Full Length Research Paper

Formulation of propranolol hydrochloride controlled release tablets: Effect of surfactant charge and mechanisms of drug release

Hassan A. Alhmoud[1], Ehab I. El-Hallous[2,4]*, Nasser E. Ibrahim[3], Attia O. Attia[2,5] and ElDessoky S. Dessoky[2,5]

[1]Pharmaceutical Unit, Deanship of Scientific Research, Taif University, Taif, KSA.
[2]Biotechnology and Genetic Engineering Unit, Deanship of Scientific Research, Taif University, Taif, KSA.
[3]Bioinformatics Department, Biotechnology and Genetic Engineering Research Institute, Sadat City University, Sadat City, Egypt.
[4]Zoology Department, Faculty of Science, Suez Canal University, Al-Arish, Egypt.
[5]Plant Genetic Transformation Department, Agricultural Genetic Engineering Research Institute (AGERI), Agricultural Research Centre (ARC), 12619, Giza, Egypt.

Controlled release drug formulation is a very important branch in pharmaceutical industry and attracts a lot of research and investments. Eudragit RL100 and sodium carboxymethylcellulose (NaCMC) are used in drug formulation due to their good coating properties. Here, we studied propranolol hydrochloride formulation with anionic polymer Eudragit RL100 alone and with other additives (lactose, sorbitol, dextrose). The formulation was also studied with Eudragit RL 100 and sodium carboxymethyl cellulose (NaCMC) with different concentrations and with other surfactants (Sodium lauryl sulfate, Sodium taurcholate, Cetrimide, Cetylpiridiniumc chloride and Betaine). The results showed that propranolol hydrochloride was completely released in less than four hours when the tablets were prepared from Eudragit RL100 alone or with lactose, sorbitol or dextrose. In contrast, when the tablets were prepared with Eudragit RL100 and NaCMC, a controlled release rate of the drug was observed. The kinetics and mechanism(s) of the drug release were discussed.

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

INTRODUCTION

Controlled release drug formulation is considered as one of the most important branches in pharmaceutical industry. It attracts a lot of research and investment to decrease patients suffering from taking daily multiple

doses and to enhance drug release efficiency. Several studies have been focused on the effect of the surfactants on the drug release rate from controlled-release matrices. These studies showed the ability of surfactants to increase the drug release rate through many different mechanisms (Effentakis, 1992b; Wells and Parrott, 1992; Nokhodchi et al., 1999; Michael et al., 2004; Jamzad and Fassihi, 2006). The surfactant charge effect on the drug release rate also has been widely discussed. Studies showed the ability of the surfactant to increase or decrease the drug release rate according to the charges of the drug and the surfactant (Feely and Davis, 1988; Dredan et al., 1998; Bolourtchian et al., 2005).

The drug release rate from controlled-released matrices is mainly relying on the composition of the matrices and their properties. Many studies have been conducted to figure out 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 (Effentakis et al., 1991; 1992a) and hydrophilic–hydrophobic polymers (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).

Nonionic surfactant Tween 80 was found not to be a good solvent for the amphoteric poorly soluble drug enrofoxacin, whereas ionic surfactants sodium dodecyl sulfate (SDS) was found to be much better solvent as compared to the cationic surfactant cetyl trimethyl ammonium bromide (CTAB) (Seedher 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 carvedilolphosphate (CP) at different pH values, 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).

The aim of the present research was to study the effects of surfactant charge, solubility and the 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, cetrimide and sodium lauryl sulphate were kindly donated from Arab Pharmaceutical Manufacturing Co., Jordan. Eudragit RL100 was purchased from Rohm Pharma. Sodium taurcholate and cetylpyridinium chloride were purchased from Fluka. Betaine was purchased from TCI. Magnesium stearate was purchased from BDH chemicals Ltd. NaCMC was purchased from FMC.

Tablets preparation

The anionic polymer Eudragit RL100 was powdered and sieved through 300 μm sieves. Formulations, as listed in Table 1, were prepared to evaluate the release rate of propranolol hydrochloride. The ingredients were blended for 5 min in a blender and tablets weighing 400 mg were compressed using direct compression technique, with a single punch tablet machine (Korch-Erweka). The diameter and thickness of the tablets were 1 and 0.4 cm, respectively. The hardness of compressed tablets was adjusted to hardness level of about 9 kg (Al-Hmoud, 2002).

In vitro dissolution study

The United State Pharmacopoeia (USP) basket method (Erweka, DT 6R, Heusenstamm, Germany) was used for all the *in vitro* dissolution studies. The test was performed at 37 ± 0.1°C with a rotation speed of 50 rpm using 900 ml of 0.1 N HCl, pH 1.2, as a dissolution medium. Samples of 5 ml were withdrawn and immediately replaced with an equal volume of the respective dissolution medium maintained at 37 ± 0.1°C. Test samples were filtered through 0.45 μm filter, and assayed for propranolol hydrochloride at 289 nm using a blank solution as reference with a UV-Vis double-beam spectrophotometer (Systronics 2202). The mean of three determinations was used to calculate the drug release rate from each of the formulations (Al-Hmoud et al., 2014). The cumulative percentage of propranolol hydrochloride dissolved was calculated using a regression equation generated from the standard data.

Kinetics and mechanism of release analysis

The data obtained from *in vitro* drug release studies were plotted according to various kinetic models to study the release kinetics. For zero order (Equation 1) that describes concentration independent drug release rate from the formulation, cumulative amount of drug released plotted versus time (Figure 1):

$$C = k_0 t \qquad\qquad (1)$$

where k_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. For first order (Equation 2) that describes concentration dependent drug release from the system, log cumulative percent drug remaining plotted versus time (Figure 2):

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

Ingredient (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Mg Stearate							1						
EudragitRL100	69	69	69	79	59	40	20	10	10	10	10	10	10
NaCMC	0	0	0	0	20	39	59	69	69	69	69	69	69
Dextrose	10	-	-	-	-	-	-	-	-	-	-	-	-
Sorbitol	-	10	-	-	-	-	-	-	-	-	-	-	-
Lactose	-	-	10	-	-	-	-	-	-	-	-	-	-
SLS	-	-	-	-	-	-	-	-	0.5	-	-	-	-
ST	-	-	-	-	-	-	-	-	-	0.5	-	-	-
Cet.	-	-	-	-	-	-	-	-	-	-	0.5	-	-
CPC	-	-	-	-	-	-	-	-	-	-	-	0.5	-
Bet.	-	-	-	-	-	-	-	-	-	-	-	-	0.5

Each tablet contains 1% Mg Stearate, 80 mg of Propranolol HCl and different concentrations of Eudragit RL100 and/or NaCMC and other additives.
NaCMC, Sodium carboxymethyl cellulose; Cet, cetrimide; CPC, cetylpyridinium chloride; SLS, sodium lauryl sulfate; ST, sodium taurcholate; Bet, betaine.

Table 2. Fitting parameters with different kinetic release models.

Batch	Zero order		First order		Higuchi		Korsmeyer-Peppas			Hixson-Crowell	
	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n	K_{KP}	r^2	K_{HC}
F1	0.461	8.41	0.986	0.040	0.914	24.51	0.962	-8.170	0.33	0.530	-0.472
F2	0.570	9.51	0.980	0.050	0.914	27.72	0.968	2.230	0.39	0.700	-0.571
F3	0.611	9.96	0.977	0.050	0.914	29.03	0.971	1.040	0.42	0.800	-0.607
F4	0.710	11.50	0.962	0.070	0.914	33.52	0.980	0.200	0.52	0.770	-0.640
F5	0.826	12.31	0.945	0.080	0.914	35.88	0.986	0	0.60	0.908	-0.688
F6	0.941	12.66	0.912	0.108	0.914	36.91	0.993	-0.180	0.72	0.930	-0.606
F7	0.985	8.70	0.872	0.129	0.914	25.36	0.997	-0.170	0.82	0.970	-0.199
F8	0.976	6.31	0.902	0.113	0.914	18.39	0.994	-0.100	0.75	0.987	-0.125
F9	0.980	5.80	0.900	0.115	0.914	16.91	0.994	-0.101	0.76	0.985	-0.111
F10	0.983	6.20	0.983	0.118	0.914	18.07	0.995	-0.110	0.77	0.990	-0.122
F11	0.978	6.96	0.902	0.114	0.914	20.29	0.994	-0.106	0.75	0.992	-0.143
F12	0.985	7.33	0.887	0.122	0.914	21.37	0.996	-0.134	0.79	0.996	-0.152
F13	0.973	6.40	0.908	0.110	0.914	18.65	0.994	-0.090	0.74	0.986	-0.129

Fitting parameters obtained with Zero order, First order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell release models.

$$\text{Log } C = \text{Log } C_0 - k_1 t/2.303 \qquad (2)$$

where C is the initial concentration of drug and k_1 is the first-order constant.

Higuchi's model (Higuchi, 1961) (Equation 3) describes the release of drugs based on Fickian diffusion as a square root of time-dependent process from swellable insoluble matrix. Cumulative percentage of drug released plotted versus square root of time (Figure 3):

$$Q = k_H t^{1/2} \qquad (3)$$

where k_H is the constant reflecting the design variables of the system. Hixson-Crowell's model (Hixson and Crowell, 1931) (Equation 4) correlates the release from systems with polymer erosion/dissolution resulting in a change in surface area and diameter of particles or tablets. The cube root of percentage drug remaining plotted versus time (Figure 4):

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC} t \qquad (4)$$

where Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in the tablet, and k_{HC} is the constant rate for the Hixson-Crowell rate equation.

For mechanism of drug release, Korsmeyer-Peppas's model (Korsmeyer et al., 1983; Peppas, 1985) (Equation 5) describes drug release from a polymeric system. The values of 60% drug release data were fitted in (Figure 5).

$$M_t/M_\infty = M_{KP} t^n \qquad (5)$$

where M/M is fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as shown in Table 2 for cylindrical shaped matrices.

Table 3. Diffusion exponent (n) and drug release mechanism for cylindrical shape.

Diffusion exponent (n)	Mechanism of drug release
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

RESULTS AND DISCUSSION

A lot of research is carried out to produce controlled release formulation. Here, we studied the formulation of propranolol hydrochloride with Eudragit RL100 alone (F4) or with addition of lactose, sorbitol, and dextrose (F1, F2 and F3, respectively) (Table 1). The results showed that the drug released in less than three hours (Figure 1). The drug release in the presence of these excipients could be ordered in lactose, sorbitol then dextrose. Lactose is less soluble (Martindale, 1996) than sorbitol or dextrose, the viscous adhesive layer that was formed around the tablets containing sorbitol or dextrose retarded the drug diffusion. Drug release in F4 took less than 4 h. This result may be attributed to the dissolution of propranolol hydrochloride from the surface of the hydrophobic matrix Eudragit RL-100 and gradually through wide pores formed within the tablets during the first hours of the dissolution (Martindale, 1996).

To study the effect of the hydrophobicity of Eudragit RL100 on drug release, a hydrophilic polymer NaCMC was added to the formulations (Table 1). The results revealed that increasing the percentage of NaCMC in the formulations (F5, F6, F7 and F8) led to a decrease in the drug release rates from F5 to F8, in comparison with F4 with no NaCMC (Figure 1).

To study the effect of surfactants on the drug release rate of propranolol hydrochloride, F8 was used as the base formulation. The addition of anionic surfactants SLS (F9) and ST (F10), cationic surfactants CP (F11) and cetrimide (F12), and amphoteric surfactant betaine (F13). The concentration of all the surfactants was 0.5% (Table 1).

The results showed that the drug release rate decreased with the addition of anionic surfactants in F9 and F10 (Figure 2). This decrease may be due to the opposite charge of the cationic drug propranolol HCl, which formed a poorly soluble complex with the anionic surfactants (Daly et al., 1984; Feely and Davis, 1988; Nokhodchi et al., 2002; Bolourtchian et al., 2005). In addition, the presence of cationic charge of the quaternary ammonium group within Eudragit RL100, also decrease the drug release rate as reported before (Efentakis et al., 1992b).

The decrease in the drug release rate was less with ST than that with SLS. These results might be attributed to the difference in solubility between these two surfactants (Martindale, 1996) or the micelles formed were small enough to reduce the drug release as that formulations with SLS, because according to practical experiments it was discovered that the CMC of ST is about 0.5%. These results could be attributed to the different wetting effects of these two surfactants on the tablets (Efentakis et al., 1992a).

Contrarily, the addition of surfactants with the same charge to the drug, like CP and cetrimide (F11 and F12, respectively) leads to increase in the drug release rate (Figure 2). This increase may be attributed to the high solubility of the surfactants in the dissolution medium and their wettability effects, leading to an increase in the size of the pores within the swollen matrix. This increase in pore size resulted in an increase in the drug release rate. The addition of cetrimide (F12) resulted in a greater increase in drug release from the tablet than the addition of CPC did. This result may be due to the difference in solubility between the two surfactants (Martindale, 1996) or the formation of a cloudy area around the surface of the tablet which reduces the increase of drug release. While the amphoteric surfactant betaine (F13) has no effect on the drug release rate.

Several kinetic models can be used to describe the drug release from its formulation. The criterion used to choose the suitable drug release model is the correlation coefficient (r) value. The highest square correlation coefficient (r^2) value is the best model fit. The data fitted against zero order kinetic (Figures 1 and 2), first order kinetic (Figure 3), Higuchi kinetic (Figure 4), Korsmeyer-Peppas kinetic (Figure 5) and Hixson-Crowell kinetic (Figure 6).

The r^2 values (r = 0.977 – 0.986) obtained for fitting the drug release data of F1, F2 and F3 indicated that the drug release mechanism is first order kinetics, or in other word drug release rate depends on drug concentration. While F4 showed Korsmeyer-Peppas model with n value of 0.2 characteristic of anomalous kinetics (non-Fickian) (Table 3).

All other formulations (F5 to F13) showed r^2 values best fitted with Korsmeyer-Peppas model. The n values ranged between -0.18 and 0, suggesting that more than one mechanism may be involved in release kinetics (Table 2).
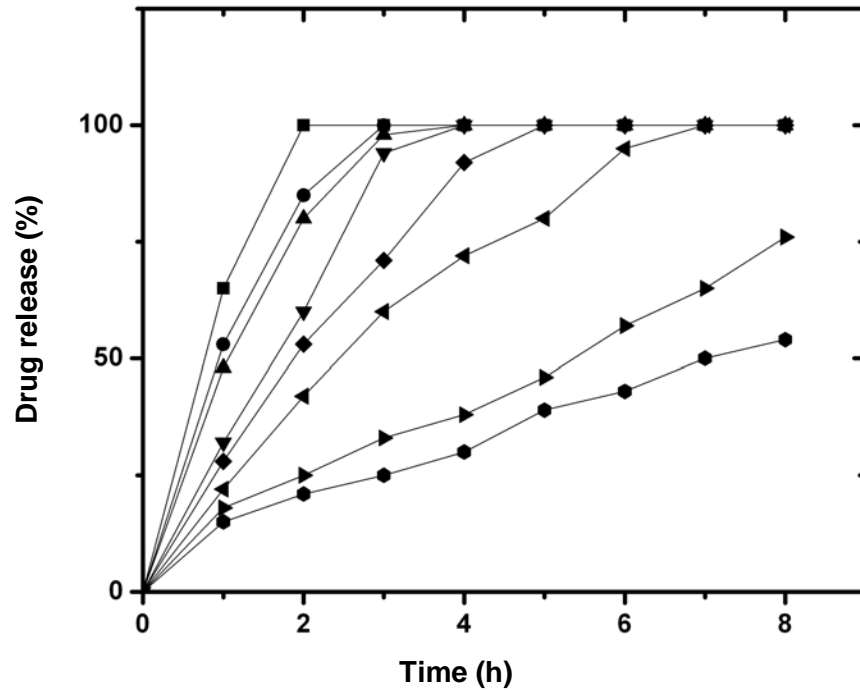
Figure 1. Propranolol-HCl release rates different formulation. The effect of different concentration combination of Eudragit RL100 and/or NaCMC and other additives on propranolol–HCl release rate (solid line with solid symbols are as follow, F1: Square, F2: Circle, F3: Triangle-up, F4: Triangle-down, F5: Diamond, F6: Triangle-Left, F7: Triangle-Right, F8: Hexagonal).
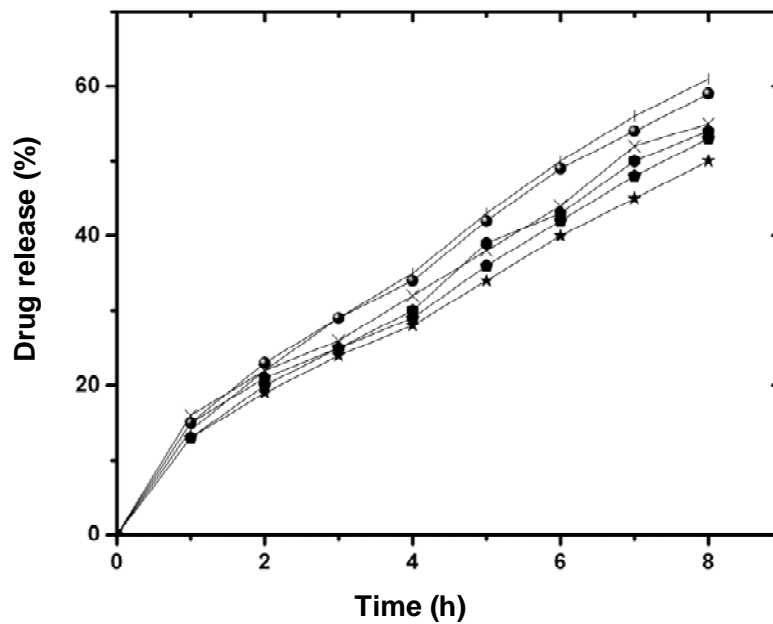

Figure 2. Propranolol-HCl release rates of different formulation. The effect of constant ratio of Eudragit RL100 and NaCMC with addition of different surfactants on propranolol–HCl release rate (solid line with solid symbols are as follow: F8: Hexagonal, F9: Star, F10: Pentagon, F11: Marked circle, F12: Vertical line, F13: Crossed line).
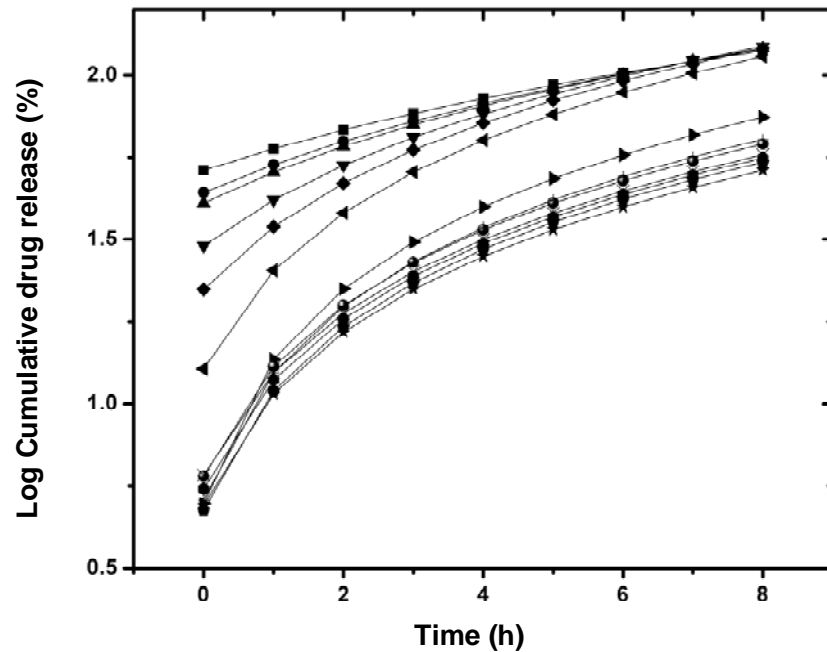
Figure 3. Plotting data with first order kinetic model. The logarithmic cumulative percentage of the drug release was plotted against time to fit data with the first order kinetic. Data were presented as solid line with solid symbols as follow, F1: square, F2: circle, F3: Triangle-up, F4: Triangle-down, F5: Diamond, F6: Triangle-Left, F7: Triangle-Right, F8: Hexagonal, F9: Star, F10: Pentagon, F11: Marked circle, F12: Vertical line, F13: Crossed line.
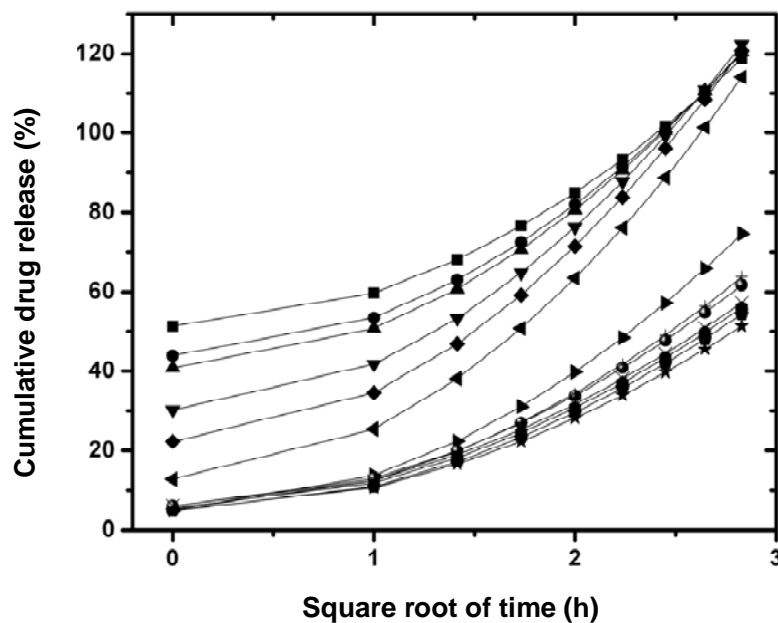
Figure 4. Plotting data with Higuchi kinetic model. The cumulative percentage of the drug release was plotted against square root of time to fit data with the Higuchi kinetic. Data were presented as solid line with solid symbols as follow, F1: square, F2: circle, F3: Triangle-up, F4: Triangle-down, F5: Diamond, F6: Triangle-Left, F7: Triangle-Right, F8: Hexagonal, F9: star, F10: Pentagon, F11: Marked circle, F12: Vertical line, F13: Crossed line.
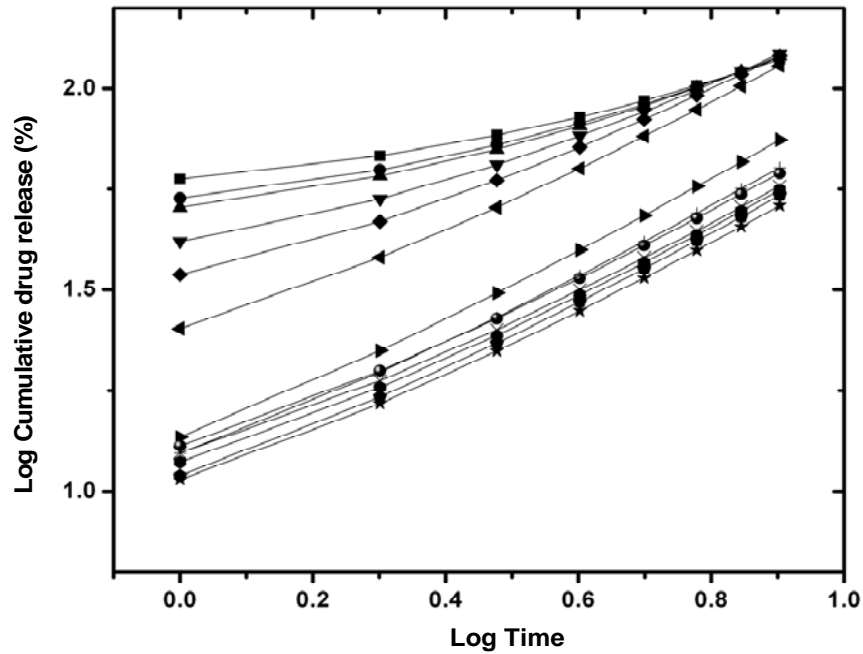
Figure 5. Plotting data with Korsmeyer-Peppas kinetic model. The logarithmic cumulative percentage of the drug release was plotted against logarithmic time to fit data with the Krosmeyer-Peppas kinetic. Data were presented as solid line with solid symbols as follow, F1: square, F2: circle, F3: Triangle-up, F4: Triangle-down, F5: Diamond, F6: Triangle-Left, F7: Triangle-Right, F8: Hexagonal, F9: star, F10: Pentagon, F11: Marked circle, F12: Vertical line, F13: Crossed line.
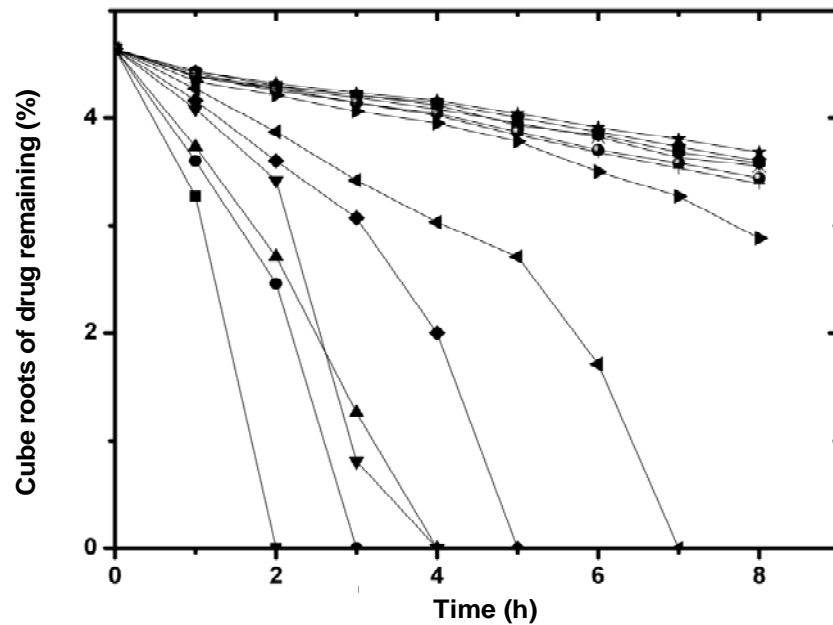
Figure 6. Plotting data with Hixson-Crowell kinetic model. The cube roots of the drug remaining percentage was plotted against time to fit data with the Hixson-Crowell kinetic. Data were presented as solid line with solid symbols as follow, F1: square, F2: circle, F3: Triangle-up, F4: Triangle-down, F5: Diamond, F6: Triangle-Left, F7: Triangle-Right, F8: Hexagonal, F9: star, F10: Pentagon, F11: Marked circle, F12: Vertical line, F13: Crossed line.

Conclusions

The type of surfactants used in drug formulation and their charges as compared to drug charge can influence the drug release rate remarkably. Surfactants that have the same charge as that of the drug lead to an increase in the drug release rate in a different manner, whereas surfactants with opposite charge lead to a decrease in the drug release rate.

Conflict of Interests

The author(s) have not declared any conflict of interests.

Abbreviations: NaCMC, Sodium carboxymethyl cellulose; **Cet,** cetrimide; **CPC,** cetylpyridinium chloride; **SLS,** sodium lauryl sulfate; **ST,** sodium taurcholate; **Bet,** betaine; **Form,** formulation; **CMC,** critical micelle concentration; **MgO,** magnesium oxide.

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