Formulation and evaluation of diclofenac controlled release matrix tablets made of HPMC and Poloxamer 188 polymer: An assessment on mechanism of drug release

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Abstract: In this study, hydrophilic hydroxypropyl methylcellulose matrices with various concentrations of Poloxamer 188 were used in the development of oral controlled release tablets containing diclofenac sodium. Four formulations of hydrophilic matrix tablets containing 16.7% w/w HPMC and 0, 6.7, 16.7 and 25.0% w/w Poloxamer 188, respectively, were developed. Tablets were prepared by direct compression and characterized for diameter, hardness, thickness, weight and uniformity of content. The influence of various blends of hydroxypropyl methylcellulose and Poloxamer 188 on the *in vitro* dissolution profile and mechanism of drug release of was investigated. In the four formulations, the rate of drug release decreased with increasing the concentration of Poloxamer 188 at the initial dissolution stages due to the increase in the apparent viscosity of the gel diffusion layer. However, in the late dissolution stages, the rate of drug release increased with increasing Poloxamer 188 concentration due to the increase in wettability and dissolution of the matrix. The kinetic of drug release from the tablets followed non-Fickian mechanism, as predicted by Korsmeyer-Peppas model, which involves diffusion through the gel layer and erosion of the matrix system.

Keywords: Poloxamer 188, iclofenac sodium, hydroxypropyl methylcellulose, dissolution rate, controlled release.

INTRODUCTION

Controlled release delivery systems are modified-release systems, which are designed to deliver drugs at programmed and predetermined rates (Arafat, 2015). They are prepared by homogeneously dispersing the active ingredient into either a water-soluble or water-insoluble polymeric matrix (Bhattari *et al.,* 2010). Several polymers have been widely used in controlled-released delivery systems such as methylcellulose (Ebube and Jones, 2004), ethyl cellulose (Samani *et al.,* 2003), hydroxypropyl cellulose (Bhattari *et al.,* 2010), hydroxypropyl methylcellulose (HPMC) (Tiwari and Rajabi-Siahboomi, 2008), sodium carboxy methylcellulose (Samani *et al.,* 2003), cellulose acetate phthalate (Giri *et al*., 2012), chitosan (Giri *et al.,* 2012), ethyl acetate (Tiwari and Rajabi-Siahboomi, 2008), methacrylic acid copolymers (Tiwari and Rajabi-Siahboomi, 2008), gur gum (Kamal *et al.,* 2017) and polymers of acrylic acid (Tiwari and Rajabi-Siahboomi, 2008) It has been shown that polymer type and concentration (Tiwari and Rajabi-Siahboomi, 2008), polymer molecular weight (Viriden *et al.,* 2010), polymer viscosity grade (Velsco *et al.,* 1999), polymer to drug ratio (Velsco *et al.,* 1999), drug solubility (Arafat, 2012; Arafat *et al.*, 2017), drug permeability (Arafat, 2016; Arafat *et al.,* 2017), formulation composition (Cao *et al.,* 2005), drug loading (Golocorbin-Kon *et al.,* 2009) and matrix shape play a significant role in controlling the release of drug from matrix systems (Tiwari and Rajabi-Siahboomi, 2008).

Recently, the use of the water-soluble polymer HPMC as polymeric platform for oral controlled release formulations has attracted increased attention (Cao *et al.,* 2005). HPMC is characterized by its non-toxic (Cao *et al.,* 2005) and non-ionic nature (Kofi *et al.,* 2006), pH-independent drug release (Kofi *et al.,* 2006), ease of manufacturing through direct compression or granulation (Ebube and Jones, 2004), and availability in different viscosity grades resulting in versatile drug release profiles (Kofi *et al.,* 2006). In addition, HPMC offered a high level of drug loading efficiency (Batravoka *et al.,* 2008). It is characterized by thermal gelation properties (Batravoka *et al.,* 2008) and high swell ability (Batravoka *et al.,* 2008), which controls the drug release kinetics. Drug release from HPMC matrices is controlled by the hydration of the polymeric matrix. Upon water penetration into the matrix, a viscous gel layer is formed

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which acts as a barrier and controls drug release (Samani *et al.,* 2003).

In this study, the hydrophilic polymer Poloxamer 188 was added to HPMC matrix tablets to modulate drug release profile. Poloxamer 188 is a nonionic surfactant composed of tri-block co-polymers of two hydrophilic poly(ethylene oxide) (PEO) and one hydrophobic poly(propylene oxide) (PPO), [PEO-PPO-PEO] (Batravoka *et al.,* 2008). Upon its incorporation into the polymeric marix, it can enhance drug solubility within the matrix and accelerates drug release (Kolasinac *et al.,* 2012). It has a lower molecular weight and higher hydrophilic proportion, compared to other Poloxamer 188 grades with high HLB value of 29 (Kolasinac *et al.,* 2012).

Diclofenac sodium (DFN) was chosen as a model drug for this study, in which, a combination of two hydrophilic polymers HPMC and Poloxamer 188 was used as a matrix system to modulate its release profile. To the best of our knowledge, no study has been carried out yet to evaluate the *in vitro* dissolution profile and mechanism of release of DFN from matrix tablets containing the two hydrophilic polymers, HPMC and Poloxamer 188. The incorporation of Poloxamer 188 may effectively modulate DFN release from hydrophilic matrices by facilitating gel layer formation upon rapid hydration of the polymeric blend. This gel layer acts as a diffusion barrier which controls the release of drug. Therefore, the objective of this study was to formulate various formulations of DFN controlled release matrix tablets using HPMC and Poloxamer 188 and investigate the effect of Poloxamer 188 concentrations on the rheological properties, *in vitro* release profile and mechanism of drug release.

MATERIALS AND METHODS

Chemicals

Diclofenac sodium (DFN) was supplied by REFARMED Chemicals (Switzerland). Microcrystalline cellulose (MCC, Avicel 102) was supplied by FMC Biopolymer (PA, USA). Poloxamer 188 (Lutrol® F68) was supplied by BASF (Ludwigshafen, Germany). Mg stearate was supplied by Orion Pharma (Espoo, Finland). Hydroxypropyl methylcellulose (HPMC, Methocel® K4M) was a gift from Colorcon® (Dartford, UK). Methanol was obtained in high-performance liquid chromatography (HPLC) grade from Merck (Darmstadt, Germany). Distilled water was used in all experiments.

Apparent viscosity measurements

The apparent viscosity of 1% HPMC solutions containing 0.00, 0.20, 0.50 and 0.75% of Poloxamer 188 was measured at 37°C using a cone and plate rheometer (Thermo Haake Rheo Stress® 1 rheometer, HAAKE, 30 mm diameter, 1° cone angle). Samples were dispersed in distilled water at 25°C and kept overnight. For each experiment, 3 mL of solution was loaded onto the plate and spread evenly over the entire surface area. Samples were allowed to relax and equilibrate at 37°C for 1 min. The upper cone was lowered until the gap between the cone and plate was 0.054 mm. The apparent viscosity was obtained from the slope of linear part (from 8 to 16 s^{-1}) of the shear strain versus shear rate plot. The apparent viscosity of the four polymeric solutions was determined for at least three independent samples.

Preparation of powder mix of matrix tablets

Four powder mix of matrix tablet formulations (F1, F2, F3 and F4) were prepared to contain 0, 6.7, 16.7 or 25%w/w Poloxamer 188, 33.3%w/w DFN, 16.7% w/w HPMC, and 1%w/w Mg- stearate. MCC was used as diluent to obtain a final mass of 300 mg per tablet. The amount of DFN and HPMC was held constant at 100 and 50 mg per tablet, respectively. The concentration of Poloxamer 188 was varied in the formulations. Table 1 illustrates the composition of the matrix tablet formulations. All ingredients, except Mg stearate, were sieved through 0.6 mm mesh screen and mixed in a powder mixer for 10 min. At the end, 1%w/w Mg stearate was added and mixed manually. Tablets were prepared by direct compression using a single punch tablet press (Manesty F3 machine, UK) with 9-mm concave punches.

Characterization of matrix tablets

Tablets of the four formulations were characterized by weight, hardness, thickness, diameter and content uniformity. The weight was obtained using an analytical balance (Sartorius, Germany). The hardness was determined using a hardness tester (Holland C50, UK). The tablet thickness and diameter were measured using a micrometer (Mitutoyo 700-118-20, USA). For weight variation, thickness and diameter tests, a sample of 10 tablets of each formulation was used. Hardness was determined for four tablets of each formulation. The sample mean and standard deviation were calculated for each test. The amount of DFN in each tablet of the four formulations was assayed using an UV-spectrophotometric method. Briefly, four tablets of each formulation were crushed and a mass correspondent to 100 mg DFN was transferred to a volumetric flask of 100 mL. The material was diluted in methanol and sonicated for at least 15 min. The mixture was filtered and properly diluted with the same solvent. The concentration of DFN was determined by UV spectrophotometer (Varian, Cary 50 UV/VIS spectrophotometer, UK) at 281 nm using a standard calibration curve of DFN prepared in methanol.

In vitro dissolution studies

The *in vitro* dissolution of DFN from the matrix tables of each formulation was monitored using the USP paddle method apparatus 2 (Sotax AT7 CH- Switzerland), at a rotation speed of 100 rpm in 1000 mL of distilled water maintained at 37.0±0.5°C. At predetermined time

intervals of 30, 90, 150, 210, 270, 330, 390, 450, 510, 570, 630, 690 and 1410 min, 5 mL of the medium was sampled and filtered. After sampling, the vessel was replaced with an equal volume of fresh dissolution medium, pre-warmed to 37.0±0.5°C, was maintained at a constant volume. The concentration of DFN in each sample was determined by UV spectrophotometry (Varian, Cary 50 UV/VIS spectrophotometer, UK) at 281 nm after appropriate dilution using a standard calibration curve of DFN prepared in distilled water. Dissolution tests were performed in triplicate for tablets of each formulation. The cumulative percentage of DFN release was calculated and the mean and standard deviation were used in the data analysis. For each formulation, the dissolution testing was run in replicates of three batches (n=3).

Mechanism of drug release

The mechanism of release of DFN from the matrix tablets of the four formulations were studied by fitting the dissolution data into equation (1) (Korsmeyer *et al*., 1983)

$$Q = Kt^n \qquad \text{Equation (1)}$$

Where Q is the fraction of drug released at time (t), K is a kinetic release constant incorporating structural and geometrical characteristic of the tablets, and n is the release exponents which indicate the drug release mechanism. The value of n = 0.5 represents Fickian release, 0.5 < n < 1.0 represents non-Fickian release (anomalous), n = 1.0 represents the case II (zero order) kinetic release, and n > 1 for super case II type of release (11). The exponent n is obtained from the initial data of the drug release profile (Q < 0.60) (Joshi, 2011).

Intrigues response surface and contour plot

The effects of the time and Poloxamer 188 concentration the on the release rate of DFN was evaluated using 3D figs. The regression polynomial was calculated using SPSS statistical software and was applied to approximate the response surface and contour plots using the PC based software Mathematica.

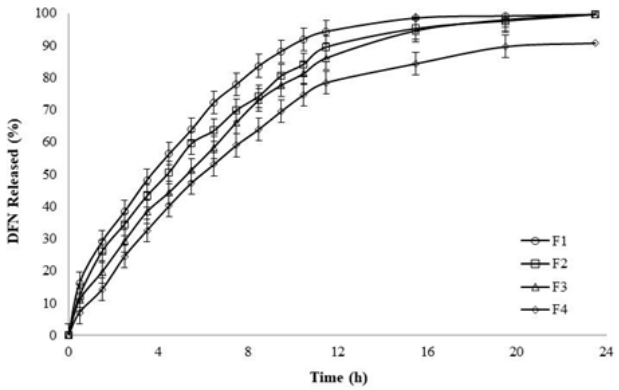
STATISTICAL ANALYSIS

A statistical analysis was performed using one-way analysis of variance to compare mean value of each variable. The result was considered statistically significant when $p<0.05$.

RESULTS

Rheological characterization of HPMC and poloxamer 188 solutions

Table 2 illustrates the apparent viscosity of 1% HPMC solution and with the addition of 0.20, 0.50 and 0.75% Poloxamer 188. We chose to work at a lower concentration of HPMC and Poloxamer 188 than that used in the matrix tablets. The apparent viscosity of 1% HPMC alone and with 0.20% Poloxamer 188 exhibited approximately equal values [33.9±2.0 mPas (n=3) and 33.9±3.1 mPas (n=3), respectively]. Upon the addition of 0.50% and 0.75% Poloxamer 188, the apparent viscosity values increased to 63.7±3.8 mPas (n=3) and 72.7±0.3 mPas (n=3), approximately 2-fold higher. Therefore, Poloxamer 188 enhanced the apparent viscosity of the HPMC at higher concentrations of 0.50 and 0.75%. In 1% HPMC without Poloxamer 188, an intermolecular hydrogen bonding between the hydroxyl groups of HPMC chains and water molecules is expected to be formed, that can lead to gelation. In solutions containing HPMC and Poloxamer 188, extra intermolecular hydrogen bonding is suggested to be formed between hydroxyl groups of HPMC chains and PEO and PPO blocks of Poloxamer 188. Thus, it can increase the viscosity of polymeric solutions. The apparent viscosity of these solutions could influence the dissolution and erosion rates of the matrix systems, thus affecting the rate of drug release from the matrix tablets.



* $p<0.05$ vs F1 without Poloxamer 188

Fig. 1: Dissolution profiles of DFN matrix tablets formulations. Data are represented as the mean ± SD (n=3).

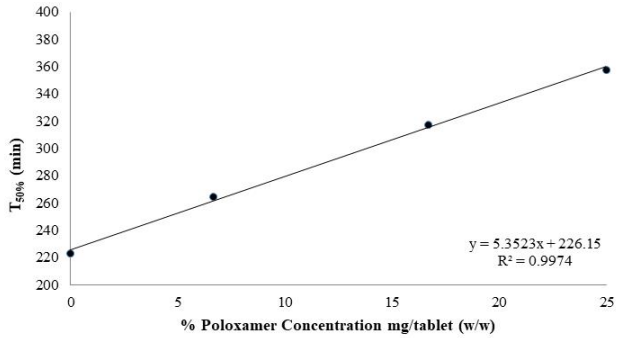


Fig. 2: Correlation between $T_{50\%}$ and Poloxamer 188 concentrations.

Characterization of matrix tablets

Table 3 presents the weight, hardness, thickness, diameter, and drug content of F1, F2, F3 and F4 matrix tablets. The

mean weight values of the F1, F2, F3 and F4 tablets were within the acceptance limit between 85.0 and 115.0% of the theoretical weight value of 300 mg. The mean crushing strength values for F1, F2, F3 and F4 matrix tables and the thickness of the F1, F2, F3 and F4 tablets was found to be within the acceptance limit as well.

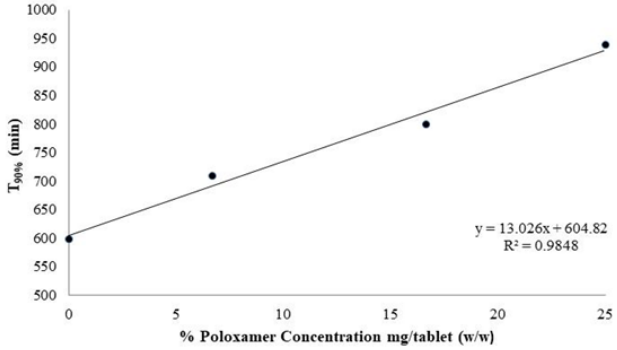


Fig. 3: Correlation between $T_{90\%}$ and Poloxamer 188 concentrations.

In vitro drug release

Considering the pKa value of 4, DFN has weak acidic properties (Velsco *et al*., 1999). Therefore, it is soluble in water and basic medium but insoluble in acidic medium. Therefore, water was used as a dissolution medium in this study. fig. 1 represents the dissolution profiles of F1, F2, F3 and F4 matrix tablets. $T_{50\%}$ and $T_{90\%}$ are parameters used to characterize drug release profile that correspond to the time necessary to release 50% and 90% of the drug, respectively. These parameters were obtained from the dissolution profiles and summarized in Table 4. In all matrix tablets, the percentage of drug release increased linearly with time. No lag time was observed in all the dissolution profiles.

In the matrix tablets F1, containing only HPMC. $T_{50\%}$ and $T_{90\%}$ were 196 and 569 min, respectively. At the end of 1410 min, 98.2% of the drug was released. At low Poloxamer 188 concentration (6.7%, F2), $T_{50\%}$ and $T_{90\%}$ were 260 and 1094 min, respectively. $T_{50\%}$ increased by 64 min compared to that of F1 (260 min versus 196 min) and $T_{90\%}$ increased by 525 min compared to that of F1 (1094 min versus 569 min). This statistically significant ($p<0.05$) increase in $T_{50\%}$ (fig. 2) and $T_{90\%}$ (fig. 2) indicates a reduction in the rate of DFN release from F2 matrix tablets. At the end of 1410 min, the amount of DFN released was relatively lower than F1 (~95%). As the concentration of Poloxamer 188 increased from 6.7 to 16.7% in F3 matrix tablets; $T_{50\%}$ and $T_{90\%}$, obtained from the dissolution data, were 265 and 862 min, respectively. $T_{50\%}$ increased by only 5 min than that of F2 (265 min versus 260 min). However, it was significantly ($p<0.05$) higher than that of F1 (265 min versus 196 min). In addition, $T_{90\%}$ was lower than that of F2 (862 min versus 1094 min) and higher than that of F1 (862 min versus 569 min). After 1410 min, 95.2% of DFN was released. At the highest Poloxamer 188 concentration (25.0%, F4), $T_{50\%}$ increased significantly ($p<0.05$) up to 285 min, representing the highest value for $T_{50\%,}$ compared to that of F1, F2 and F3 (196, 260 and 265 min, respectively). $T_{90\%}$ was reduced to 630 min, lower than that of F2 and F3 (1094 and 862 min, respectively), however, it was significantly ($p<0.05$) higher than that of F1 (569 min). After 1410 min, the percentage of DFN released reached 93.9%.

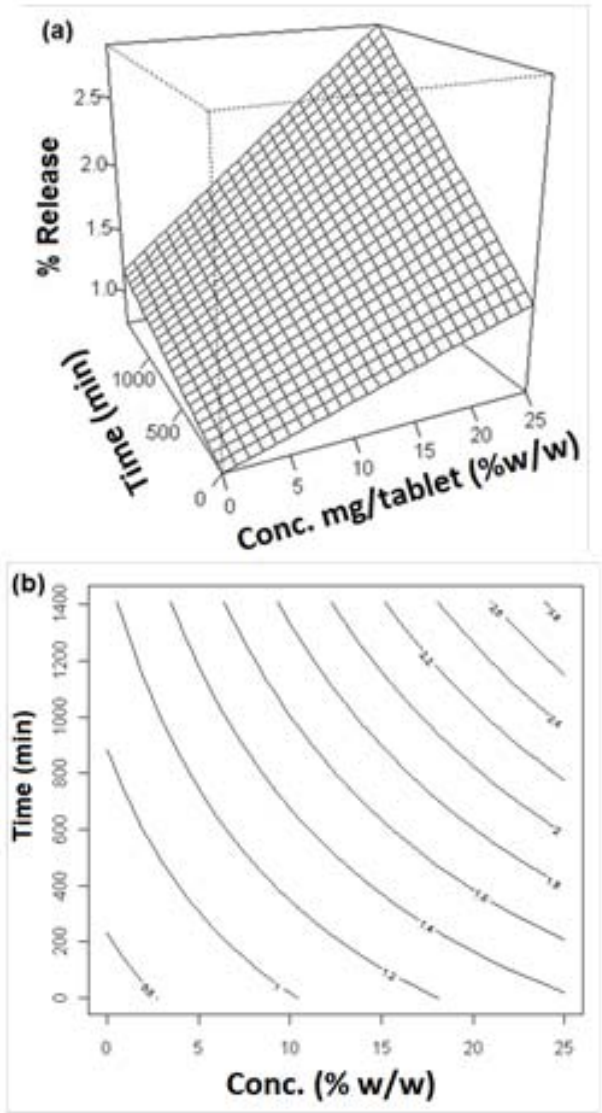


Fig. 4: Estimated response surface plot (a) and contour plot (b) illustrating the relationship between the percentages of DFN release from tablet matrix formulations prepared with various Poloxamer 188 concentrations.

The three dimensions of response surface plot (RSP) and contour plot (CP) are a collection of mathematical and statistical data generated from DFN tablets release experiments for empirical model building (Myers *et al*., 2011). By careful design of experiment runs, the objective is to optimize a response (output variable) of drug release

Table 1: Compositions of DFN matrix tablet formulations.

Components	Amount (mg/tablet) (%w/w)			
	F1	F2	F3	F4
DFN	100 (33.3%)	100 (33.3%)	100(33.3%)	100 (33.3%)
HPMC (K4M)	50 (16.7%)	50 (16.7%)	50 (16.7%)	50 (16.7%)
Mg stearate	3 (1.0%)	3 (1.0%)	3 (1.0%)	3 (1.0%)
Poloxamer 188	0 (0.0)%	20 (6.7%)	50 (16.7%)	75 (25.0%)
MCC	q.s. 300	q.s. 300	q.s. 300	q.s. 300

Table 2: The apparent viscosity of 1% HPMC and mixtures of 1%HPMC and different concentrations of Poloxamer 188 dispersion, Data are represented as mean ± SD (n=3).

Polymeric solutions (w/v)	Apparent Viscosity (mPas)
1% HPMC	33.9 ± 2.0
1% HPMC and 0.20% Poloxamer 188	33.9 ± 3.1
1% HPMC and 0.50% Poloxamer 188	63.7 ± 3.8
1% HPMC and 0.75% Poloxamer 188	72.7 ± 0.3

Table 3: Characterization of F1, F2, F3 and F4 matrix tablets, Data are represented as mean ± SD (n=3).

Matrix tablets	Mass (mg)	Thickness (mm)	Diameter (mm)	Drug Content (%)	Hardness (N)
F1	295.6 ± 5.3	5.25 ± 0.03	9.06 ± 0.01	88.1	48.1 ± 3.4
F2	309.8 ± 10.5	5.22 ± 0.02	9.04 ± 0.01	92.4	62.7 ± 15.2
F3	313.9 ± 6.8	5.15 ± 0.01	9.04 ± 0.01	91.0	71.7 ± 4.8
F4	309.4 ± 4.7	5.09 ± 0.01	9.03 ± 0.01	95.3	62.1 ± 5.0

Table 4: *In vitro* release kinetic values [$T_{50\%}$, $T_{90\%}$, exponent release constant (n), kinetic release constant (K), and coefficients of determination (R^2)] of matrix tablets.

Matrix tablets	$T_{50\%\ (min)}$	$T_{90\%\ (min)}$	n	K	R^2
F1	196	569	0.5494	0.4380	0.9970
F2	260	1094	0.5353	0.3967	0.9897
F3	265	862	0.5589	0.3327	0.9963
F4	285	630	0.6188	0.1722	0.9908

rate which is influenced by several independent variables (input variables) such as Poloxamer 188 concentration and time (min). The response surface and contour plot in fig. 4 (a) and (b) showed that the drug released rate from four matrix tablet formulations increased gradually with an increase in both Poloxamer 188 concentration and time. The profile exhibited by drug release response surface is 'hillside' and varies in linear slope fashion. With increasing in concentration of Poloxamer 188, the line gets steeper than response time in buffer medium, indicating that the effect of response time seems to be less effective as compared to that of Poloxamer 188 concentrations. This can be explained based on two independent factors that have an effect on the release rate of DFN from tablet matrix. These factors are 1- polymer concentrations (Poloxamer 188) and 2-timing. The slope of Poloxamer 188 vs DFN release rate is steeper than the slope of timing vs release rate. This variation in slope indicates the effectiveness of polymer concentrations on controlling DFN release rate from tablet matrix, the steeper the more controlled.

The maximum amount of drug release at higher values of Poloxamer 188 (25%) in the response time after 10 h showed in fig. 4. In the contour plot, the drug release response is a linear function for all values of concentration of Poloxamer 188 and at all the values of response time. This result demonstrated that the release rate of DFN showed steeper slop as the concentration of Poloxamer 188 increased in the formulation.

DISCUSSION

Based on the $T_{50\%}$ values of F1, F2, F3 and F4, $T_{50\%}$ increased with the addition of Poloxamer 188 to the matrix tablets. As the concentration of Poloxamer 188 increased, $T_{50\%}$ increased; prolonging the drug release time during the initial stages of the dissolution profiles. The profound slope of the line indicates that Poloxamer 188 concentration has high impact on $T_{50\%}$. On the other hand, values of $T_{90\%}$ showed that F1 (matrix tablets containing 0% Poloxamer 188) represented the lowest $T_{90\%}$ value. This indicates that DFN release in matrix

tablets containing no Poloxamer was faster compared to those containing Poloxamer 188. This indicates that the addition of Poloxamer 188 to the matrix tablets prolonged the drug release time during the late dissolution stages. It is apparent that increasing Poloxamer 188 concentration decreases $T_{90\%}$ (fig. 3), enhancing the rate of DFN release from matrix tablets during the late dissolution stages. The steep slope of the line indicates that Poloxamer 188 concentration has a high impact on $T_{90\%}$, suggesting a significant role of Poloxamer 188 on drug release mechanism during the late dissolution stages.

Drug dissolution profiles and the dissolution parameters $T_{50\%}$ and $T_{90\%}$ suggested that two mechanisms operated at different stages of the drug release process. In the initial stages, when the polymeric matrix tablet comes in contact with the dissolution medium, the polymer hydrates forming a gel layer on the surface. This gel layer acts as a barrier, which controls the diffusion of drug through the matrix. As the viscosity of the gel layer increases upon the addition of Poloxamer 188 (table 2), the penetration of dissolution medium into the strong gel network significantly reduced. As a result, the rate of dissolution of the matrix tablets decreased, retarding the release of DFN. Therefore, diffusion across the gel layer is the primary release mechanism for DFN from hydrophilic matrices during the initial dissolution stages.

During the late dissolution stages, the outer gel layer of HPMC of the F1 matrix tablets becomes fully hydrate, the polymeric barrier becomes completely relaxed and disentangled leading to erosion of the matrix ($T_{90\%}$ =569 min). Based on the $T_{90\%}$ values of F2, F3 and F4 matrix tablets, the rate of DFN release increases in the following order F4>F3>F2. As the concentration of Poloxamer 188 in the matrix tablets increased, $T_{90\%}$ decreased and the dissolution rate of DFN increases. This is attributed to the surface activity of the Poloxamer 188, which reduces the surface tension at the tablet interface, improving drug wettability and solubility. Therefore, erosion dominates in the late dissolution stages.

With respect to mechanism of DFN release, the dissolution data for the initial portion (the first 60% drug release data) of DFN release profiles of F1, F2, F3 and F4 matrix tablets was only used and fitted to the mathematical proposed by Korsmeyer-Peppas (Korsmeyer *et al.,* 1983). This model is generally used to describe drug release from hydrophilic polymeric systems and when the release mechanism is not known or involves more than one type of release mechanism (Korsmeyer *et al.,* 1983). In this model, the release mechanism was obtained by plotting log Q versus log t, where a straight line is obtained and n, which determines the mechanism of drug release, was obtained from the slope of the linear equation: $\log Q = n \log t + \log K$.

The n values for F1, F2, F3 and F4 matrix tablets are summarized in Table 4. The exponent release constant (n) was between 0.5 and 1.0 for all matrix tablets, indicating a non-Fickian release mechanism, where both diffusion and erosion occurred were taking place in the matrices. Comparing the n values of F2, F3 and F4 matrix tablets, n value increased with increasing Poloxamer 188 concentrations (table 4). This slight increase in n value indicates a greater role of matrix erosion. The non-Fickian release mechanism of DFN from the four matrix systems, obtained using the Korsmeyer-Peppas model (Korsmeyer *et al.,* 1983), where n is between 0.5 and 1.0, was in accordance with the *in vitro* dissolution studies.

CONCLUSION

The *in vitro* release of DFN from hydrophilic matrix tablets was governed by matrix hydration at the initial dissolution stages, where diffusion of drug through the gel layer predominate the drug release mechanism. However, at the late dissolution stages, Poloxamer 188 increased drug solubility and wettability, where matrix erosion predominate the drug release mechanism. The kinetic of drug release fits to Korsmeyer-Peppas model with diffusion and erosion mechanisms. These results indicate that the combination of HPMC and Poloxamer 188 may play an important role in modulating and controlling drug release from the hydrophilic matrix tablets.

ACKNOWLEDGMENTS

The authors wish to thank the Dana Pharmaceuticals Factory, Nablus-West Bank, Palestinian Authority for providing the MAR research grant in support of this work.

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