Stamford Journal of Pharmaceutical Sciences

S. J. Pharm. Sci. 2(1): 37-43

In Vitro Release Kinetic Study of Ciprofloxacin HCl from Methocel K15M CR, Methocel K4M CR and Methocel K4M Premium Matrix Tablets

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Received- 11 November, 2008 *Accepted for Publication- 10 Janurary, 2009*

ABSTRACT

In the present study Ciprofloxacin HCl sustained release matrix tablet was prepared by utilizing different grades of hydroxypropyl methylcellulose (HPMC) polymers such as Methocel K4M CR, Methocel K4M Premium & Methocel K15M CR by direct compression method. Different amount of Methocel K15M CR was used to develop matrix builder in the three proposed formulations (F1-F3) for the study of release rate retardant effect at 5%, 6%, and 7% of total weight of tablet matrix respectively. The dissolution study of Methocel K15M CR based tablet matrices of those proposed formulations were carried out in the simulated gastric medium (pH 1.3) for 8 hours using USP dissolution apparatus II. Similarly Methocel K4M premium was used to develop matrix builder in another three proposed formulations (F4-F6). It was found that formulations F-4 (15%), F-5 (17%) and F-6 (18.3%) met the desired release rate of Ciprofloxacin HCl for 8hrs period. The release kinetics of formulation F-4, F-5 and F-6 followed Higuchi kinetic order. Again Methocel K4M premium was used for another three proposed formulations (F7-F9). It was found that formulations F-7 (6.7%), F-8 (12.3%) and F-9 (15.6%) met the desired release rate of Ciprofloxacin HCl for 8hrs period. The release kinetics of formulation F-7, F-8 and F-9 followed Higuchi kinetic order. Among these three polymers, Methocel K4M Premium showed better release retardant effect than Methocel K4M CR and Methocel K15M CR.

Key Words: Ciprofloxacin HCl, Direct compression, Controlled release, Methocel K15M CR, Methocel K4M CR and Methocel K4M premium.

INTRODUCTION

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 (Martindale, 2002). Ciprofloxacin HCl sustained release tablet matrix was prepared by direct compression method by utilizing different grades of Hydroxypropyl methylcellulose (HPMC) that were Methocel K15M CR and Methocel K4M CR and Methocel K4M premium. These polymers are hydrophilic in nature and can hold active ingredients firmly that depend on the concentration or ratio of the polymers used (Aulton *et al*., 1981). Oral sustained release dosage form by direct compression technique is a very simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms (Longer, 1990). Sustained or controlled drug delivery occurs while embedded within a polymer that may be natural or semi-synthetic or synthetic in nature. The polymer is judiciously combined with the drug or other active ingredients in such a way that the active agent is released from the material in a predetermined fashion and released the drug at constant rate for desired time period (Lordi, 1990). There are number of techniques applied in the formulation and manufacturing of sustained release dosage form. However, the matrix tablet by direct compression has attracted much attention due its technological simplicity in comparison with other controlled release systems. Direct compression method has been applied for preparation of tablet matrix that involved simple blending of all ingredients used in the formulations and then underwent direct compression. It required fewer unit operations, less machinery, reduced number of personnel and reduced processing time, increased product stability and faster production rate (Shangraw and Demarest 1993). A wide array of polymers has been employed as drug retarding agents each of which presents a different

approach to the matrix concept. Polymers that primarily forming insoluble or skeleton matrices are considered as the first category of retarding materials and are classified as plastic matrix systems. The second class represents hydrophobic and water-insoluble materials, which are potentially erodable and the third group exhibits hydrophilic properties (Reza, 2003). There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, erosion, and swelling followed by diffusion. The release of drug from the tablet matrix depends on the nature of polymer. Both Methocel K15M CR and Methocel K4M premium are hydrophilic polymers that become hydrated, swollen and facilitates to diffuse the drug (Bidah and Vernaud 1991). In the present study an attempt has been made to formulate Ciprofloxacin HCl magnesium as sustained release tablet matrix with the addition of release retarding polymers Methocel K15M CR, Methocel K4M CR and Methocel K4M premium in different ratios. The effect of viscosity grade and polymer loading on drug release were recorded and release kinetics was evaluated.

EXPERIMENTAL

Drug: Ciprofloxacin HCl (Tasc Pharmaceuticals Limited, India); **Polymers:** Hydroxypropyl methylcellulose-Methocel K15M CR Premium USP/EP, Hydroxypropyl methylcellulose-Methocel K4M CR and Hydroxypropyl methylcellulose-Methocel K4M Premium USP/EP (Dow Chemical Company, Midland, MI, USA); **Other excipients:** Microcystalline Cellulose (Avicel-200) (Hanau Chemicals Ltd., Japan); Polyvinnyl Pyrrolidone (Povidone K-30) (Hanau Chemicals Ltd., Japan); Colloidal Anhydrous Silica (Aerosil 200) (Hanau Chemicals Ltd., Japan); Magnesium Stearate (Hanau Chemicals Ltd., Japan); **Solvents and reagents:** Hydrochloric acid (Merk, Germany); **Equipments:** Single Punch Tablet Press; Simadzu UV Spectrophometer; Digital pH meter; Electronic Hardness tester (Ereweka, Germany); Electrolab Tablet Dissolution Test machine (XXII); Sartorius Electronic Balance.

Preparation of dissolution medium

For dissolution simulated gastric medium (pH 1.3) was required. For 0.1N HCl, 8.4 ml of Hydrochloric acid (37% w/v) was diluted with sufficient water to produce 1000 ml.

Preparation of matrix tablet

Drug, polymer and other excipients were weighed separately for 50 tablets per formulation as per proposed formulations. The proposed formulations were coded as F-1, F-2, F-3, F-4, F-5, F-6, F-7, F-8, and F-9. The amounts of drug and excipients are expressed in milligram unit. Then active ingredient, microcrystalline cellulose, povidone K-30, polymer and aerosil were blended for 15 minutes and then magnesium stearate was added and further blended for another 1 minute. Blended mass was taken in the hopper and then die and punch were adjusted to get the desired weight of the tablet (900 mg). After compression the tablets were weighed and tablet weight was found 902 mg -906 mg. The tablets were prepared by direct compression; the types and amounts of polymers used are shown in Table-1.

In vitro dissolution study of the tablet matrix:

Dissolution studies were conducted according to USP method (USP XXII) using apparatus II paddle at a speed of 50 rpm and the temperature was maintained at 37.0 ± 0.5^{o} C. The total duration of dissolution was 8 hours in which the tablet matrices were subjected to simulated gastric media (0.1 N HCl, pH 1.3). 900 ml of 0.1 N HCl was placed in each vessel and the apparatus was assembled. Six tablets from each formulation were weighed and placed in the baskets. The operation in the acid stage was carried out for 8 hours. After each hour 10 mL of sample solution was withdrawn and filtered. The released drug was assayed by using UV spectrophotometer at 276 nm. At each withdrawal 10 ml of fresh dissolution medium was added.

Kinetic analysis of release data

The release of drug from sustained release dosage form is regulated by several processes. These are extraction or diffusion of drug from matrix and erosion of matrix; alternatively the drug may be dissolved in the matrix material and then released by diffusion through membrane. In some cases, drug may be released by osmotic process. Different kinetic equations (Zero order, First order, and Higuchi's equation) were applied to interpret the release rate from the tablet matrix. The best fit of higher correlation ($R^2 > 0.98$) was found with well-known Higuchi equation. Higuchi derived the rate of release of drugs dispersed in an inert matrix system (Higuchi, T.).

Table-1: Ciprofloxacin HCl, Methocel K15M CR, Methocel K4M CR, Methocel K4M premium and other excipients used in the proposed formulation F1 – F9.

Proposed Formulation	Ciprofloxacin HCl (mg)	Methocel K15M CR (mg)	Methocel K4M CR (mg)	Methocel K4M premium (mg)	Avicel (PH 200) (mg)	Magnesium stearate (mg)	Aerosil (mg)	Total Wt. (mg)	Percentage of various grades of Methocel in different formulation
F-1	582	45	-	-	266	4.5	2.5	900	5
F-2	582	54	-	-	257	4.5	2.5	900	6
F-3	582	63	-	-	248	4.5	2.5	900	7
F-4	582	-	135	-	176	4.5	2.5	900	15
F-5	582	-	153	-	158	4.5	2.5	900	17
F-6	582	-	165	-	146	4.5	2.5	900	18.3
F-7	582	-	-	61	250	4.5	2.5	900	6.7
F-8	582	-	-	111	200	4.5	2.5	900	12.3
F-9	582	-	-	141	170	4.5	2.5	900	15.6

RESULTS AND DISCUSSION

In this study, three different grades of cellulose derivatives- Methocel K15M CR and Methocel K4M CR and Methocel K4M premium were used for the development of Ciprofloxacin HCl sustained release tablet matrix by direct compression method. The effect of Methocel K15M CR and Methocel K4M premium on Ciprofloxacin HCl sustained release dosage was assessed. Different percentage of hydroxypropyl methylcellulose-Methocel K15 M CR (5%, 6%, 7%, of total weight of tablet matrix), different percentage of hydroxypropyl methylcellulose-Methocel K4M CR (15%, 17%, 18.3% of total weight of tablet matrix) and different percentage of hydroxypropyl methylcellulose-Methocel K4M premium (6.7%, 12.3%, 15.6 of total weight of tablet matrix) containing tablet matrices were placed in the dissolution media according to design of study. The percent release from all the respective polymer matrix systems were plotted against time to observe the drug release pattern. It was seen that percent of drug release was decreased by increasing the amount of Methocel K15M CR and Methocel K4M CR and Methocel K4M premium in the formulations (Table- 2).

Table-2: Effect of Methocel K15M CR (F1-F3), Methocel K4M CR (F4-F6) and Methocel K4M premium (F7-F9) on Ciprofloxacin HCl release in simulated gastrointestinal fluid (Zero order plots)

Time (hours)	% Release								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0
1	34.125	28.635	21.616	35.420	33.851	29.694	25.141	25.612	24.082
2	45.722	43.539	44.948	49.578	46.542	39.168	34.451	34.456	31.382
3	63.509	59.463	58.530	64.501	61.867	50.615	47.499	47.386	42.870
4	78.254	64.316	65.693	72.785	70.497	60.683	60.910	60.207	56.234
5	84.826	69.722	74.766	81.812	79.180	70.768	72.214	71.975	67.022
6	88.907	74.822	85.485	89.235	84.364	79.929	82.684	82.443	80.618
7	94.903	80.504	89.498	94.686	91.708	87.291	91.958	91.479	88.579
8	98.245	84.065	94.057	97.398	96.358	95.073	98.846	97.068	95.082

The polymer Methocel K15M CR was used alone with Ciprofloxacin HCl as the matrix builder in the proposed formulations F-1, F-2, F-3, as 5%, 6%, 7% of the total weight of the tablet respectively (Table-1).The variable ranges of Methocel K15 M were selected by considering physicochemical behavior of the polymer in the physiological fluid and physicochemical properties of the drug. According to USP for an ideal sustained release dosage form like theophylline SR, percent release in 1st hour should be not more than 30% and in 10^{th} hour not less than 80% (USP, 2006). The release pattern of Ciprofloxacin HCl magnesium from the proposed formulation 2 (6% Methocel K15M CR), and proposed formulation 3 (7% Methocel K15M CR) met the desired sustained release pattern (Table-2). This indicated that at a minimum percent (6%) of Methocel K15M CR the desired sustained release of Ciprofloxacin HCl was obtained by direct compression

method which is evident from 1st hour to 8th hour *in vitro* dissolution studies. Again, Methocel K4M CR alone was used with Ciprofloxacin HCl as the matrix builder in the proposed formulations F-4, F-5, and F-6 as 15%, 17%, and 18.3% of the total weight of the tablet respectively (Table 1). Similarly, Methocel K4M premium was used with Ciprofloxacin HCl as the matrix builder in the proposed formulations F-7, F-8, and F-9 as 6.7%, 12.3%, and 15.6% of the total weight of the tablet respectively (Table 1). The same variable ranges of Methocel K4M premium were selected on the basis of physicochemical behavior of the polymer in the physiological fluid and physicochemical properties of the drug. The drug release order in the proposed formulation F-7 (6.7% Methocel K4M premium), F-8 (12.3% Methocel K4M premium), and F-9 (15.6% Methocel K4M premium) met the desired sustained release action (Table-2).

Figure- 1: Effect of Methocel K15M on Ciprofloxacin HCl from proposed formulations F1-F3 in simulated gastrointestinal fluid.

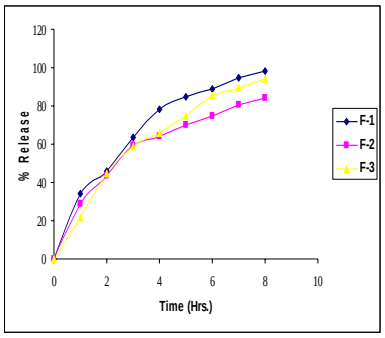

Figure-1.1: Zero order release of Ciprofloxacin HCl from Methocel K15M CR based formulations (F1– F3).

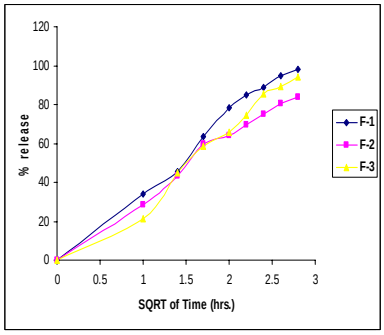

Figure-1.2: Higuchi release of Ciprofloxacin HCl from Methocel K15M CR based formulations (F1 – F3).

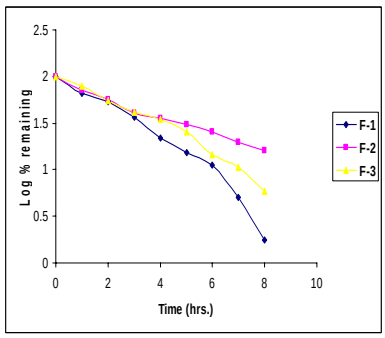

Figure-1.3: First order release of Ciprofloxacin HCl from Methocel K15M CR based formulations (F1– F3).

Determination of release mechanism from multiple coefficients

The drug release data of the proposed formulations F-1, F-2, F-3 were treated in different kinetics orders such as Zero Order Plot (Table- 2, Fig.-1), First Order Plot (Fig.-1) and Higuchi Plot (Fig.-1) and their correlation coefficients were determined graphically to identify their release mechanism. From Table-3 it was observed that proposed formulations F-1, F-2, & F-3 although followed first order and Higuchi release kinetics however, the release kinetics was very close to 1 in case of Higuchi plot than other kinetic orders that indicated Higuchi release kinetics was predominant here. In case of Methocel K4M premium the drug release data were treated in different kinetic orders (Fig.-2) such as zero order, first order and Higuchi release kinetics to assess the release mechanism of Ciprofloxacin HCl. From Table-3 it was observed that F-4, F-5, F-6 followed both first order and Higuchi release mechanism. It is also added that correlation coefficients of Higuchi were very close to 1 that reflected predominant Higuchi release mechanism. From the above discussion it can be predicted that Methocel K4M premium was better than Methocel K15M CR for Ciprofloxacin HCl sustained release tablet matrix. Methocel K4M premium at 6.7% can give expected sustained release by direct compression method and that may be better to combat against infectious diseases more effectively.

Table-3: Multiple coefficients determination data by using different percent of polymer Methocel K15M CR and Methocel K4M premium in simulated dissolution media.

	Multiple coefficient of determination (R^2)		
Formulation code	Zero Order	First Order	Higuchi
F-1	0.8946	0.9550	0.9885
F-2	0.8782	0.9877	0.9828
F-3	0.9288	0.9808	0.9896
F-4	0.8962	0.9661	0.9956
F-5	0.9081	0.9588	0.9973

F-6	0.9592	0.9261	0.9886
F-7	0.9801	0.8231	0.9697
F-8	0.9773	0.9018	0.9706
F-9	0.9843	0.9167	0.9574

Figure- 2: Effect of Methocel K4M on Ciprofloxacin HCl from proposed formulations F4-F6 in simulated gastrointestinal fluid.

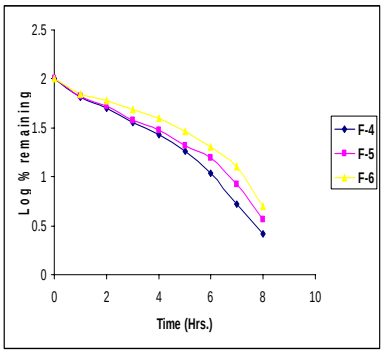

Figure-2.1: Zero order release of Ciprofloxacin HCl from Methocel K4M CR based formulations (F4– F6).

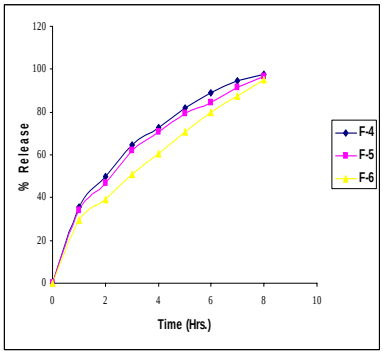

Figure-2.2: Higuchi release of Ciprofloxacin HCl from Methocel K4M CR based formulations (F4 – F6).

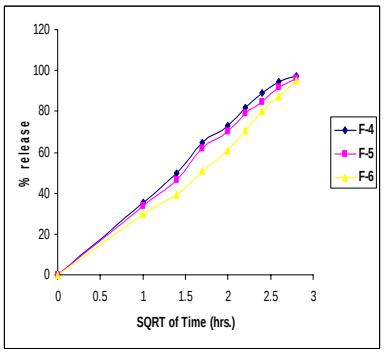

Figure-2.3: First order release of Ciprofloxacin HCl from Methocel K4M CR based formulations (F4– F6).

The proposed mechanism of Methocel K15M CR and Methocel K4M premium:

The proposed drug release mechanism of Methocel K15M CR, Methocel K4M CR and Methocel K4M premium is as follows-hydration, swollen and diffuse the drug particles. Methocel K15M CR, Methocel K4M CR and Methocel K4M premium are hydrophilic polymers first hydrated while get in contact with dissolution fluid and then swollen and allow gradual dissolution and diffusion of drug from the matrix (Arthur, 2000). When those polymers get hydrated in contact with dissolution fluid, a number of porous channels were formed within the polymeric structure. Through that porous channels, fluid enter slowly and dissolve the drug on the basis of partition coefficient. The drug solution is then diffused or released from the matrix. The dissolution and diffusion of the drug molecule depend on rate and extent of polymer hydration, number of channel formation, amount of fluid enter into the porous channel, number of multilayer formation, partition coefficient of the drug. From the study it is evident that Methocel K15M CR is quite better than Methocel K4M CR and Methocel K4M premium as rate retardant. The minimum percent i.e.6% Methocel K15M CR exhibited desired sustained release action whereas only 15% Methocel K4M CR and 6.7% Methocel K4M premium showed desired sustained release action whose molecular weight was higher than Methocel K4M CR and Methocel K4M premium. The release rate of the water soluble polymer depends on molecular weight; the larger the molecule, the stronger the forces holding the chains together (Renoylds et al., 1998). More energy has to be expended to force the chain apart in the liquid.

The velocity of penetration (*S*) of a solvent into the bulk polymer obeys the relationship

$S=kM^{-A}$

Where M is the molecular weight, k and A being constants.

The dissolution process from the polymer matrix was complicated than from ordinary crystalline materials. It is frequently observed that swollen layer and gel layers form next to the diffusion layer (Sungthongjeen, 1999). We also observed that when the percent of polymer increased then the release of the drug was decreased and in case of 7 % Methocel K15M CR polymer the release was 94% at 8th hour. This was occurred due to multilayer formation in the tablet matrix. When the tablet matrix was hydrated then it became swollen and made channel to penetrate

water into the matrix and dissolved the drug and finally diffused. Due to formation of multilayer, the pathway was not straight forward and drug release was retarded.

Figure- 3: Effect of Methocel K4M premium on Ciprofloxacin HCl from proposed formulations F7-F9 in simulated gastrointestinal fluid.

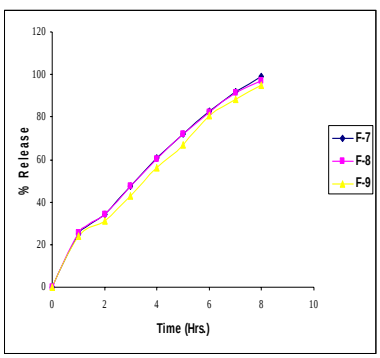

Figure-3.1: Zero order release of Ciprofloxacin HCl from Methocel K4M premium based formulations (F7 – F9).

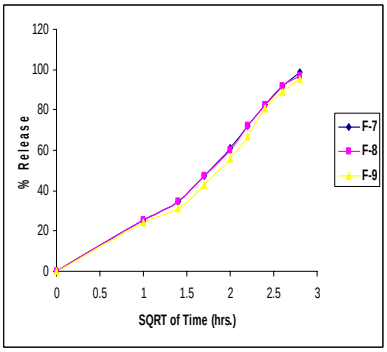

Figure-3.2: Higuchi release of Ciprofloxacin HCl from Methocel K4M premium based formulations (F7– F9).

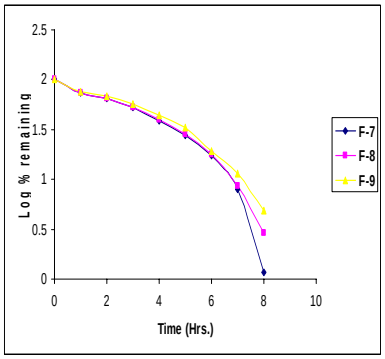

Figure-3.3: First order release of Ciprofloxacin HCl from Methocel K4M premium based formulations (F7 – F9).

CONCLUSION

Ciprofloxacin HCl is widely used against infection. Infectious diseases are very common where the patients take medicine regularly. Sustained release dosage form of Ciprofloxacin HCl can provide better patient compliance and prolonged action against infectious disease. The half life of Ciprofloxacin HCl is 4-6 hours for oral dosage. Due to its rapid elimination and posology, this drug will be a suitable candidate if formulated into sustained release dosage forms. The present study was investigated in order to formulate Ciprofloxacin HCl sustained release with addition of release retarding polymer Methocel K15M CR, Methocel K4M CR and Methocel K4M premium. From the study it was concluded that at least 6% Methocel K15M CR showed desired sustained release and at least 15% Methocel K4M CR and 6.7% Methocel K4M premium met the desired sustained release action. Besides, Methocel K15M CR was better than Methocel K4M CR and Methocel K4M premium for Ciprofloxacin HCl sustained release tablet matrix by direct compression. We also observed that Higuchi release kinetics was predominant among all the release kinetics. The use of direct compression method may increase high production, performance, save valuable time in manufacturing plan, less involvement of labor, reduce cost and increase profit. The proposed formulations (F-2 and F-6) may be used for the development of Ciprofloxacin HCl sustained release matrix and meet the patient's demand in order to combat against infection more precisely.

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