3.34	F28	6.20	7.34
F13	7.61	10.08	F29	5.43	6.22
F14	7.99	11.28	F30	4.65	5.03
F15	6.62	9.45	-	-	-

MDT: mean dissolution time.

shown in Table 2. All the r² values were higher than 0.985, indicating that the drug release rate followed zero order kinetics (Table 3).

Time required for 50% drug release ($T_{50\%}$) and mean dissolution time (MDT) were calculated from dissolution data and presented in Table 4. The MDT value was found

to be a function of surfactant type and its concentration. Lower MDT indicates a higher dissolution rate of the formulation.

Conclusion

The process of drug release from matrices involves many routes each to a varying extent, depending on the properties of the drug, as well as the polymer of matrices and additives such as surfactants. According to our results, the presence of the surfactants has an important role on the drug release rate improvement. The extent of drug release rate improvement relays on the physic-chemical properties such as concentration and solubility of surfactants.

ABBREVIATIONS

Cet, Cetrimide; **CPC,** cetylpyridinium chloride; **SLS,** sodium lauryl sulfate; **ST,** sodium taurcholate; **Bet,** betaine; **Form,** formulation; **CMC,** critical micelle concentration; **MgO,** magnesium oxide.

Conflict of interest

Authors reported none.

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