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Evaluation of Various Grades of Hydroxypropylmethylcellulose Matrix Systems as Oral Sustained Release Drug Delivery systems

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Abstract

PURPOSE: The present work reports an attempt was to formulate matrix systems for oral sustained release drug delivery systems using diverse grades of hydroxypropyl methylcellulose (Methocel K4M, K15M, K100M and K100LV), in order to investigate the effect of various grades of these polymer on release mechanism from matrix tablets. Diclofenac Sodium was used as a model drug to evaluate its release characteristics from different matrices.

METHODS: HPMC matrix tablets of Diclofenac Sodium using HPMC (methocel K100LV K4M, K15M, K100M CR) lactose were prepared by direct compression process. The USP paddle method was selected to perform the dissolution profiles carried out by USP apparatus 2 (paddle) at 50 rpm in 900 ml 0.1 N HCl, and phosphate buffer. Drug release was analyzed according to their kinetic models. A One way analysis of variance (ANOVA) was used to interpret the result.

RESULTS: Statistically significant differences were found among the drug release profile from different matrices. At a fixed polymer level, drug release from the higher viscosity grades (K100M) was slower as compared to the lower viscosity grades (K100LV). The best-fit release kinetics was achieved with the zero-order plot, followed by the Higuchi and Korsmeyer equations. Two formulations showed drug release is more controlled. The data obtained proved that the formulations are useful for a sustained release of Diclofenac.

CONCLUSIONS: From these formulations corresponded more controlled of the drug release by the higher viscosity grade of HPMC. The release of the model drug from these HPMC matrix tablets was prolonged; as a result, an oral release dosage form to avoid the gastrointestinal adverse effects was achieved.

Keywords: Diclofenac sodium, HPMC, Matrix tablets, Sustained Release.

INTRODUCTION

The matrix tablet by direct compression has attracted much attention due to its technological simplicity in comparison with other controlled release systems. It required fewer unit operations, less machinery, reduced number of personnel and processing time, increased product stability and production rate [1]. HPMC, a semisynthetic derivative of cellulose, is a swellable and hydrophilic polymer. Some research groups have worked on the usage of swellable HPMC as the retarding polymer to sustain the release of different drugs [2-4]. It is very suitable to use as a retardant material in CR matrix tablets, as it is nontoxic and easy to handle [5]. Matrix tablets prepared using HPMC on contact with aqueous fluids gets hydrated to form a viscous gel layer through which drug will be released by diffusion and/or by erosion of the matrix [6]. Previous studies developed by Williams et al. [7] led to the conclusion that the type and level of excipient influenced the rate and extension of drug release. Recently, Samani et al. [8] investigated the effect of polymer blends on release profiles of sodium diclofenac from matrices and the results showed that the drug release depends on the kind of polymer, its proportion in the formulation and its viscosity grade. Hydroxypropylmethylcellulose, is used to control drug release from several pharmaceutical systems because of its non-toxic nature, easy compression, swelling properties and accommodation to high levels of drug. This cellulose derivative excipient has been widely investigated in our laboratory [9–11]. Despite the high number of papers on

this subject, few of them discuss the drug-release processes from both methylcellulose [12,13] and hydroxypropylcellulose [14,15].

Diclofenac sodium is a non-steroidal anti-inflammatory agent, which is widely used in long-term therapy for rheumatoid arthritis. The biological half-life of diclofenac sodium is about 1-2 h, therefore it requires multiple dosing to maintain therapeutic drug blood level. The most frequent adverse side effects of diclofenac sodium on long-term administration are gastro-intestinal disturbances, peptic ulceration, and perforation [16]. Numerous studies have been carried out in order to achieve a desirable release rate of several non-steroidal anti-inflammatory drugs to treat rheumatoid arthritis, and osteoarthritis [17]. Diclofenac Sodium, one of the most useful NSAIDs agent, it is a practically insoluble compound in acidic solution (pK a =4.0), but dissolves in intestinal fluid and water. The biological half-life of diclofenac sodium is about 1-2 h, therefore it requires multiple dosing to maintain therapeutic drug blood level. The most frequent adverse side effects of diclofenac sodium on long-term administration are gastro-intestinal disturbances, peptic ulceration, and perforation [18]. In order to eliminate these adverse effects, enteric coated and/or SR forms have been developed and commercialized [19-22]. Diclofenac sodium is poorly soluble in water and acidic pH (1-3) but is rapidly soluble in alkaline pH 5-8 [23].

Hence, an effort was made to formulate a Sustained release dosage form containing different grades of HPMC for diclofenac sodium, which eliminates the need for multiple dosing thereby increasing patient compliance and decreasing the occurrence of adverse effects [24]. In addition, it was reported that a matrix material based on Eudragit NE40D was evaluated for preparing release tablets of Diclofenac Sodium [25]. In another study, five matrix-tablet formulations were prepared by granulating two viscosity grades of HPMC, and in-vitro/in-vivo correlations of Diclofenac Sodium release systems were investigated. The sustained release ability of the formulations was demonstrated in an in-vivo study, showing the presence of the drug in plasma for about 14 h [26].

MATERIALS AND METHODS

Materials

Diclofenac Sodium was obtained as gift sample from Square Pharmaceuticals Ltd. Gazipur, Bangladesh. HPMC (methocel K4M, K15M, K100M, K100LV CR) was a gift sample received from Colorcon Asia Pvt.Limited. Lactose was purchased from the Lactose Co. of Newzealand Ltd., (Newzealand). Magnesium stearate, was procured from Hanua Chemicals Limited, (Japan). Aerosil was procured from CABOT, India.

Preparation of matrix tablets

Tablets were prepared by direct compression process. In all cases, the amount of the active ingredient was 100 mg and the total weight of the tablet was 705 mg (Table-1).

During granulation process matrix-forming agents (methocel K100LV, K4M, K15M, K100M CR) aerosil, magnesium stearate, lactose and the active ingredient were weighed properly. Firstly active ingredient, talc and HPMC were mixed for 10 minutes properly. Dried granules were sieved through 20 mesh SS screen to get compressible particle. Lubricants are added during blending part. During blending total mass was taken in a container and blended in a laboratory designed small drum blender machine for about 30 minutes. Particular attention was given to ensure thorough mixing and phase homogenization. The appropriate amounts of the mixture were accurately weighed in an electronic balance for the preparation of each tablet and finally compressed using Pressima D type 4-station compression machine, Germany, with a 13.00 mm punch. Before compression, the surfaces of the die and punch were lubricated with purified talc. All the preparations were stored in airtight containers at room temperature for further study.

Physical characterization of matrix tablets

The tablets of the proposed formulations (DF1 to DF4) were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of 10 matrix tablets from each formulation was measured using

Hardness tester (Erweka GMBH, 300H model, Germany). Friability of the tablets was determined by testing 10 tablets in a Roche friabilator (Campbell Electronics, Mumbai) for 4 minutes at 25 rpm performed in triplicate. A slide calipers was used to measure the thickness for 5 tablets. Weight variation test was performed by taking 10 tablets using an electric balance (OHAUS LS 200, Switzerland) according to the official method. Drug content for Diclofenac Sodium was carried out by measuring the absorbance of the sample at 271 nm using Shimadzu 1240 UV visible spectrophotometer, Japan and comparing the content from a calibration curve prepared with standard Diclofenac Sodium in the same medium by taking 20 tablets were taken, weighed and finely powdered. An accurately weighed quantity of this powder was taken, suitably dissolved in pH 6.8 phosphate buffer, making dilution and analyzed and carried out in triplicate and mean was taken.

In Vitro Drug Dissolution Studies

Drug release profiles were evaluated in vitro using a dissolution test apparatus (VEEGO VDA 8 DR, Germany). The USP paddle method was selected to perform the dissolution profiles of Diclofenac Sodium from HPMC. The test for all the formulations was carried out in 900 ml 0.1 N HCl, and phosphate buffer, maintained at 37.5 ^{0}C (± 0.5°C) at a paddle rotation speed of 50 rpm. Withdrawing 5 ml filtered samples at preselected intervals up to 8 hours monitored progress of the dissolution. The release rates from these hydrophilic polymeric matrices were conducted in a medium of changing pH by starting with a tablet in HCl solution (pH=1.2) for 2 hours. Then, the tablets were immersed into a phosphate buffer (pH=7.4) for 6 hours. The sample solutions were analyzed for Diclofenac Sodium by UV absorbance at 278 nm using a UV Spectrophotometer (UV-1240 mini, SHIMADZU, Japan). Cumulative percentage of drug release was calculated and the mean of six tablets was used in data analysis.

Release Kinetics

Different kinetic models (zero-order, first-order, Higuchi's , korsmeyer's and Hixon Crowell) were applied to interpret the release profile (the order and mechanism of Diclofenac Sodium release) from matrix system. To study the mechanism of drug release from the matrix tablets, the release data were fitted to zero-order, first-order, and Higuchi equation. However, two factors diminish the applicability of Higuchi's equation to matrix systems. This model fails to allow the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the well-known exponential equation (Korsmeyer equation), Eq. (1), which is often used to describe the drug release behavior from polymeric systems.

$$\text{Log} (M_t / M_f) = \text{Log } k + n \text{ Log } t \quad \ldots\ldots. (1)$$

Where, Mt is the amount of drug release at time t; Mf is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release. Talukder et al [27] applied this equation to evaluate the drug release mechanism from xanthan gum matrix tablets. To clarify the release exponent for different batches of matrix tablets, the log value of percentage drug dissolved was plotted against log time for each batch according to the equation 1. A value of n = 0.45 indicates Fickian (case I) release; >0.45 but <0.89 for non-Fickian (anomalous) release; and >0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release [28].

The Hixon - Crowell cube root equation is:

$$M^{1/3} = M_o^{1/3} - K_c t \quad \ldots\ldots\ldots\ldots (2)$$

Where, K_c is the cube root dissolution rate constant. Cube roots of percent releases are plotted against time (hour) to demonstrate the Hixon Crowell plot.

Mean dissolution time (MDT) was calculated from dissolution data using the following equation (Mockel and Lippold) [29]. $MDT = (n / n+1).K^{-1/n}$ ……. (3)

Statistical Analysis:

A one way analysis of variance (ANOVA) was used to analyze the dissolution data obtained for each batch of formulation to compare the drug release rate and comparison of mean dissolution time (MDT) of all formulations. A confidence limit of $P < .05$ was fixed and the theoretical calculated values of *F (Fcrit and Fcal)* were compared for the interpretation of results. ANOVA was determined using SPSS software (Version 12, SPSS Inc., USA).

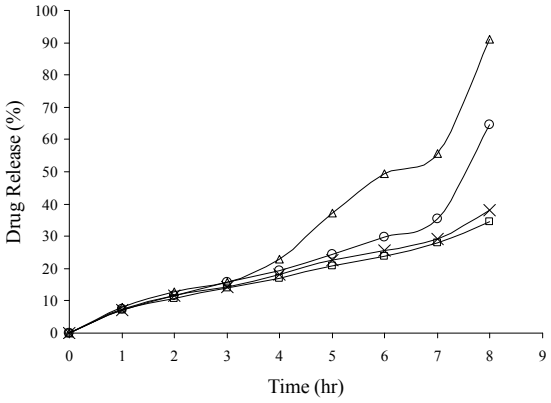
RESULTS

Physical Evaluation of Diclofenac Sodium matrix tablets

The tablets of the proposed formulations (DF1 to DF4) were evaluated for hardness, weight variation, thickness, friability and drug content. The thickness (mean ± SD, n=5) of the tablets were (3.99±0.01, 4.07±0.02, 4.12±0.03, 4.02±0.02 respectively) ranged from 3.99 to 4.12 mm. The hardness (mean ± SD, n=10) and percentage friability (< 1%) of the tablets of all batches (8.05±0.27, 8.10±0.3, 8.5±0.27, 8.90±0.4 respectively) ranged from 8.05 to 8.90 kg/cm2 and 0.55% to 0.67 %, respectively. The average percentage weight deviation of 10 tablets of each formula was less than ± 5%. Drug content (mean value ± SD within 0.9) among different batches of tablets ranged from 100.6501mg to 100.6505mg.

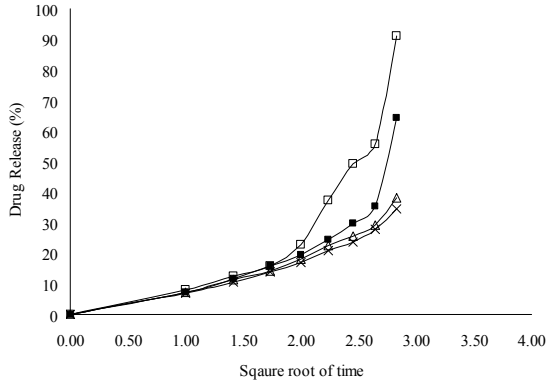
Effect of different grade of HPMC on release pattern of Diclofenac Sodium

Matrix tablets of Diclofenac Sodium were formulated using direct compression technique. Different grade of HPMC (Hydroxypropyl methylcellulose) matrix tablet containing Diclofenac as active ingredient having HPMC (methocel K100LV, K4M, K15M, K100M CR) polymer in the matrix tablet with the formulation code DF1, DF2, DF3, DF4 were prepared to evaluate the effect of these polymer. After preparation according to formulation shown in the table 1, their dissolution studies were carried out in basket method at 50 rpm in 900ml, phosphate buffer pH 7.4 medium at 37 ^{0}C (±0.5^{0}C). Six tablets from each formulation were used in dissolution study. The release profile of Diclofenac Sodium was monitored up to 8 hours (Initial 2 hours in simulated gastric fluid (pH 1.2) and next 6 hours in phosphate buffer of pH 6.8).



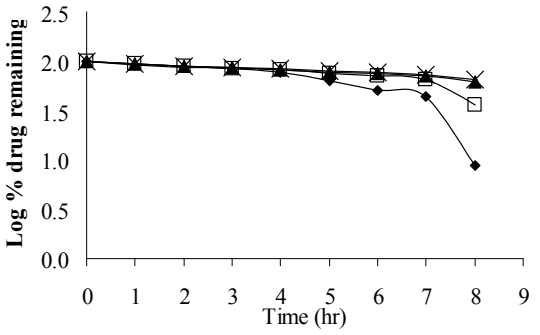
DF1 (Δ), DF2 (○), DF3 (×), DF4 (□)

Fig. 1A: Zero order plot of release kinetics of Diclofenac Sodium matrix tablets



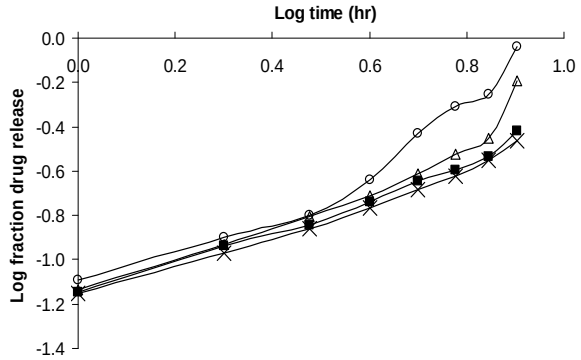
DF1 (□), DF2 (■), DF3 (Δ), DF4 (×)

Fig.1B: Higuchi plot of release kinetics of Diclofenac Sodium matrix matrix tablets



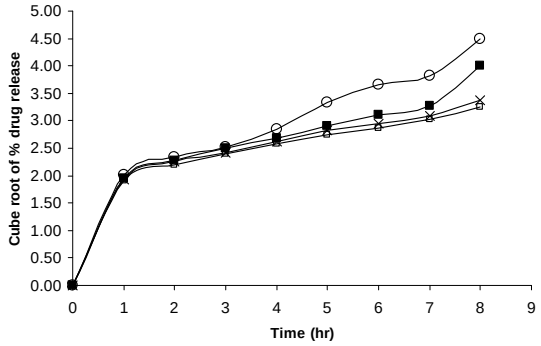
DF1 (■), DF2 (□), DF3 (Δ), DF4 (×)

Fig. 1C: First order plot of release kinetics of Diclofenac Sodium matrix tablets



DF1 (○), DF2 (Δ), DF3 (■), DF4 (×)

Fig. 1D: Korsmeyer plot of release kinetics of Diclofenac Sodium matrix tablets



DF1 (○), DF2 (■), DF3 (×), DF4 (□)

Fig. 1E: First order plot of release kinetics of Diclofenac Sodium matrix tablets

A release profile of Diclofenac Sodium containing having HPMC (methocel K100LV, K4M, K15M, K100M CR) polymeric matrix tablets of the formulations was obtained from the graphs (Fig. 1A- 1E). The total % of Diclofenac Sodium release (mean value ± SD within 0.5, n = 6) from the formulations DF1, DF2, DF3, DF4 was 91.09, 64.45, 38.20, 34.61 respectively. It has been observed that the release rate has been extended with the increase of polymeric viscosity grade from K100LV CR to K100M CR. The highest percent of drug release within 8 hours is (91.09 %) obtained from DF4 where containing polymeric viscosity grade (K100LV) is lower. But in DF3, the higher viscosity grades (K100M) polymer is present and the release of drug is more controlled with 34.61 % within 8 hours. At a fixed polymer level, drug release from the higher viscosity grades (K100M) was slower as compared to the lower viscosity grades (K100LV).

Table 1. Formulation of HPMC based Diclofenac Sodium sustained release matrix tablets

Formulation Code	Diclofenac Sodium (mg/tablet)	Methocel K100LV CR	Methocel K4M CR	Methocel K15M CR	Methocel K100M CR	Lactose	Aerosil
DF1	100	500	----	----	----	100	2
DF2	100	----	500	----	----	100	2
DF3	100	----	----	500	----	100	2
DF4	100	----	----	----	500	100	2

Each formulation also contains 3 mg magnesium stearate. Compression weight of each formulation was 705 mg.

Table 2: Release kinetics of formulated Diclofenac Sodium from various grades of HPMC based matrices

Code	Zero order		First order		Higuchi		Korsmeyer		Hixon Crowell	
	R^2	K_o% h^{-1}	R^2	K_1% h^{-1}	R^2	K_h% $h^{-0.5}$	R^2	n	R^2	K_c% h^{-1}
DF1	0.90	10.03	0.65	0.10	0.73	27.50	0.93	1.13	0.88	0.45
DF2	0.86	6.45	0.74	0.04	0.73	17.99	0.92	0.92	0.81	0.37
DF3	0.98	4.26	0.97	0.02	0.92	12.54	0.98	0.77	0.73	0.31
DF4	0.99	3.91	0.98	0.02	0.93	11.56	0.98	0.73	0.72	0.30

R^2, Correlation coefficients, K_0, K_1, K_h, K_c Release rate constant for zero order, first order, Higuchi, and Hixon Crowell release equation, respectively, n, diffusional exponent, indicative of release mechanism in Korsmeyer equation. DF1, DF2 = (Super Case II), DF3, DF4 = Non-Fickian (Anomalous) Release

Table 3: Successive fractional dissolution time of Diclofenac Sodium matrix tablets formulated with different grades of HPMC

Formulation	$T_{25\%}$	$T_{50\%}$	$T_{80\%}$	MDT	Release rate (%/√hr)
DF1	3.37	6.21	9.39	6.08	27.50
DF2	4.44	9.39	15.62	9.55	17.99
DF3	5.51	13.63	25.18	14.61	12.54
DF4	6.14	15.78	29.94	17.18	11.56

The rate of drug release was found to be inversely related to the viscosity grade of HPMC (methocel K100LV, K4M, K15M, K100M CR) present in the matrix structure, i.e. the drug release increased with lower viscosity grade polymer content of the matrix tablet. The release rate was significantly dependent on the viscosity grade of the polymer. A statistically significant decrease *(P <.05, Fcrit (3, 20) = 3.10 and Fcal = 58.38)* at the end of first hour, *(P <.05, Fcrit (2, 20) = 3.10 and Fcal = 1106) at* the end four hours, *(P <.05, Fcrit (3, 20) = 3.10 and Fcal = 5467)* at the end of eight hours, was observed % drug release in the formulation DF1 to DF4 as the polymeric viscosity grade HPMC (methocel) increase from K100LV to K100M.

From the table 2, it is mentioned that the proposed formulations DF1, DF2, DF3 followed zero order with regression values between 0.90 and 0.99. DF3, DF4 followed first order with regression values between 0.97 and 0.98. All formulations followed Korsmeyer with regression values between 0.92 and 0.98. Higuchi model was followed by DF3 and DF4.

The release rate was fastest from the formulation containing HPMC (methocel K100LV CR) a $t_{50\%}$ value of 6.20 hr. The release rate was slowest from the formulation containing higher viscosity grade polymer HPMC (methocel K100M CR) a $t_{50\%}$ value of 15.62 The decrease in release rate in formulations with lower viscosity grades was more pronounced and significant as compared with that of formulations with higher viscosity grades (Table 3).

In case HPMC (methocel K100LV) containing formulations, formulation DF1 showed (table 3) lowest MDT (mean dissolution time) with $T_{50\%}$, $T_{80\%}$ values are 6.33 hr, 6.20 hr, 9.39 hr respectively of all as it increased the release rate. But, as the polymeric viscosity grade of HPMC (methocel K4M, K15M, K100M) increased in the latter formulations (DF2, DF3, DF4), MDT values were increased 9.55, 14.61, 17.18 i.e increase polymer viscosity increase MDT value. As polymer viscosity was increased from K100LV to K100M at fixed amount of polymeric matrix, the release rate extended more than 8 hours.

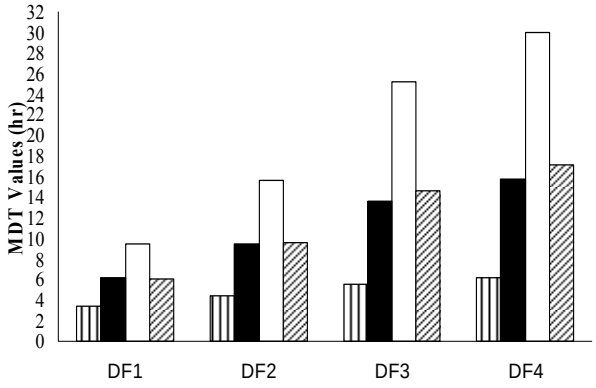


Figure 2: Successive release [$T_{25\%}$(▨) , $T_{50\%}$(■), $T_{80\%}$(□), MDT Value(▨)] of Diclofenac Sodium containing various grades of HPMC matrices

$T_{25\%}$, $T_{50\%}$, $T_{80\%}$ and MDT values of the designed tablets are also shown in figure 2.

Formulation DF4 containing higher viscosity grade polymer, K100M CR showed highest MDT (17.18 hr) value with $T_{50\%}$ (15.78 hr), $T_{80\%}$ (29.94hr). The MDT values increased significantly *P < .05, Fcrit (3, 20) = 3.10 and Fcal = 1260)* as polymer viscosity was increased from K100LV to K100M.

DISCUSSION

Physical Evaluation of Diclofenac Sodium matrix tablets

The present study was carried out to formulate oral sustained release drug delivery system for Diclofenac Sodium as Matrix Tablets. The drug content of all formulations was between 100.32 and 100.33 %, indicating

the presence of an acceptable amount of drug in the formulations. Furthermore, all the formulations showed acceptable hardness and friability.

***In vitro* dissolution study of tablets**

All the formulations showed no evidence initial brust release within the 2-hour dissolution test period in pH 1.2 buffer. However the later formulations DF2 to DF4 containing higher grade of HPMC(methocel K4M, K15M and K100M) polymer was observed more controlled within two hours probably to the low solubility of the drug at pH 1.2 and higher viscosity grade and retained their shape throughout the 8 hour dissolution period . They showed slow drug release from 0 to 2 hours followed by faster but controlled release from 2^{nd} to 8^{th} hour. This phenomenon may be attributed to surface erosion or initial disaggregation of the matrix tablet prior to gel layer formation around the tablet core [30]. In addition, release from K100LV was found to be more sensitive to polymer level changes.

At the same amount of polymer of higher viscosity induces greater chain entanglement than a polymer of low viscosity. Therefore, it is harder for longer chains to dissolve because of the high energy required for pulling them off the matrix. Thus, higher viscosity polymers induce the formation of a thicker gel layer after hydration. As discussed the effect of polymer viscosity was mainly due to the differences in their molecular weights. The molecular weights of HPMC K100LV, K4M, K15M, and K100M were reported to be 25, 95, 120, and 250 kDa, respectively [31]. There is a strong relationship that exists between the polymer molecular weight (MW) and polymer disentanglement concentration (Cp, dis) [32]:

$C_{p,\,dis} = 2700/\,MW$---------- (4)

The release rate decreased significantly and the drug release prolonged as the polymer viscosity was increased. Such increase in polymer viscosity grade results in a decrease in the drug release rate due to a decrease in the total porosity i.e. release is extended to long period.

According to the relationship (equation 4), the Cp, dis decreases with increasing MW and approaches a plateau at high MW. It was, however, reported that the change in the polymer disentanglement concentration between K100LV and other viscosity grades was appreciable leading to a higher release rates for the K100LV matrices.

For the formulation DF4 containing highest grade of polymer drug release is more controlled both pH 1.2 (less than 10% in first hour) and phosphate buffer pH 7.4 (extended more than 8 hours). This may be owing to a more rigid complex formed by presence of higher proportion of HPMC which helped in retaining the drug in matrix and did not allow rapid diffusion of drug from the matrix. According to USP specification, for controlled release drug delivery system (Tablet/capsule), at time equal to 0.25D, 20 - 50% drug will be dissolved, at time equal to 0.5D, 45-75% dissolved and thereafter at any time up until 1.0D, not less than 75% of drug will be dissolved where D is the labeled usual dosing frequency or interval [33]. With this objective in view, it is observed that only DF2 and DF3 show drug release according to USP specification.

Kinetic modeling of the drug release

The drug release data obtained were extrapolated by Zero order, First order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell equations to know the mechanism of drug release from these formulations. In this experiment, the in vitro release profiles of drug from DF3 and DF4 formulations could be best expressed by Zero equation as the plots showed highest linearity (R^2: 0.98 to 0.99). To confirm the diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation. The formulations DF3 and DF4 showed good linearity (0.98) with slope (n) values ranging from 0.73 to 0.77 indicating that diffusion was the predominant mechanism of drug release from these formulations indicating that the release mechanism was non-Fickian or anomalous release ($0.45 < n < 0.89$). It can be inferred that the release was dependent on both drug diffusion and polymer relaxation, which appears to indicate a coupling of diffusion and erosion mechanisms-so called anomalous diffusion [28]. Formulation DF3 and DF4 released by super case II ($n = 0.92$ to $1.13 > 0.89$) which indicate zero-order release due to

the dissolution of polymeric matrix and relaxation of the polymer chain. The poor correlation coefficients (R^2 values ranged from 0.83 to 0.94) observed for the kinetic parameters based on the first order model equation were mainly due to the drug release mechanism. First order plot for all formulation showed poor linearity. The release profile of Diclofenac Sodium from all these formulations displayed very poor fitting with Hixson-Crowell cube root model of drug release, which were related, with the method of manufacture followed. Formulation DF3 and DF4 followed fairly all models except Hixson-Crowell.

MDT value is used to characterize the drug release rate from the dosage form and the retarding efficacy of the polymer. A higher value of MDT indicates a higher drug retarding ability and vice-versa. From table 3, the lowest MDT value (6.33 hrs) was found with formulation DF1 which also showed a low value of T_{50} (6.20 hrs) and a high value of Higuchi release rate (27.5%/√time). On the other hand all the formulations containing HPMC(methocel K4M, K15M, K100M CR) exhibited a higher value of MDT and a low value of Higuchi release rate than that of batch DF1 indicating the higher drug-retarding ability of these formulations. An inverse relationship was found between viscosity grade of HPMC in the formulations and the MDT values of the dosage form. The MDT value was found to decrease viscosity of HPMC was increased in the formulations (Table 3).

CONCLUSION

From the study, it is possible to conclude that the selected excipients are likely to be suitable for the preparation of tablet formulations direct compression method. According to the release studies, the decrease in the release rate was observed with an increase in the viscosity of the polymeric system. Polymer with higher viscosity polymer HPMC (methocel K4M, K15M, K100M) was shown to be beneficial than lower viscosity of HPMC (methocel K100LV) in controlling drug release. The results of release studies indicated the possibility of achieving a suitable modulation of Diclofenac Sodium release rate by opportunely varying the HPMC (methocel K100M, K4M, K15M, K100M CR) in the matrix tablet.

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REFERENCES

[1]. Reddy RK, Mutalik S, Reddy S. Once daily sustained release matrix tablets of Nicorandil: formulation and in vitro evaluation. *AAPS. Pharm Sci Tech*. 2003, *4, (4),* 25-29.

[2]. Bravo SA, Lamas MC, Salomon CJ. Swellable matrices for the controlled-release of diclofenac sodium: formulation and in vitro studies. *Pharm Dev Technol*. 2004, *9,* 75-83.

[3]. Velasco MV, Ford JL, Rowe P, Rajabi-Siahboomi AR. Influence of drug:hydroxypropyl methylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC matrices. *J Control Release*. 1999, *57,* 75-85.

[4]. Heng PWS, Chan LW, Easterbrook MG, Li X. Investigation of the influence of mean HPMC particle size and number of polymer particles on the release of aspirin from swellable hydrophilic matrix tablets. *J Control Release*. 2001, *76,* 39-49.

[5]. Lee BJ, Ryu SG, Cui JH. Formulation and release characteristics of hydroxypropyl methylcellulose matrix tablet containing melatonin. *Drug Dev Ind Pharm*. 1999, 25, 493-501.

[6]. Katzhendler I, Mader K, Friedman M. Structure and hydration properties of hydroxypropylmethylcellulose matrices containing naproxen and naproxen sodium. *Int. J Pharm.* 2000, *200,* 161-179.

[7]. R.O. Williams III, T.D. Reynolds, T.D. Cabelka, M.A. Sykora, V. Mahaguna, Investigation of excipient type and level on drug release from controlled release tablets containing HPMC, *Pharm. Dev. Tech*. 2002, *7, (2),* 181–193.

[8]. Samani S.M., Montaseri H., Kazemi A., The effect of polymer blends on release profiles of diclofenac sodium from matrices, *Eur. J. Pharm. Biopharm*. 2003, *55*, 351- 355.

[9]. Salsa T., Veiga F., Teixeira-Dias J.J.C., Pina M.E., Effect of polymer hydration on the kinetic release of drugs: a study of ibuprofen and ketoprofen in HPMC matrices, *Drug Dev. Ind. Pharm.* 2003, *29 (3)* 289–297.

[10]. Veiga F., Salsa T., Pina M.E., Influence of technological variables on the release of theophylline from hydrophilic matrix tablets, *Drug Dev. Ind. Pharm.* 1997, *23,* 547–551.

[11]. Pina M.E., Veiga F., The influence of diluent on the release of theophylline from hydrophilic matrix tablets, *Drug Dev. Ind. Pharm*. 2000, *26,* 1125–1128.

[12]. Mitchell K., Ford J.L.,. Armstrong D.J, Elliott P.N.C., Rostron C., Hogan J.E., The influence of concentration on the release of drugs from gels and matrices containing Methocelw, *Int. J. Pharm*. 1993, *100*, 155–163.

[13]. Mitchell K.,. Ford J.L, Armstrong D.J.,. Elliott P.N.C, Hogan J.E., Rostron C., The influence of concentration on the properties of gels and swelling characteristics of matrices containing methylcellulose or hydroxypropylmethylcellulose, *Int. J. Pharm.* 1993, *100*, 165–173.

[14]. Alvarez-Lorenzo C., Go´mez-Amoza J.L., Martı´nez-Pacheco R., Souto C., A. Concheiro, The stability of theophylline tablets with a hydroxypropylcellulose matrix, *Drug Dev. Ind. Pharm.* 2000, *26,* 13–20.

[15]. Panomsuk S.P., Hatanaka T., Aiba T., Katayama K., Koizumi T.A., Study of the hydrophilic cellulose matrix: effect of indomethacin and a water-soluble additive on release mechanisms, *Chem. Pharm. Bull*. 1995, *43 (6),* 994–999.

[16]. Scholer DW, Ku EC, Boettacher I, Schweizer A., Pharmacology of diclofenac sodium. *Am J Med*. 1986, *80,* 34-8.

[17]. Todd, P.A., Sorkin, E.M., Diclofenac Sodium; a Reappraisal of its Pharmacodynamic and Pharmacokinetics Properties, and Therapeutic Efficacy. *Drugs* 1988, *35*, 244-285.

[18]. Scholer DW, Ku EC, Boettacher I, Schweizer A. Pharmacology of diclofenac sodium. *Am J Med*. 1986, *80, (4B),* 34-8.

[19]. Lin SY, Kao YH., Tablet formulation study of spray-dried sodium diclofenac enteric- coated microcapsules. *Pharm Res* 1991, *8*, 919-24.

[20]. Vilivalam VD, Adeyeye CM. Development and evaluation of controlled-release diclofenac microspheres and tabletted microspheres. *J Microencapsul* 1994, *11*, 455-70.

[21]. Torres D, Garcia-Encina G, Seijo B, Vila-Jato JL., Biopharmaceutical evaluation of microencapsulate ion-exchange resins containing diclofenac*., Eur J Pharm Biopharm*.1995, *41,* 127-31.

[22]. Okada M, Suzuki M, Ono K, Kasai S, Iwasa A, Dissolution mechanism and optimization of enteric coated long acting diclofenac sodium preparation. *Proc Int Symp Control Rel Bioact Mater*. 1996, *23*, 559-60.

[23]. Tripathi KD., Essential of medical pharmacology. 4th ed., Delhi, Jaypee Brothers Medical Publishers (P) Ltd, 1998.

[24]. Chien YW., Controlled and modulated-release drug delivery systems, 3rd ed., New York, Marcel Decker Inc, 1991.

[25]. Billa, N., Yuen, K.D., Peh, K., Diclofenac Sodium Release from Eudragit Containing Matrices and Effects of Thermal Treatment. *Drug Dev Ind Pharm*, 1998, *24,* 45-50.

[26]. Liu, C-H., Kao, Y-H., Chen, S-C., Sokoloski, T.D., Sheu, M-T., In Vitro and In Vivo Studies of the Diclofenac Sodium Release Matrix Tablets*. J Pharm Pharmacol*, 1995, *47*, 360-364.

[27]. Talukder MM, Michoel A, Rombaut P and Kinget R. Comaprative study on xanthun gum and hydroxypropyl methyl cellulose as matrices for controlled-release drug delivery. *Int. Pharm.* 1996, *129,* 231-241.

[28]. Shato H, Miyagawa, Y, Okabe T, Miyajima M and Sunada H. Dissolution mechanism of diclofenac sodium from wax matrix granules. *J. Pharm. Sci.*1997, *86,* 929-934.

[29]. Mockel JE, Lippold BC. Zero order release from hydrocolloid matrices. *Pharm Res*. 1993, *10,* 1066- 1070.

[30]. Ebube NK, Hikal A, Wyandt CM, Beer DC, Miller LG, Jones AB. Sustained release of acetaminophen from heterogeneous matrix tablets, influence of polymer ratio, polymer loading and coactive on drugrelease. *Pharm Dev Technol*. 1997, *2,* 161-170.

[31]. Gao P., Skoug J. W., Nixon P. R., Ju T. R., Stemm N. L., and Sung K. C.. Swelling of hydroxypropyl methylcellulose tablets. 2. Mechanistic study of the influence of formulation variables on matrix performance and drug release, *J. Pharm. Sci.* 1996, *85*, 732–740.

[32]. Lee P. I. and Peppas N. A. Prediction of polymer dissolution in swellable controlled release systems*, J. Control. Release*. 1987, *6,* 207–215.

[33]. Banakar, U. Dissolution of modified-release dosage forms. In: Pharmaceutical dissolution testing, 1st Edn., Marcel-Dekker, Inc., New York, 1992, pp.322.