Research Article

FORMULATION AND EVALUATION OF HYDROXYPROPYLMETHYLCELLULOSE BASED MATRIX SYSTEMS AS ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEMS FOR CIPROFLOXACIN HYDROCHLORIDE

Md. Mofizur Rahman[1*], Sumon Roy[2], Sreedam Chandra Das[2], Mithilesh Kumar Jha[1], Md. Qamrul Ahsan[3], Md. Shahparan[2], Md. Selim Reza[4]
[1]Department of Pharmacy, Bangladesh University, Dhaka, Bangladesh,
[2]Department of Pharmacy, Southeast University, Dhaka, Bangladesh,
[3]Department of Pharmacy, Southern University, Bangladesh,
[4]Department of Pharmaceutical Technology, University of Dhaka, Bangladesh.
*Corresponding author's E-mail: rmfi02@yahoo.com

Accepted on: 17-12-2010; **Finalized on:** 03-02-2011.

ABSTRACT

The purpose of the study was to formulate matrix systems for oral sustained release drug delivery systems using diverse grades of hydroxypropylmethylcellulose (Methocel K100LV, K4M, K15M, and K100M CR), in order to investigate the effect of various grades of these polymer on release mechanism from matrix tablets. Ciprofloxacin Hydrochloride was used as a model drug to evaluate its release characteristics from different matrices. HPMC matrix tablets of Ciprofloxacin Hydrochloride using various HPMC grades, 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 distilled water. Drug release was analyzed according to their kinetic models. A One way analysis of variance (ANOVA) was used to interpret the result. 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 Higuchi plot, followed by the zero-order, Korsmeyer and Hixson Crowell equations. The data obtained proved that the formulations are useful for a sustained release of Ciprofloxacin Hydrochloride. From these formulations corresponded controlling of the drug release by the higher viscosity grade of HPMC. The release of the model drug from these HPMC matrix tablets was faster in case of lower viscosity grade, useful for poor soluble drugs. Prepared sustained release Ciprofloxacin HCl could be better than conventional dosage form.

Keywords: Ciprofloxacin HCl, 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. Various formulation factors influence the drug release form HPMC matrices, viz., polymer viscosity, polymer particle size, drug/polymer ratio, drug solubility, drug particle size, drug loading, compression force, tablet shape, formulation excipients, coatings, processing techniques, as well as the testing medium[8]. 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. 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[9]. Despite the high number of papers on this subject, few of them discuss the drug-release processes from both methylcellulose[10,11] and hydroxypropylcellulose[12,13]. Among the different approaches studied with this aim, matrix systems still appear as one of the most attractive from both the economic as well as the process development and scale-up points of view[14]. Moreover, it has been shown that the suitable combination of more types of polymers as matrix-forming materials enables appropriate modifications of the release characteristics of the drug from the dosage form[15, 16].

Ciprofloxacin HCl acts as bactericidal for susceptible strains near the minimum inhibitory concentration (MIC), is indicated for the treatment of infections caused by susceptible organisms, e.g., infectious diarrhea, complicated Intra abdominal infections, typhoid lever, bone and joint infections, skin and skin structure infections, lower respiratory infections, urinary tract infections, urethral and cervical gonococci infections, chronic bacterial prostatitis and acute sinusitis etc[17].

Ciprofloxacin is a fluorinated quinolone having broad antimicrobial activity and is effective after oral or parenteral administration. Side effects with the use of ciprofloxacin are relatively few and development of resistance by microbes is not rapid.[18]

An oral dosage of ciprofloxacin in adults is 250 to 750 mg every 12 hours. The serum half-life of Ciprofloxacin ranges from 3 to 5 hour[19].

Table 1: Formulation of HPMC based Ciprofloxacin Hydrochloride sustained release matrix tablets

Formulation Code	Ciprofloxacin HCl	Methocel K100LV CR	Methocel K4M CR	Methocel K15M CR	Methocel K100M CR	Lactose	Aerosil
	(mg/tablet)						
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.

MATERIALS AND METHODS

Materials

Ciprofloxacin hydrochloride was obtained as gift sample from Square Pharmaceuticals Ltd. Gazipur, Bangladesh. HPMC (methocel K100LV, K4M, K15M, K100M 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 Ciprofloxacin Hydrochloride was carried out by measuring the absorbance of the sample at 276 nm using Shimadzu 1240 UV visible spectrophotometer, Japan and comparing the content from a calibration curve prepared with standard Ciprofloxacin Hydrochloride 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 distilled water, 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 Ciprofloxacin Hydrochloride from HPMC. The test for all the formulations was carried out in 900 ml 0.1N HCl and distilled water, 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 sample solutions were analyzed for Ciprofloxacin Hydrochloride by UV absorbance at 276 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. The dissolution study was continued for 8 hours (Initial one hour in simulated gastric fluid (pH 1.2) and next 7 hours in distilled water) to get a simulated picture of the drug release in the in-vivo condition and drug dissolved at specified time periods was plotted as percent release versus time (hours) curve. This drug

release profile was fitted into several mathematical models to get an idea of the release mechanism.

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 Ciprofloxacin Hydrochloride 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.

$$\text{Log } (Mt / Mf) = \text{Log } k + n \text{ Log } t \quad \ldots\ldots\ldots\ldots (1)$$

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 [20] 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[21].

The Hixon - Crowell cube root equation is:

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

Where, K_c is the cube root dissolution rate constant. Cube roots of percent drug remaining 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) [22].

$$MDT = (n / n+1).K^{-1/n} \quad \ldots\ldots\ldots (3)$$

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).

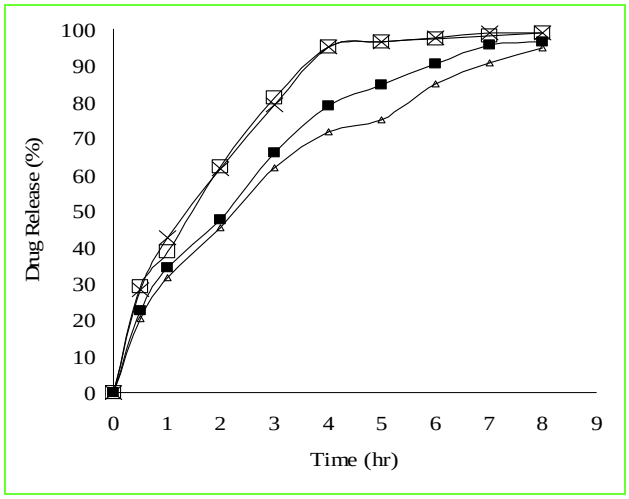
RESULTS

Physical Evaluation of Ciprofloxacin Hydrochloride 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 97.75 mg to 102.50 mg.

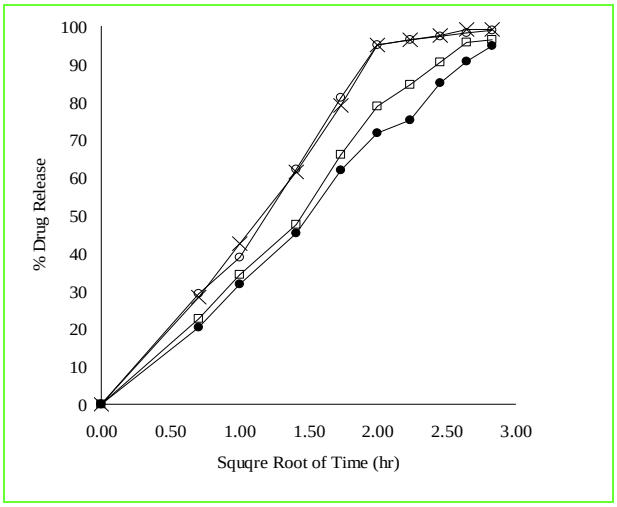
Effect of different grade of HPMC on release pattern of Ciprofloxacin Hydrochloride

Matrix tablets of Ciprofloxacin Hydrochloride were formulated using direct compression technique. Different grade of HPMC (Hydroxypropylmethylcellulose) matrix tablet containing Ciprofloxacin Hydrochloride 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, distilled water medium at 37 ^{0}C (±0.5^{0}C). Six tablets from each formulation were used in dissolution study. The release profile of Ciprofloxacin Hydrochloride was monitored up to 8 hours. A release profile of Ciprofloxacin Hydrochloride containing having HPMC (methocel K100LV, K4M, K15M, K100M CR) polymeric matrix tablets of the formulations was obtained from the graphs (Fig. 1A- 1E).



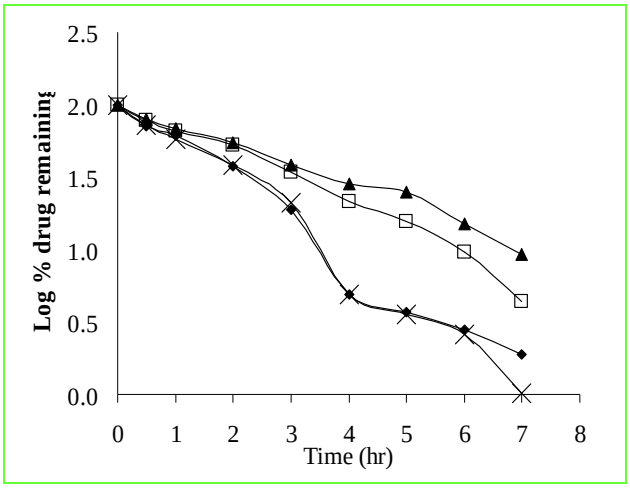
DF1 (×), DF2 (□), DF3 (■), DF4 (Δ)

Fig. 1A: Zero order plot of release kinetics of Ciprofloxacin Hydrochloride matrix tablets



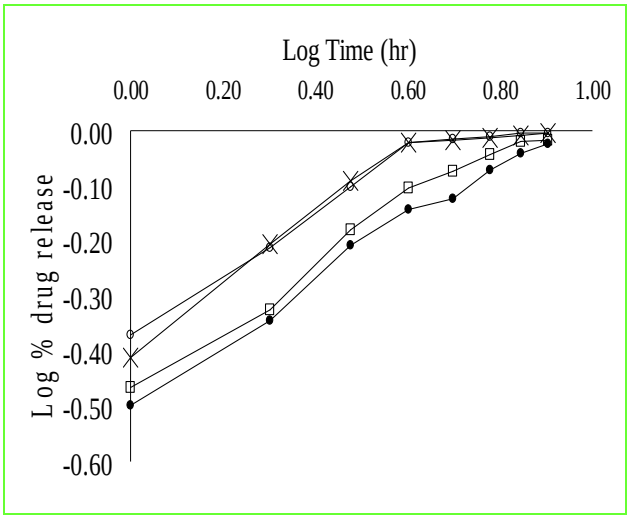
DF1 (×), DF2 (○), DF3 (□), DF4 (●)

Fig. 1B: Higuchi plot of release kinetic of Ciprofloxacin Hydrochloride matrix tablets



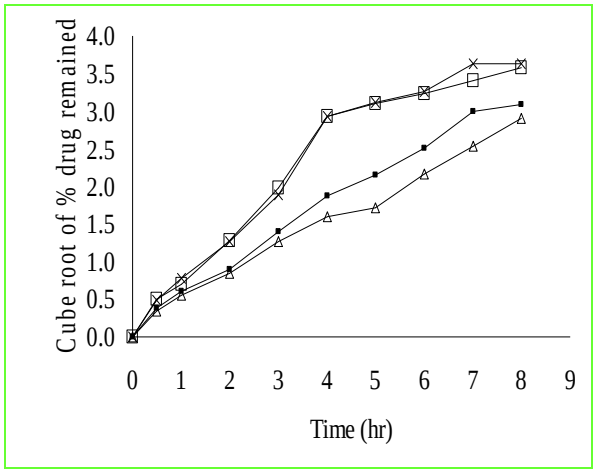
DF1 (×), DF2 (■), DF3 (□), DF4 (Δ)

Fig. 1C: First order plot of release kinetics of Ciprofloxacin Hydrochloride matrix tablets



DF1 (○), DF2 (×), DF3 (□), DF4 (●)

Fig. 1D: Korsmeyer plot of release kinetics of Ciprofloxacin Hydrochloride matrix tablets



DF1 (×), DF2 (□), DF3 (■), DF4 (Δ)

Fig. 1E: Hixson Crowell plot of Ciprofloxacin Hydrochloride matrix tablets

The total % of Ciprofloxacin Hydrochloride release (mean value ± SD within 0.5, n = 6) from the formulations DF1, DF2, DF3, DF4 was 98.98, 98.82, 98.31 97.82 and 94.82 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 (98.98 %) obtained from DF1 where containing polymeric viscosity grade (K100LV) is lower. But in DF4, the higher viscosity grades (K100M) polymer is present and the release of drug is controlled with 94.82 % 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).

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 = 172.77)* at the end of first hour, *(P <.05, Fcrit (2, 20) = 3.10 and Fcal = 1017.06) at* the end four hours, *(P <.05, Fcrit (3, 20) = 3.10 and Fcal = 37.10)* 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 DF4 followed zero order with regression value 0.92. All formulations followed first order, Higuchi, Korsmeyer and Hixson Crowell with regression values between 0.96 to 0.99, 0.94 to 0.99, 0.92 to 0.99 and 0.92 to 0.99 respectively.

The release rate was fastest from the formulation containing HPMC (methocel K100LV CR) a $t_{50\%}$ value of 1.87 hr. The release rate was slowest from the formulation containing higher viscosity grade polymer HPMC (methocel K100M CR) a $t_{50\%}$ value of 6.14 hr. The

decrease in release rate in formulations with lower viscosity grades was more pronounced and not so significant as compared with that of formulations with higher viscosity grades because of higher solubility of the drug. (Table 3)

Table 2: Release kinetics of formulated Ciprofloxacin Hydrochloride 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	0.794	11.21	0.979	0.287	0.949	37.68	0.923	0.42	0.939	0.478
DF2	0.791	11.27	0.969	0.265	0.943	37.73	0.900	0.45	0.928	0.378
DF3	0.893	12.01	0.982	0.181	0.987	36.68	0.977	0.53	0.990	0.391
DF4	0.928	11.97	0.986	0.137	0.995	34.97	0.990	0.54	0.993	0.139

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 = Fickian (Case I release), DF2- DF4 = Non-Fickian (Anomalous) Release.

Table 3: Successive fractional dissolution time of Ciprofloxacin Hydrochloride matrix tablets formulated with different grades of HPMC

Formulation	$T_{25\%}$	$T_{50\%}$	$T_{80\%}$	MDT	Higuchi Release rate (%/√hr)
DF1	0.2305	1.2009	3.6770	1.850	37.68
DF2	0.2833	1.3218	3.7565	1.914	37.73
DF3	0.5300	1.9601	4.7577	2.511	36.68
DF4	0.6187	2.2332	5.3326	2.827	34.97

In case HPMC (methocel K100LV) containing formulations, formulation DF1 showed (table 3) lowest MDT (mean dissolution time) with $T_{50\%}$, $T_{80\%}$ values are 1.85 hr, 1.2 hr, 3.6 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 slightly i.e increase polymer viscosity increase MDT value due to high soluble drug and pH independent solublity. As polymer viscosity was increased from K100LV to K100M at fixed amount of polymeric matrix, the release rate extended.

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

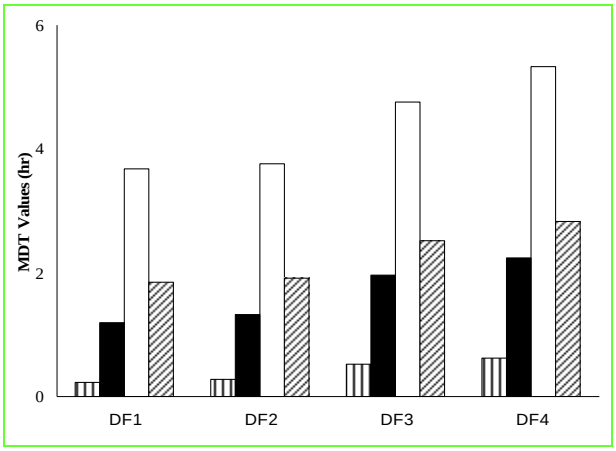


Figure 2: Successive release [$T_{25\%}$(□) , $T_{50\%}$(■), $T_{80\%}$(□), MDT Value(▨)] of Ciprofloxacin Hydrochloride containing various grades of HPMC matrices

Formulation DF4 containing higher viscosity grade polymer, K100M CR showed highest MDT (2.8 hr) value with $T_{50\%}$ (2.2 hr), $T_{80\%}$ (5.3hr). The MDT values increased significantly *P < .05, Fcrit (3, 20) = 3.10 and Fcal = 104.17)* as polymer viscosity was increased from K100LV to K100M.

DISCUSSION

Physical Evaluation of Ciprofloxacin Hydrochloride matrix tablets

The present study was carried out to formulate oral sustained release drug delivery system for Ciprofloxacin Hydrochloride as Matrix Tablets. The drug content of all formulations was between 98% and 100%, 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 except DF4 initial brust release within the first hour of dissolution test period in pH 1.2 buffer and within 1.9 hours release was 50% and within 4 hours release was > 75%. However the later formulation DF4 containing higher grade of HPMC (methocel K100M CR) polymer was observed controlled, 50% release was observed within 2.2 hours and 80% release was observed within 5.3 hours. This phenomenon may be attributed to surface erosion or initial disaggregation of the matrix tablet prior to gel layer formation around the tablet core[23]. 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[24]. There is a strong relationship that exists between the polymer molecular weight (MW) and polymer disentanglement concentration (Cp, dis)[25]:

$C_{p,\,dis}$ = 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. But the change in the Cp, dis between K4M, K15M, and K100M was small that the drug release profiles for these three HPMC formulations. Probably, the diffusion coefficient of the highly soluble ciprofloxacin HCl might also have been least affected once the viscosity increased beyond 4,000 cPs (i.e., above K4M), and thus, the release rates remained almost same. Other research groups have reported similar results that the drug release rate decreased with increasing molecular weight for low-molecular-weight HPMCs and became independent of molecular weight for high-molecular-weight HPMCs [26-27].

For the formulation DF4 containing highest grade of polymer drug release is controlled both pH 1.2 (less than 30% in first hour) and distilled water (extended to 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.

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: 0.94 to 0.99). It confers that drugs are released by diffusion. To confirm the diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation. All the formulations showed good linearity (0.90 to 0.99) with slope (n) values ranging from 0.45 to 0.54 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[21]. The good correlation coefficients (R^2 values nearly to unity) 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 good linearity. This indicates that the amount of drug released is dependent on the matrix drug load. The poor correlation coefficients (R^2 values ranged from 0.83 to 0.94) observed for the kinetic parameters based on the zero order model equation were mainly due to the drug release mechanism. The release profile of Ciprofloxacin Hydrochloride from all these formulations displayed good fitting with Hixson-Crowell cube root model of drug release, confers that the drug releases by dissolution and with the changes in surface area and diameter of the particles or tablets[28].

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 (2.8 hrs) was found with formulation DF1 which also showed a low value of T_{50} (1.85 hrs) and a high value of Higuchi release rate (37.5%/√time). On the other hand all the formulations containing HPMC (methocel K4M, K15M, K100M CR) exhibited comparatively 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 K100M) was shown to be beneficial than lower viscosity of HPMC (methocel K4M, K15M, K100LV) in controlling drug release for higher soluble drugs. The results of release studies indicated the possibility of achieving a suitable modulation of Ciprofloxacin Hydrochloride release rate by opportunely varying the HPMC (methocel K100M LV, K4M, K15M, K100M CR) in the matrix tablet.

Acknowledgement: The authors are thankful to Colorcon Asia Pvt. Ltd., Bangladesh for their generous donation of various grades of HPMC. The authors are also thankful to

The South East University (SEU), Bangladesh University and the University of Dhaka for their supports and co-operations.

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 Ciprofloxacin Hydrochloridefrom HPMC matrices. J Control Release. 1999, 57, 75-85.
4. Heng PWS, Chan LW, Easterbrook MG, Li X. Investi gation 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 hydroxypropyl methylcellulose 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. K. V. Ranga Rao, K. Padmalatha Devi, and B. Buri. Cellulose matrices for zero-order release of soluble drugs. Drug Dev. Ind. Pharm. 14:2299–2320 (1988).
9. Katzhendler I, Mader K, Friedman M. Structure and hydration properties of hydroxypropyl methylcellulose matrices containing naproxen and naproxen sodium. Int J Pharm. 2000;200:161-179.
10. 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 Methocel w, Int. J. Pharm. 1993, 100, 155–163.
11. 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 hydroxypropyl methylcellulose, Int. J. Pharm. 1993, 100, 165–173.
12. 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.
13. 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.
14. Ordi, N., 1986. Sustained release dosage forms. In: Lachman, L., Lieberman, H.A., Kanig, J.L. (Eds.), The theory and practice of Industrial Pharmacy, 3rd. Lea and Febiger, Philadelphia, pp. 430–478.
15. Rey, H., Wagner, K.G., Wehrle´, P., Schmidt, P.C., 2000. Development of matrix-based theophylline sustained-release microtablets. Drug Dev. Ind. Pharm. 26, 21–26.
16. Rodriguez, L., Caputo, O., Cini, M., Cavallari, C., Grecchi, R., 1993. In vitro release of theophylline from directlycompressed matrices containing methacrylic acid copolymers and/or dicalcium posphate dihydrate. Il Farmaco 48, 1597–1604.
17. Martindale. (2002) The 'Complete Drug Reference. 32nd Edition. Pp 1225.
18. William, A. and Petri, Jr. 2001. In: Goodman and Gilman's. The pharmacological basis of therapeutics (Hardman, J.G. and Limbird, L.E., Eds.), Mc Graw Hill, New York, pp. 1179.
19. William, A. and Petri, Jr. 2001. In: Goodman and Gilman's. The pharmacological basis of therapeutics (Hardman, J.G. and Limbird, L.E., Eds.), Mc Graw Hill, New York, pp. 1182.
20. 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.
21. Shato H, Miyagawa, Y, Okabe T, Miyajima M and Sunada H. Dissolution mechanism of Ciprofloxacin Hydrochloridefrom wax matrix granules. J. Pharm. Sci.1997, 86, 929-934.
22. Mockel JE, Lippold BC. Zero order release from hydrocolloid matrices. Pharm Res. 1993, 10, 1066-1070.
23. 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 drug release. Pharm Dev Technol. 1997, 2, 161-170.

24. 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.

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

26. J. L. Ford, M. H. Rubinstein, and J. E. Hogan. Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl methylcellulose matrices. Int. J. Pharm. 24:327– 338 (1985).

27. L. C. Feely and S. S. Davis. Influence of surfactants on drug release from hydroxypropyl methylcellulose matrices. Int. J. Pharm. 41:83–90 (1988).

28. Hixson AW, Crowell JH, (1931) Dependence of reaction velocity upon surface and agitation. Ind Eng Chem. 23: 923-931.

****