

## FORMULATION AND IN VITRO EVALUATION OF DICLOFENAC SODIUM SUSTAINED RELEASE MATRIX TABLETS USING CARNAUBA WAX AS A MATRIX FORMER

MOHAMMED K. AHMED\* AND YEHIA I. KHALIL\*\*

\*Department of Pharmaceutics, College of Pharmacy, University of Mosul, Mosul, Iraq, \*\*Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq. Email: hussein917@yahoo.com

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### ABSTRACT

**Objective:** The main objectives of the present study is to develop sustained release matrix tablet of diclofenac sodium (DS) using carnauba wax (CW) as a matrix former, in addition, polyethylene glycol (PEG<sub>6000</sub>) and polyvinyl pyrrolidone (PVP k30) were used as channeling agents to modify and control the release of DS from CW based matrix system.

**Methods:** The matrix tablet was prepared at different drug-polymer ratio namely 5:2, 5:3, 5:4 and 1:1. The physical properties and post compression parameters of all the prepared formulas were determined and studied. The in vitro dissolution studies were carried out for all formulas and compared to that of a reference marketed product using the similarity factor ( $f_2$ ) equation to choose the best formula.

**Results:** Formula (F9) showed the highest similarity with the reference marketed product and thus selected as the optimized formula. The release rate of DS from CW based matrix system was found to be affected by many factors including the concentration of the rate retarding polymer in the formula, type and concentration of the channeling agent used, type of filler used, pH of the medium, compression force and method of preparation of the sustained release granules. It was observed that the release rate decreased as the amount of the polymer increased in the formula, also the release rate of DS was highest in formulas contain PEG<sub>6000</sub>, lactose and in formulas prepared by solvent evaporation method. The dissolution data of the optimized formula were fitted to various release kinetic models in order to determine the principal mechanism responsible for release of DS from CW based matrix system.

**Conclusion:** Based on the results obtained from this study, it can be concluded that carnauba wax-polyethylene glycol (CW-PEG) system can be used successfully as a matrix former to sustain the release of DS to more than 8hrs. depending on amount of polymer used, PEG/CW ratio, pH of the system and method of preparation.

**Keywords:** Matrix tablet, Sustained release, Diclofenac Sodium, Carnauba wax.

### INTRODUCTION

Hydrophilic polymers alone are not so efficient in controlling the release of water soluble drugs. Hydrophobic polymers with or without pore forming agents have been extensively investigated for sustaining the release of drugs. They provide several advantages over hydrophilic polymers in that they show good stability profile over a wide pH-range with good drug retarding capacity and high ability to accommodate high drug load [1].

The matrix system is commonly used for manufacturing sustained-release dosage forms because it makes such manufacturing easy. Insoluble-erodible polymers and waxes are commonly utilized as matrix forming components and are extensively used for sustaining the release of drugs [2].

In spite of the recent technological advances in the fabrication of oral controlled-release dosage forms, particular attention has been paid to the regulation of drug release by means of monolithic devices [3].

Embedding a drug within an insoluble matrix provides a convenient mean of controlling the drug release. In such a system, drug release is preceded by penetration of the dissolution medium into the porous matrix to dissolve the drug, followed by diffusion of the dissolved molecules out of the matrix. Solid drug on the matrix surface will be dissolved and released first to provide an immediate shot of the drug. Upon exhaustion of the surface drug, the depletion zone will then increased progressively and sustained drug release is achieved. In such a system, the release rate is a function of the square root of time and liquid penetration to the matrix is the rate limiting step in drug release unless channeling agent is used [4]. Carnauba wax, due to its ease of handling, safety of application, high drug embedding ability, compatibility and chemical inertness has been chosen and used in this study as rate retarding polymer or matrix former.

DS (sodium 2-[2, 6-dichlorophenyl] amino] phenyl] acetate is a sparingly water soluble drug, it is aryl acetic acid derivative having a non-selective COX inhibitor activity. It is a non steroidal anti-inflammatory, antipyretic analgesic official in the Martindale Extra Pharmacopeia for long term treatment of rheumatoid arthritis, osteoarthritis and other painful and inflammatory conditions. It has a plasma half life of about 1.5 hrs which necessitate frequent dosing. The most troublesome side effects are gastrointestinal and are dose related. The dose of DS in adult individuals is 100-300mg/day. The sustained release dosage form is thus required to improve the bioavailability of drug, reduce the severity of side effects and improve the patient compliance by giving the drug on once or twice daily basis [5].

### MATERIALS AND METHODS

#### Materials

DS (Loba laboratories, India). Carnauba wax (BDH, England). Lactose (The Lactose Co. of New Zealand, New Zealand). PEG<sub>6000</sub>, PVP K<sub>30</sub> (FMC Biopolymer, USA). Dibasic calcium phosphate dihydrate (Haward Pharmaceuticals Limited. Bangalore. India). All other reagents used were of analytical grade.

#### Methods

##### Preparation of the monolithic system by melt granulation or fusion method

Fusion method is done by melting the rate retarding polymer gradually in beaker on a hot plate (90°C) with continuous mixing, then adding drug material that is pre pulverized and passed through mesh No. 60, diluents and any other additive to the molten mass with continuous stirring until a homogeneous mixture is produced, the molten mass is then allowed to cool and solidify at room temperature, crushed and screened (mesh No. 20) to produce granules of wanted size, which stored properly for further studies[6].

### Preparation of the monolithic system by solvent evaporation method

Solvent evaporation method is generally done by dissolving the rate retarding polymer in a little amount of chloroform that is pre warmed with mixing until a thin suspension is produced, there after adding the drug, diluent and any other additive to the previous suspension with continuous stirring till a thick suspension is achieved which is then sprayed on a hot surface to facilitate the removal of the solvent forming a uniform mass that crushed, dried and screened (mesh No. 20) to produce granules of wanted size, which stored properly for further studies [7].

### Preparation of DS SR Matrix Tablet

Table (1) shows the composition of all formulas of DS matrix tablet. The granules (whether prepared by fusion or solvent evaporation method) are accurately weighed and mixed with the exact amount of talc for 3min by tumbling in stoppered bottle, thereafter take exactly 300mg of the above mixture and feed manually to a 9mm die of flat face single punch tablet press and compress to a tablet using a compression force of 6 tones for 10 seconds, thereafter DS SR matrix tablet is ejected from the die, collected and stored properly for further studies.

**Table 1: Different Formulas of Diclofenac Sodium SR matrix tablet**

Formula number	Diclofenac sodium	Carnauba wax	PVP K30	PEG6000	Talc	DCP	Lactose	C.F. (ton)	Method	Total weight
F1	75	30 (5:2)			5	190		6	F	300
F2	75	45 (5:3)			5	175		6	F	300
F3	75	60 (5:4)			5	160		6	F	300
F4	75	75 (1:1)			5	145		6	F	300
F5	75	75 (1:1)	15 (5:1)		5	130		6	F	300
F6	75	75 (1:1)	30 (5:2)		5	115		6	F	300
F7	75	75 (1:1)	45 (5:3)		5	100		6	F	300
F8	75	75 (1:1)		15 (5:1)	5	130		6	F	300
F9	75	75 (1:1)		30 (5:2)	5	115		6	F	300
F10	75	75 (1:1)		45 (5:3)	5	100		6	F	300
F11	75	75 (1:1)			5		145	6	F	300
F12	75	75 (1:1)			5	145		5	F	300
F13	75	75 (1:1)			5	145		7	F	300
F14	75	75 (1:1)		30 (5:2)	5	115		6	S	300

[All amounts given in mg and percentage given as w/w]

**Table 2: post compression parameters of DS SR tablets**

Formula No.	% Friability	Hardness kg.	% Drug content
F1	0.28	7.8	100.07
F2	0.26	8.7	97.54
F3	0.23	9.9	95.46
F4	0.22	10.9	99.84
F5	0.11	11.8	98.65
F6	0.09	12.6	98.43
F7	0.06	13.1	98.37
F8	0.45	6.9	99.94
F9	0.58	6.1	99.98
F10	1.18	4.7	99.79
F11	0.26	10.4	98.76
F12	0.31	7.2	99.16
F13	0.86	10.1	99.34
F14	0.56	10.6	98.73

### Assessment of post compression parameters

#### Hardness Test

The tablet hardness was measured in triplicate using a Monsanto® hardness tester and the force required to break tablets was recorded in kilogram [8].

#### Friability Test

The friability test was done for the prepared tablet using Roche friabilator for 4minutes at 25 rpm. 20 tablets were weighed then placed in the friabilator. After their revolution, they are dusted and re-weighed and the friability calculated as percent weight loss according to equation (1) below [8].

$$\%F = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100 \dots\dots(1)$$

#### Content Uniformity test

Five tablets were pulverized, passed through mesh 60, then an amount equal to one tablet dissolved in 50ml flask using phosphate buffer (pH 6.8), sonicated for 15mn. Then transfer exactly 5ml of the

above solution to a 100ml flask and dilute with the buffer to the mark, filter, discard the first few milliliters of filtrate, then the exact amount of drug is determined by using the UV spectrophotometer at wave length of 276nm [9].

#### Dissolution study

The dissolution studies were carried out using the USPXXX dissolution apparatus type II or basket method at 37°C ± 0.5°C and a rotation speed of 100 rpm.

One tablet of each formula was running out in a dissolution jar containing 900ml of 0.1 N HCl (pH 1.2) for two hours, then in 900ml of phosphate buffer (pH 6.8) for the rest of the experiment, 5ml samples were withdrawn hourly, the volume was replaced with buffer after each withdrawal to keep a constant sink condition. Samples were filtered and the absorbance was measured at λ max of 276nm against blank by using UV spectrophotometer, the procedure was done in triplicate and the mean results reported. The amount of drug was evaluated by using the calibration curve equation [9].

## Variables affecting release profile of DS SR matrix tablet

### Effect of polymer concentration

Formulas F1-F4 contain 10%, 15%, 20% and 25% w/w of the total tablet weight were prepared and used for this purpose.

### Effect of pH of dissolution medium

All formulas were studied by using 0.1N HCL (pH 1.2) for the first 2hrs and phosphate buffer (pH 6.8) for the rest of the experiment.

### Effect of channeling agent type

Formulas F7 and F10, contain two different types of channeling agents namely PVP K<sub>30</sub> and PEG<sub>6000</sub> in concentration of 15% (w/w) of the total tablet weight were used for this purpose.

### Effect of channeling agent concentration

Formulas (F5-F10) were used for this purpose. F5, F6 and F7 contain (PVP K<sub>30</sub>) at a concentration of 5%, 10% and 15% w/w of the total tablet weight respectively and F8, F9 and F10 contain (PEG<sub>6000</sub>) in the same concentration mentioned above were used.

### Effect of changing the diluents type

Formulas F4 and F11 which contain the same amount of DCP and lactose respectively were used for this purpose.

### Effect of changing the compression force

Formulas F4, F12 and F13 prepared at a compression force of 6, 5 and 7 tons, respectively were used for this purpose.

### Effect of changing the method of preparation

Formulas F9 and F14 prepared by melt-granulation and solvent evaporation methods, respectively, were used for this purpose.

### Comparative dissolution study and selection of best formula

The best formula was chosen according to comparative dissolution study with a reference marketed product of DS SR tablet (Divon SR), employing the similarity factor equation ( $f_2$ ) introduced by Moore and Flanner [10], as shown in equation (2) below.

$$f_2 = 50 \times \log \left\{ \left[ 1 + \frac{1}{n} \sum_{t=1}^n |R_t - T_t|^2 \right]^{-0.5} \times 100 \right\} \dots\dots(2)$$

Where n is the number of dissolution time points,  $R_t$  and  $T_t$  are the reference and test dissolution values at time t, respectively.

### Analysis of release kinetics for the optimized formula

The cumulative amount of DS released from the selected formula at different time intervals were fitted to zero order, first order, Higuchi and Korsmeyer–Peppas models to characterize the release kinetics and propose a mechanism of drug release [11].

## Results and Discussion

### Assessment of post compression parameters for the prepared tablets

Table (2) shows the results obtained for friability, hardness and % drug content of DS SR tablets. All the prepared formulas (except than F10) showed acceptable weight loss (less than 1%), this result may be attributed to the presence of retarding polymers in considerable amount (10-25% w/w) of the total tablet weight which improve the compressibility and hence physical parameters of the tablets [12].

### Content uniformity test

All the prepared formulas of DS SR matrix tablet showed a % drug content between 95.46% to 100.07%. These results complied with USP specification for tablet monographs which is 90% to 110% of drug content [9].

## Variables affecting Diclofenac Sodium release from SR tablet

### Effect of concentration of rate retarding polymer

The effect of polymer content on DS release as a function of time was found to be significantly different ( $p < 0.05$ ) among different

concentrations of CW as shown in figure (1) below. It can be observed that (regardless to the type of the rate retarding polymer used) the drug release is inversely proportional to the level of rate retarding polymer present in the matrix system [5].

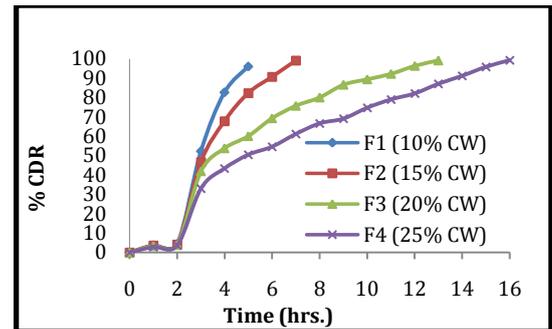


Fig.1: effect of concentration of CW on DS release

### Effect of pH of the dissolution medium

The pH of the dissolution medium was found to affect significantly ( $P < 0.05$ ) on the release rate of DS from the matrix system. In fact, all formulas show a characteristic biphasic release profile characterized by a very slow initial release phase at pH 1.2 (0.1N HCl) followed by a rapid, sharp and bursting release phase at pH 6.8 (phosphate buffer). This finding can be attributed to the very low aqueous solubility of DS at acidic pH (due to very poor wettability) which becomes more soluble at pH 6.8 [13].

### Effect of type of channeling agent

The investigation was undertaken to observe the effect of using different types of channeling agents (PVP K<sub>30</sub> and PEG<sub>6000</sub>) on DS release from wax based matrix tablets in formulas F4 contains no channeling agent, F7 contains 15% w/w PVP and F10 contains 15% w/w PEG<sub>6000</sub>. From figure (2) below, the rate and extent of DS released were found to be significantly different ( $P < 0.05$ ) among these three formulas and were found to be governed by the type and content of the channeling agents. It was observed that without the presence of channeling agent, drug release from the formula (F4) was very slow, this effect was due to the fact that carnauba wax is extremely hydrophobic in nature with low wettability; leading to a decrease in the effective interfacial area between the drug and the dissolution medium; which results in a reduction of the matrix wettability [14,15], whereas in formulas F7 and F10 the presence of channeling agents remarkably improve drug release due to improved matrix wettability.

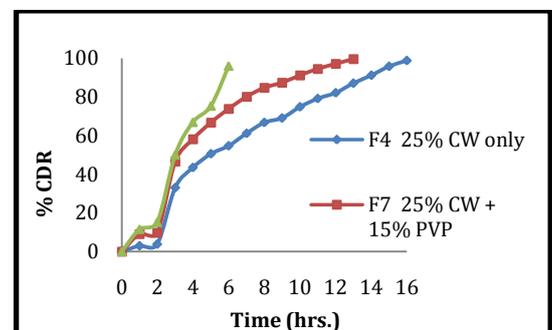


Fig. 2: effect of channeling agent type on DS release

### Effect of concentration of channeling agent

Formulas F5-F10 was designed and the release profile from these formulas was compared to that of F4 containing no channeling agent, as shown in fig. (3) and (4) below. It has been observed that (except than F5 containing 5% w/w PVP), all these formulas showed significant difference ( $P < 0.05$ ) in release rate of DS compared to F4 [16]. It has been observed that F7 containing PVP in concentration of 15% w/w of the total layer weight had showed 90% DR in about 10hrs. compared to F6 and F5 containing PVP in concentration of

10% and 5% w/w of the total layer weight and showed 90% DR in about 11.5 and 12hrs. respectively. On the other hand, F10 containing PEG<sub>6000</sub> in concentration of 15% w/w of the total layer weight had been disintegrated in less than 5hrs. and showed 90% DR in about 5.5hrs. compared to F9 and F8 containing PEG<sub>6000</sub> in concentration of 10% and 5% w/w of the total layer weight and showed 90%DR in about 9.5 and 11.5hrs. respectively. These results suggest that the matrix with higher channeling agent concentration provides less tortuous and/or more porous pathway, leading to formation of hard tablet. The channeling agents act by creating void spaces in the hydrophobic matrix of CW [17], causes the formation of channels/pores for entry of the dissolution medium [18].

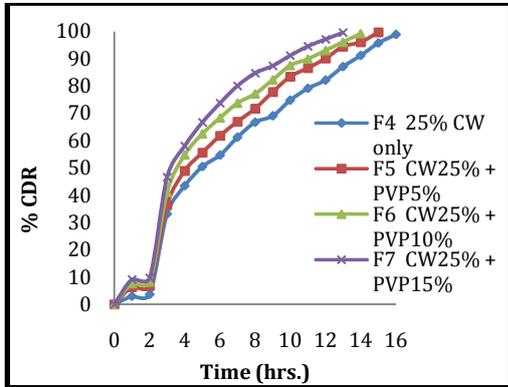


Fig.3: Effect of PVP K30 concentration on DS release

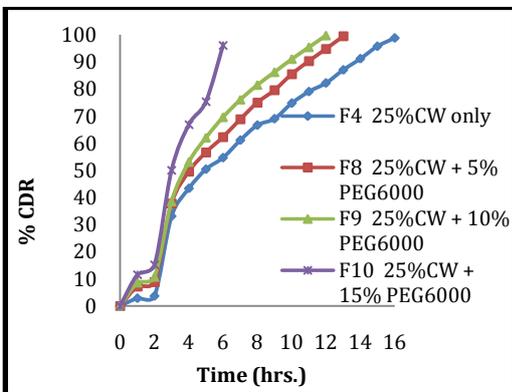


Fig.4: Effect of PEG6000 concentration on DS release

**Effect of changing the diluents type**

The effect of different fillers have been extensively studied and in many situations found to be of little effect on release rate for drugs that are embedded with hydrophilic polymers like HPMC. However, switching of an insoluble filler by a more soluble one (as in case of DCP and lactose) have found to possess a large impact and play an important role in drug release from waxy based matrices as in case of carnauba wax [17,19].

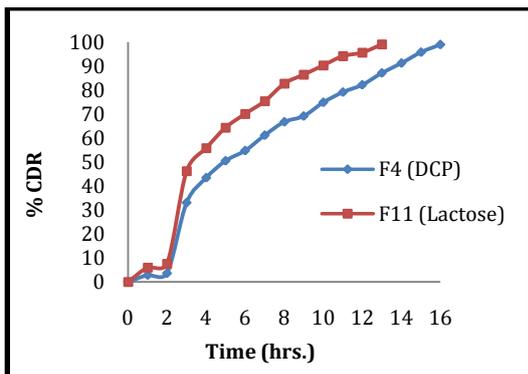


Fig.5: Effect of diluent type on DS release from matrix tablet

In this study, F11 containing lactose as diluent was designed and the release rate and extent from this formula were compared with those obtained from the corresponding F4 that contain DCP as a diluent, as shown in figure (5) below. It was found that the drug release was increased from 79.1% in F4 containing dibasic calcium phosphate dihydrate to 94.4% in F11 containing lactose at the end of 12hrs. This finding can be explained simply by the fact that lactose is soluble exceptant and dissolve rapidly when become in contact with the dissolution medium leaving behind pores and micro cavities which lead to decreasing the total matrix tortuosity and/or porosity, i.e acting as channeling agent. Also, by its osmogenic impact, lactose will dissolve and produce a local increase in the osmotic pressure within the matrix system causing solvent drag leading to more drug to be dissolved and released [20].

**Effect of changing the compression force**

Different compression force have been found to pose a great impact on the release characteristics and found significantly ( $P < 0.05$ ) affect on release rate of DS from CW based matrix system as shown in figure (6) below.

CW is a water insoluble, non swellable, non digestible and slowly erodible matrix former; therefore, the compression force is a very important factor that controls the rate of drug release from such a polymer. It was observed that at a constant die fill, an increase in the compression force to a certain limit results in a proportional increase in tablet hardness and decrease in tablet thickness, usually associated by a decrease in drug release rate [21].

This finding can be explained as following; at low compression force there might be insufficient tablet strength and a great level of porosity which allow for larger amount of solvent to get access to the matrix system, leading to increasing the drug diffusivity out of the system. Once a sufficient compression force is applied, optimal tablet hardness is reached and continuous matrix is formed, beyond this point farther increase in the compression force is not necessarily accompanied by a significant change in the release rate of DS but instead may accompanied by some tablet problems like chipping and lamination [22,23].

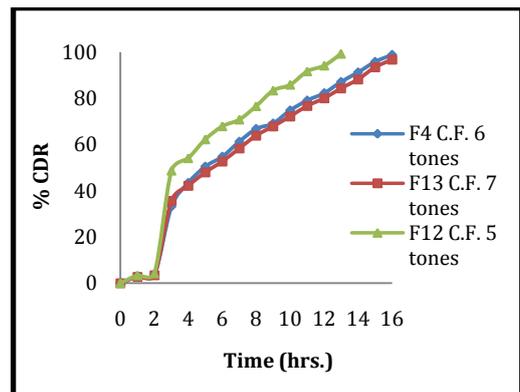


Fig. 6: Effect of compression force on DS release from matrix tablets

**Effect of Changing Method of Preparing the Sustained Release Granules**

It was observed that the method of preparation of the sustained release DS granules (F9 and F14) was significantly ( $P < 0.05$ ) affect the release rate and extent of the drug from CW based matrix system as shown in figure (7) below. Heat treatment of the tablets made by melt granulation in F9 further retarded drug release because heat treatment above the melting point of the carnauba wax redistributed the wax, producing thermal binder forming a new matrix system with higher tortuosity [24].

Heat treatment of the wax seemed to cause one or more of the following effects [24]:

- Formation of a thermal binder.

- Formation of welded bonds.
- Formation of recrystallizing bonds.

While for formula F34 which was prepared by solvent evaporation method, it seems that chloroform making carnauba wax more wetttable and easily dispersible in the dissolution medium, causing formula F14 to disintegrate in few hours releasing more than 98% of DS incorporated [25].

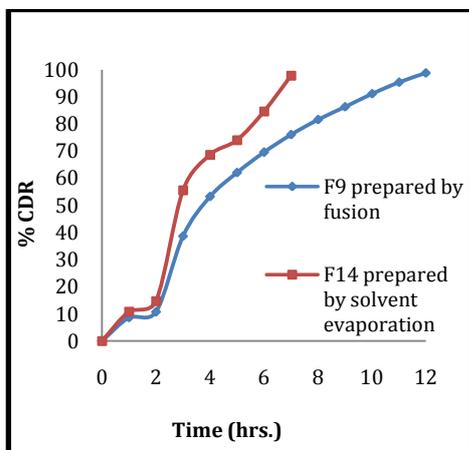


Fig. 7: Effect of different methods of preparation on DS release

#### Comparative Dissolution Study and Selection of the Best Formula

Figure (8) below shows the similarity in the dissolution profile of the selected formula (F9) and the reference marketed product of DS.

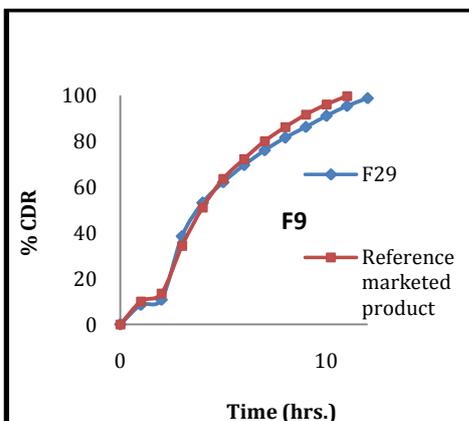


Fig. 8: Similarity between F9 and marketed product

Formulas F3, F4, F5, F6, F7, F8, F9, F11, F12 and F13 all showed a dissolution profile extended for 8hrs. or more and appeared to be promising for SR DS matrix tablet. All these formulas were subjected to the similarity factor ( $f_2$ ) test and compared with marketed product for this purpose. Among all of these formulas, F9 appeared to have the highest similarity (67.41) with the reference marketed product and thus was selected as the best formula for SR DS matrix tablet.

#### Mathematical Analysis of Release Kinetics

The release kinetics of DS from the selected formula (F9) was determined by finding the best fitting of the dissolution data to the mathematical models of drug release. Correlation of dissolution data to these models revealed a good fitting of F9 to Higuchi model with ( $R^2 = 0.976$ ) [26,27]. The release mechanism was further confirmed by Peppas model which revealed a value of the release exponent "n" higher than one (1.243) suggesting super case II transport indicating that two or more mechanisms were involved in the process of drug release, including diffusion [28].

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