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Original Article

Design and Evaluation of Diclofenac Sodium Megaloporous Matrix System Aimed for Colonic Drug Delivery

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Abstract

Megaloporous controlled release tablets of diclofenac sodium (DS) were prepared with two kinds of granules. One of them is the restraining-phase matrix granule (RMG) and it controls the release rate of the drug. The other one is the soluble housing-phase matrix granule (HMG) and controls liquid penetration into the system. Carnauba wax and Eudragit L 100 polymers were used to constitute the restraining and housing matrix phases, respectively. The prepared tablets were evaluated for various parameters. *In vitro* drug release study was carried out in simulated gastric fluid (pH 1.2) for the first 2 h and in phosphate buffer (pH 7.2) for the next 10 h following USP 25 paddle method. Two independent model methods, AUC and Lin Ju and Liaw's difference factor (f_1) and similarity factor (f_2) were used to compare various dissolution profiles. The fabricated megaloporous matrix tablets released only 3 to 5% of DS in pH 1.2 depending on the proportion of carnauba wax used in the RMG. Increase in polymer content/hardness value of the tablet resulted in a significant decrease in $AUC_{0\text{-}2}$ h and $AUC_{2\text{-}12}$ h values . The f_1 and f_2 analysis also confirms the discrimination between corresponding dissolution pairs. The dissolution profiles of an ideal matrix formulation containing 15.77% carnauba wax and 6.76% Eudragit L100 was found to be comparable with the reference product (Voveran® SR) and theoretical release profile. The drug release from all fabricated products and reference product followed better Higuchi model than the zero order and first order kinetic models. Ritger-Peppas model analysis indicated that the DS release followed non-Fickian transport mechanism. From the above analysis, it is evident that the release mechanism of DS from matrix tablet is influenced by both hardness and polymer contents. The stability profiles indicate that the physico-chemical properties of the tablets are not affected on storage at 45°C /75% RH up to 6 months.

Keywords: Colonic targeting; Diclofenac sodium; Megaloporous matrix tablets; Release kinetics; Sustained release.
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1. Introduction

Diclofenac sodium (DS) is a well-known representative of non-steroidal anti-

inflammatory drugs (NSAIDs), widely used to control pain and inflammation of rheumatic and non-rheumatic origin [1]. The conventional DS tablets make the drug immediately available for absorption in upper gastrointestinal (GI) tract resulting local GI toxicity varying from minor gastric discomfort to ulceration and bleeding of the mucosa [2]. It is well documented that the GI toxicity is not only caused by the inhibition of the prostaglandin synthesis, but is probably also due to direct contact of the drug with the mucosa [3]. In addition, due to the rapid systemic clearance of this drug, repeated daily dosing of 3 to 4 times a day is required in maintenance therapy that influences patient compliance. Colon targeted controlled release formulations are thus warranted to promote patient compliance and to reduce upper GI toxicity to some extent. DS is well adsorbed in the colon [4] and thus colon-specific release can be used for the treatment of widespread inflammatory bowel diseases.

The colon-specific drug delivery may be designed based on one of the following mechanisms viz., prodrugs [5], pH-sensitive polymer [6], time-controlled dissolution [7], and microflora-activated drug release [8]. Geometric shape controlled matrix systems [9], inert matrix systems [10], megaloporous matrix systems [11, 12], lipid matrix systems [13] and hydrogel matrix systems [14] are the various options available to achieve controlled drug release in matrix systems.

Principally, the megaloporous matrix system comprises two kinds of granules, namely restraining-phase matrix granule (RMG) and the soluble housing-phase matrix granule (HMG), which operate together to release the drug from the dosage form with a constant rate over an extended period of time. Usually, the RMG structure comprises the drug and rate controlling material and the other structure, HMG comprises the drug and a penetration rate controlling material. Previous studies on megaloporous matrix systems [11,12], reveals the use of substances such as carnauba wax, carbopol 934, Eudragit L, stearyl and cetyl alcohol, calcium hydrogen phosphate, talc and Encompress for RMG while polyethylene glycol 6000, lactose, magnesium stearate, calcium hydrogen phosphate and Encompress for HMG.

In the present work, megaloporous DS

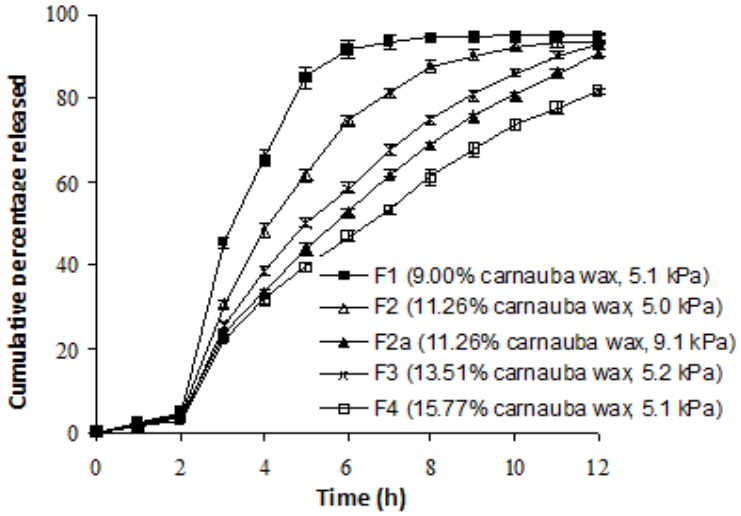

Figure 1: The effect of carnauba wax content and tablet hardness on the release profile of diclofenac sodium in simulated gastric fluid (pH 1.2) for the first 2 hours and in phosphate buffer (pH 7.2) for the next 10 hours. Values are given in mean±SD, (n=6).

controlled release matrix system has been developed using carnauba wax polymer in RMG and Eudragit L100 polymer in HMG.

2. Materials and methods

2.1. Materials

Diclofenac sodium was obtained from HATTI drugs, Maharashtra. Eudragit L100 was procured from Rohm GmbH, Germany. Carnauba wax was purchased from Koster Keunen Inc. USA. Microcrystalline cellulose (Avicel® PH 101) was purchased from, FMC Corp., Philadelphia. Lactose I.P was obtained from Genuine Chemicals, Mumbai. Polyvinylpyrrolidone (PVP K30 with approximate molecular weight 50 000) was purchased from Merck, Germany. The commercially available DS sustained release tablets (Voveran® SR-75 mg) were procured from Novartis, Mumbai. All other reagents used were of analytical or pharmaceutical grade.

2.2. Preparation and characterization of matrix tablets

The megaloporous matrix tablets were prepared from HMG and RMG as shown in Table 1. The HMG were prepared by wet mixing of DS, Eudragit L100 and Avicel® PH 101 in 101-capacity rapid mixer-granulator (Rotamix HSMG 10, Kevin Engineers, India) for 5 min. using isopropyl alcohol as granulating fluid. At semi-dried condition the granules were screened through sieve #14 and then dried at 40 °C in a tray drier (Bombay Engineering Works, India) until loss on drying became 2.0% in IR balance (Advanced Ltd. Mumbai, India). The dried granules were screened through sieve #14 and then sieve #80. The RMG were prepared by similar method as HMG employing DS, carnauba wax and lactose using 10% w/v PVP K30 and isopropyl alcohol as granulating agent. Finally, required portions of HMG and RMG were mixed, lubricated with magnesium stearate and compressed on a single punch tablet machine (Korsh, Germany) using 9.0 mm flat punches. The tablets were evaluated for their physical characters [15] like, weight variation, thickness and hardness. The drug content of each formulation was determined spectrometrically at 276 nm, in a Shimadzu UV-160A spectrophotometer. Friability [16] was measured on a Roche friabilator (Hoffman la

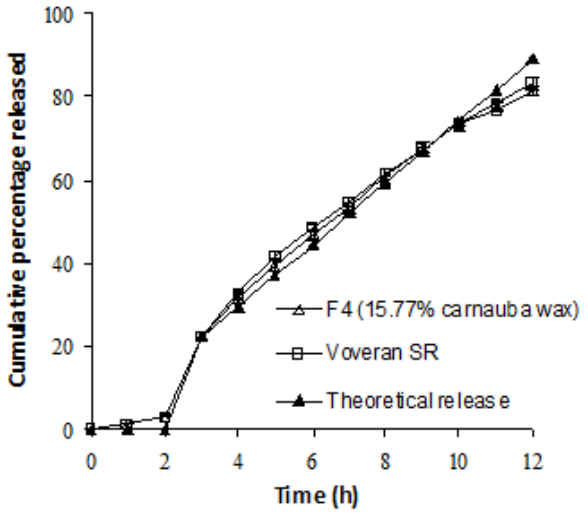

Figure 2: Comparison of release profiles of an ideal formulation containing diclofenac sodium (F_4), reference product (Voveran® SR) and theoretical release. Values are given in mean±SD, (n=6).

Roche, Basel).

2.3. Plotting of theoretical release profile

The theoretical release profile was designed from the pharmacokinetic parameters of the drug [17, 18] according to Krüger-Thiemer and Eriksen [19] and Robinson and Eriksen [20]. The theoretical release profile was proposed purposely designed for obtaining a controlled release profile characterized by an initial phase (2 h) of lag-time followed by a controlled release phase (12 h), according to zero order kinetics. The theoretical release profile was composed of initial and sustaining doses and the drug was considered to be released from both the portions simultaneously [21]. In order to select an ideal formulation among various formulations studied, the respective dissolution profiles were compared with the theoretical release profile for similarity.

2.4. In vitro release studies

The *in vitro* release of DS from the formulated tablets was carried out in USP 25 dissolution test apparatus II [15] using 900 ml of dissolution medium maintained at 37.0±0.5°C and a stirring rate of 50 rpm. Six tablets from each formulation were tested individually in simulated gastric fluid (pH 1.2) for the first 2 h and in phosphate buffer (pH 7.2) for the following 10 h. At every 1 h interval, samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the amount of DS present in each sample was determined spectrophotometrically at 276 nm.

2.5. Independent-model method (data analysis)

In order to compare the dissolution profiles, two model-independent methods were used: Area under dissolution curve (AUC), obtained by trapezoidal rule [22] and Lin Ju and Liaw's [23] difference factor (f_1) and similarity factor (f_2).

In the present study, AUC was considered instead of mean dissolution time (MDT), because this parameter can probably provide a better indication of *in vivo* performance [24]. In order to assess the statistical significance between AUC values, a single factor analysis of variance (ANOVA) followed by Duncan's multiple range test (DMRT) [25] was carried out, at a 5% significance level.

The f_1 and f_2 factors provide a simple

Table 1: Formulation and characteristics of megaloporous tablets containing diclofenac sodium (Batch size-5000 tablets).

Composition (mg)		Formulation code				
		F_1	**F_2**	**F_{2a}**	**F_3**	**F_4**
HMG	DS	25	25	25	25	25
	Eudragit L100	15	15	15	15	15
	Avicel® PH 101	55	50	50	45	40
RMG	DS	50	50	50	50	50
	Carnauba wax	20	25	25	30	35
	Lactose	50	50	50	50	50
	PVP K30	5	5	5	5	5
	Magnesium stearate	2	2	2	2	2
Physical characteristics						
Weight (mg),	n=20	222±1	221±1	222±1	221±1	223±1
Drug content (mg),	n=3	74.89±0.80	75.59±1.10	75.39±0.70	76.12±0.80	74.92±1.00
Hardness (kPa),	n=10	5.1±1.1	5.0±1.0	9.1±1.3	5.2±1.2	5.1±1.2
Thickness (mm),	n=10	3.22±0.02	3.22±0.06	3.17±0.05	3.21±0.04	3.22±0.06
Friability (%),	n=20	0.31±0.40	0.17±0.30	0.09±0.10	0.32±0.30	0.21±0.20

F_1 to F_4-fabricated formulations, HMG-housing matrix granules, RMG-restraining matrix granules.

measure of similarity between pairs of dissolution profiles. The difference factor ($f1$) is the percentage difference between two dissolution profiles at each time interval:

$$f_1 = \{[\Sigma \mid R_t - T_t \mid] / \Sigma R_t\} \times 100 \quad (1)$$

where, R_t indicates the released amount of drug of reference formulation; and T_t, the released amount of drug of test formulation. If the dissolution profiles are superimposed, f_1 reaches a value of 0, whereas the factor value increases when the differences between dissolution profiles also increase. From a practical point of view, values of f_1 between 0 and 15 can be considered as superimposed dissolution profiles. The similarity factor (f_2) can be calculated using the following expression:

$$f_2 = 50 \times \log \{[1 / (1 + (\Sigma (R_t - T_t)^2) / N)]^{1/2} \times 100\} \quad (2)$$

where, N indicates the number of experimental data. Values of f_2 between 50 and 100 can be considered as superimposed dissolution profiles.

2.6. Dependent-model method (data analysis)

In order to describe the DS release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models [26]: Zero order, first order, and Higuchi [27], respectively.

$$Q_t = Q_0 + K_0 t \quad (3)$$

where, Q_t is the amount of drug released at time t; Q_0 the amount of drug in the solution at t = 0, (usually, $Q_0 = 0$) and K_0 the zero order release constant.

$$\log Q_t = \log Q_\alpha + (K_1 / 2.303) t \quad (4)$$

Q_α being the total amount of drug in the matrix and K_1 the first order kinetic constant.

$$Q_t = K_H \cdot t^{1/2} \quad (5)$$

where, K_H is the Higuchi rate constant.

Further, to better characterise the mechanism of drug release from matrices, dissolution data were analyzed using the equation proposed by Harland *et al.* [28].

$$Q_{(t-l)} / Q_\alpha = K_K \cdot (t-l)^n \quad (6)$$

where, Q_t corresponds to the amount of drug released in time t, l is the lag time (l = 2 h), Q_α is the total amount of drug that must be released at infinite time, K_K a constant comprising the structural and geometric characteristics of the tablet, and 'n' is the release exponent indicating the type of drug release mechanism. To determine the exponent 'n', only the points in the release curves where $Q_{(t-l)}/Q_\alpha > 0.6$ were used. If 'n' approaches to 0.5, the release mechanism can be Fickian. If

Table 2: Pharmacokinetic data and calculated parameters of diclofenac sodium for designing theoretical release profile.

Pharmacokinetic data	**Reported values [16, 17]**	**Values taken**
Elimination half life ($t_{1/2}$)	1-2 h	1.5 h
Peak plasma conc. (C_p)	1 µg/ml	1 µg/ml
Peak plasma conc. time (T_p)	2-3 h	2.5 h
Volume of distribution (V_d)	0.17±0.11 l/kg	0.17 l/kg (or) 11.9 l*
Bioavailability fraction (F)	0.54±0.02	0.54
Desired time of release (T)	-	12 h
Calculated parameters	**Formula [18-20]**	**Results**
Elimination rate constant (K_{el})	$0.693/t_{1/2}$	0.462 h^{-1}
Zero-order release rate (K_0)	$C_p.V_d.K_{el}$	5.50 mg/h
Initial dose (D_b)	$C_p.V_d.1/F$	22.04 mg
Corrected initial dose (D_i)	$D_b - (T_p.K_0)$	8.29 mg
Maintenance dose (D_m)	$K_0.T$	66 mg
Total dose ($_W$)	$D_i + D_m$	74.29 mg ≃75.00 mg
In vitro drug release (X)	$X=D_i + t.K_0$	For t=1
for any time t, (t=1 to12)		X=13.79 mg

*Based on average adult body weight, 70 kg.

'n' approaches to 1, the release mechanism can be zero order and on the other hand if 0.5<n<1, non-Fickian (anomalous) transport could be obtained [28]. Anomalous (non-Fickian) transport generally refers to the drug release by the summation of both diffusion and erosion of the polymeric matrix. The criteria employed to select the "best model" was the one with the highest coefficient of determination (R^2). Further, the selected "best model" was confirmed by evaluating the statistical differences between R^2 values of various kinetic models, using one way ANOVA followed by DMRT analysis. The values were considered statistically significant if the $p<0.05$.

2.7. Stability studies

To assess the stability of DS megaloporous matrices, tablets of batch F_4 were stored at 45°C/75% RH for 6 months [29]. The matrix tablets were observed for changes in physical appearance, color, drug content and dissolution characteristics after each month for 6 months. The assay of DS and the dissolution study followed the same procedure as previously described.

3. Results and discussion

Theoretical release profile was worked out based on pharmacokinetic parameters of DS as shown in Table 2. The theoretical release profile designed in this study composed of initial and sustaining doses with simultaneous release of the drug from both the portions [21]. The initial dose portion is to bring the blood level of DS immediately to therapeutic concentrations and the sustaining dose portion is to sustain this level for a period of 12 h. The order of release was theoretically set to be zero [30]. The obtained theoretical release values were as follows; dose required to give the desired blood level, when given in an immediately available form (D_b) is 22.04 mg, zero-order release rate (K_0) is 5.50 mg/h, corrected initial dose (D_i) is 8.29 mg, maintenance dose (D_m) is 66 mg and total dose (W) is 74.29 mg, which is approximated to 75 mg.

3.1. Physico-chemical characteristics of DS matrices

As summarised in Table 1, the evaluation of the prepared matrix tablets containing DS showed that the drug content of all formulations ranged from 99.85 to 101.49%, indicating an uniform amount of drug in the formulations. All formulations, except F_{2a} yielded matrix tablets with a mean hardness value from 5.0 to 5.2 kPa. The formulation F_2 and F_{2a} are similar in composition but they differ in manufacturing in only hardness, with the difference of approximately 4 kPa units. All formulations passed the friability test (F<1%).

3.2. Effect of pH of the dissolution medium

The effect of pH of the dissolution medium on the release of DS is shown in Figure 1.

Table 3: AUC values for fabricated products containing diclofenac sodium (F_1 to F_4), reference product (Voveran®SR) and theoretical release profile.

Formulation code	$AUC_{0\text{-}2\ h}$ (% h)	$AUC_{2\text{-}12\ h}$ (% h)
F_1	5.01±0.17[a]	808.21±13.69[a]
F_2	4.07±0.13[b]	708.08±10.11[b]
F_{2a}	3.28±0.10[c]	572.42±09.34[c]
F_3	3.16±0.10[c]	619.15±08.04[d]
F_4	2.87±0.16[d]	515.68±11.38[e]
Voveran® SR	2.81±0.12[d]	520.09±13.66[e]
Theoretical release	0.00±0.00[e]	512.67±00.00[e]

Values are given in mean±SD, n=6. Values not sharing a common superscript letter differ significantly at $p<0.05$ (DMRT). The AUC values should be compared within columns only.

Insignificant amount of DS was released after 2 h in pH 1.2 solution, whereas in pH 7.2 dissolution medium, the release was reasonable. This initial lag period of 2 h may be due to (i) pH dependent solubility characteristics of both DS and Eudragit L100 (ii) hydrophobic nature of carnauba wax. DS, being a weak acid (pKa 4.0) and Eudragit L100, an enteric polymer (whose solubility begins only at pH>6.0) are practically insoluble in acidic solution, which limits the drug release from the matrix surface in pH 1.2 dissolution medium. On the other hand, carnauba wax is extremely hydrophobic, water repellant and insoluble in aqueous media irrespective of the pH. Owing to the high solubility of DS in pH 7.2 dissolution medium, large portion of the drug from the matrix surface may be released initially, generating many pores and cracks that facilitate further release of the drug. The release of DS was also attributed by the slow dissolution of Eudragit L100 in HMG providing a network of channels and pores that facilitates the solvent front penetration and elevation of drug release from the internal core to be possible. Similar result was also reported by Billa *et al* [31].

3.3. Effect of hardness

The effect of tablet hardness on the release rate was evaluated and the results compared to each other (Figure 1). Usually an increase in hardness of a tablet is accompanied by a decrease in release rate, due to a decrease in porosity of the tablet [32]. Thus F_{2a} formulation, having higher hardness value of approximately 4 kPa units than F_2, showed a significant decrease in the release profile. Significant decrease in AUC of F_{2a} against F_2 demonstrates the influence of tablet hardness on DS release (Table 3). The f_1 and f_2 analysis also showed a dissimilarity between the dissolution profiles of F_2 and F_{2a} (Table 4). This suggests that the formulation is slightly sensitive to moderate changes in hardness, with regard to the release rate. Since slight changes in hardness values cause nonuniformity of the release profile, hardness of the tablet should be taken into consideration during its commercial production.

3.4. Effect of carnauba wax and Avicel® PH 101 content

The effect of carnauba wax and Avicel® PH 101 content on the release of DS is shown in Figure 1. The drug release rate decreased with increasing amount of carnauba wax, probably due to the extreme hydrophobic and water repellant nature of carnauba wax polymer [21]. The drug release rate increased with increasing amount of Avicel® PH 101, (replaced by the reduced amount of carnauba wax) where by its swelling behavior, allowed further penetration of the aqueous medium, resulting in rapid erosion of the polymer matrices. These two factors can be ascribed for the higher release rate of drug with formulations containing lower percentage of carnauba wax and higher percentage of Avicel® PH 101. Analogously, a significant decrease ($p<0.05$) in AUC values was observed between products F_1 to F_4 (Table 3).

On the other hand, the difference between the AUC values of F_4, reference product and theoretical release profile was found to be statistically insignificant ($p>0.05$). The f_1 and f_2 analysis (Table 4) also suggest that the

Table 4: Difference factor (f_1) and similarity factor (f_2) analysis of various dissolution pairs.

Dissolution pairs	f_1	f_2
F_2 *vs* F_{2a}	22.25	43.23
F_4 *vs* Voveran® SR	1.75	91.29
F_4 *vs* Theoretical release	5.07	74.45
F_4 *vs* F_4^*	2.36	88.99

*After storage at 45°C/75% RH for 6 months.

dissolution profile of F_4 is superimposable with the reference product and theoretical release profile (Figure 2). Hence, F_4 was adopted as an ideal formulation for further studies.

3.5. Release kinetics

The *in vitro* release data were fitted to various kinetic models and the respective drug release rates and release mechanisms were established (Table 5). Since the release of drug in acidic medium was negligible, the portions of the dissolution curves within the interval 3 to 12 h were only considered for the kinetic analysis. The formulation F_1 was not considered for the analysis, because in this case more than 80% of the drug was released within the 5th h. As indicated by higher R^2 value, the drug release from all formulations and reference product followed Higuchi model than the zero order and first order equations. This observation was further confirmed by ANOVA and DMRT studies, that the differences between R^2 values of various kinetic models were statistically significant at $p<0.5$. In addition, a negative linear relationship was observed for polymer content (carnauba wax) versus Higuchi's rate plot (R^2=0.9991) i.e., increase in polymer content results in a decrease in Higuchi's rate which is due to decrease in the total porosity of the matrices (initial porosity plus porosity due to the dissolution of the drug). There was a rapid drug release at about 3rd h in each formulation, which may be composed of the drug release from the tablet surface and from the initial dissolution of soluble HMG phase of the megaloporous tablet. After about 3rd h the porous system gets activated and then the release pattern approached to zero order kinetic. Nevertheless, for the ideal formulation F4, the drug release profile between 5 and 10 h (R^2=0.9992) follows zero order kinetic. Ideally, the profile of drug release is best to follow a zero order pattern, because it could minimize fluctuation within the blood serum levels of the drug. However, it is difficult to achieve it and with a lot of controlled release matrix tablet, a Higuchi model of drug release is obtained.

The analysis of experimental data in the light of the Harland et al equation, as well as the interpretation of the corresponding values of n, leads to a better understanding of the balance between these mechanisms. For formulations F_2 to F_4, n ranged from 0.573 to 0.718 (Table 5). This indicates that the release mechanism of DS from these matrices is non-Fickian transport, which suggests that both dissolution and diffusion of the drug in matrices and also its own erosion modulate drug release.

3.6. Stability studies

The ideal batch F_4 showed no changes in physical appearance, color, drug content and

Table 5: Results of model fitting of diclofenac sodium controlled release tablets.

Formulation code	Higuchi		Zero-order		First-order	
	K_H (%$h^{-1/2}$)	R^2	K_0 (%h^{-1})	R^2	K_1 (%h^{-1})	R^2
F_2	43.596±0.147	0.952±0.004[a]	8.651±0.033	0.910±0.005[b]	0.140±0.008	0.824±0.005[c]
F_3	39.349±0.226	0.989±0.001[a]	7.387±0.044	0.962±0.002[b]	0.129±0.002	0.874±0.003[c]
F_{2a}	39.303±0.130	0.997±0.001[a]	7.421±0.026	0.981±0.003[b]	0.139±0.003	0.907±0.004[c]
F_4	34.939±0.362	0.998±0.001[a]	6.616±0.061	0.988±0.003[b]	0.135±0.002	0.924±0.007[c]
Voveran®SR	34.959±0.820	0.999±0.001[a]	6.617±0.165	0.988±0.004[b]	0.133±0.004	0.915±0.007[c]

Formulation code	Ritger-Peppas			
	K_K (h^{-n})	R^2	n	Mechanism
F_2	24.951±1.093	0.932±0.005[d]	0.573±0.018	Anomalous/zero
F_3	21.368±0.851	0.987±0.003[a]	0.599±0.016	Anomalous/zero
F_{2a}	15.711±0.985	0.996±0.002[a]	0.708±0.023	Anomalous/zero
F_4	13.956±1.839	0.988±0.004[b]	0.718±0.050	Anomalous/zero
Voveran®SR	13.062±1.418	0.998±0.001[a]	0.749±0.045	Anomalous/zero

Values are given in mean±SD, n=6. Values not sharing a common superscript letter differ significantly at $p<0.05$ (DMRT). The R^2 values should be compared within rows only.

dissolution characteristics upon storage at 45 °C/75% RH for 6 months. The f_1 and f_2 analysis also showed a superimposable dissolution curves before and after the period of this storage (Table 4).

4. Conclusions

In conclusion, the megaloporous tablets prepared with two simple granules could be used as an ideal dosage forms at the dosage intervals of every 12 h. The dissolution profiles of the ideal formulation F_4 containing 15.77% carnauba wax and 6.76% Eudragit L100 was found to be superimposed with the theoretical and reference product release profile. The method developed for the megaloporous matrix preparation is simple and cheap and they do not need additional equipment and procedures for the industrial applications. Further, extrapolating the ideal formulation to commercial scale is also easily feasible by performing sufficient scaling up studies. Possibly, by focusing more attention in particular to ensure homogenous mixing of ingredients and consistent tablet hardness during industrial production, the similar dissolution profiles as the ideal formulation may be obtained.

The analysis of the release profiles in the light of distinct kinetic models (zero-order, first-order, Higuchi and Harland *et al.*) led to the conclusion that, the drug release from all formulations followed Higuchi model and the release mechanism of DS from these matrices is anomalous (non-Fickian) transport. The ideal batch F_4 showed no change in physical appearance, drug content and dissolution profile upon storage at 45°C/75% RH for 6 months.

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