Comparison of Gastro Retention Time and *in vitro* Release Profile studies of Ciprofloxacin HCl from Co-matrix Tablets of Hydrophilic Polymers

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ABSTRACT: Controlled release co-matrix tablets of Ciprofloxacin HCl were prepared with different types of bio-adhesive polymers e.g. Methocel K4M, Methocel K 15M CR and Methocel K 100LV, Povidone K-30, and Xanthan gum. Tablets prepared by direct compression method were subjected to *in-vitro* drug dissolution study for 8 hours in a simulated gastric fluid media using USP dissolution apparatus II with 50 rpm at 37±0.5ºC. The bio-adhesive property was investigated in terms of retention time following *in-vitro* wash-off method. The concentrations of polymers were varied to investigate whether these variations can cause any change in release of Ciprofloxacin HCl molecule and bio-adhesion property or not. In most of the cases it is found that Methocel K4M and Methocel K100LV based co-matrix tablets release greater percentage of active drug than Methocel K15M CR based co-matrix tablets. Bio-adhesive strength of Methocel K15M CR and Xanthan gum based co-matrix tablets was proved to be maximum followed by Methocel K4M and Xanthan gum based co-matrices. Whereas Methocel K100LV and Xanthan gum based co-matrices showed little or poor muco-adhesion. Methocel K4M, K15M CR and Xanthan gum based formulations showed nearly zero-order release, on the other hand Methocel K100LV and Xanthan gum based formulation showed a burst release within one hour of dissolution. Finally it was revealed that Xanthan gum provided optimum bio-adhesion functioning as a synergist in co-matrices and comply the USP specification as a most suitable controlled release polymer.

Key words: Gastro retention time, Direct Compression, Ciprofloxacin HCl, Methocel K4M, Methocel K15M CR, Methocel K100LV, Xanthan gum.

INTRODUCTION

Orally administered controlled release dosage form shows mainly two adversities; first too short gastric retention time (GRT) and secondly unpredictable gastric emptying time. A relatively brief gastro intestinal (GI) transit time of most of the products (8-12 hours) impedes the formulation of single daily dosage forms. These problems can be overcome by altering the gastric emptying time, which is affected by age, sex, and health condition of a subject. It is therefore desirable to formulate a sustained release dosage form that gives an extended GI residence time. Various approaches have been worked out to improve the retention time of an oral dosage form in the stomach including bio-adhesive (gastro retentive) systems.[1] Bio-adhesive systems are usually exploited to localize a delivery device within the cavity of body to improve the drug absorption

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process in site-specific manner [2]. The matrix system is commonly used for manufacturing sustained release dosage forms because; it makes such manufacturing easy.[3] Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium does not disintegrate but immediately after hydration develops a highly viscous gelatinous surface barrier which controls the drug release from and the liquid penetration into the center of the matrix system, that increases the retention time on mucosal surfaces and may lead to adhesive interaction.[4] The present study is designed to study the capacity of hydrophilic polymers as release retarding ingredient and muco-adhesive agent over drug molecule in terms of dissolution study, gastro retention time and subsequent data analysis.

MATERIALS AND METHODS

Ciprofloxacin HCl monohydrate was procured from Beximco Pharmaceuticals Limited. Methocel K4M, Methocel K15M CR and Methocel K100LV were collected from Colorcon, USA . Povidone K-30, Sodium bicarbonate ($NaHCO_3$), Citric acid, Microcrystalline cellulose (Avicel PH 102) and Xanthan gum were collected from Loba Chem pvt. Ltd, India. Magnesium stearate and Aerosil were obtained from Hanau Chemicals Ltd. (Japan). For determining bio-adhesive strength, gastric mucosa of cow was obtained from a local slaughterhouse in Dhaka. All other reagents employed were of analytical or pharmaceutical grade.

Preparation of Co-matrix tablets by direct compression technique. The method includes blending of the active ingredients with polymers, filler, lubricant and flow promoter followed by direct compression. Table-1 represents the formulation of co-matrix tablets with their formulation code. Amount of active drug was constant (582 mg) in all cases. Total weight of tablets was 1000 mg. The required amount of active drug and polymers were weighted separately mixed thoroughly in a drum blender. Co-matrix tablets were prepared by Manesty 16 station rotary press applying a compression force of 3 ton. All the tablets were then stored in air tight containers at room temperature for further investigation.

***In-vitro* Dissolution study**. *In-vitro* drug release studies of the prepared co-matrix tablets were carried out in a USP XXII dissolution apparatus II (paddle) equilibrated at 37 ± 0.5°C with 50 rpm. The dissolution study was performed for 8 hours in 900 mL of 0.1 N HCl (hydrochloric acid, pH 1.2) under sink condition. Sample solution was analyzed for Ciprofloxacin HCl at 276 nm[5] by an UV spectrophotometer (Shimadzu, Japan). The amount of drug present in the sample tablets was calculated with appropriate calibration curve constructed from reference standards. Drug dissolved at specified time period was plotted as percent release versus time (hours) curve.

Bio-adhesive testing by *in-vitro* wash-off test. The bio-adhesive property of the prepared tablets was evaluated by an *in-vitro* adhesion testing method known as wash-off method. Freshly excised pieces of intestinal mucosa (4X3 inch) from cow were mounted on the stainless steel slide, connected with a suitable support. Three tablets were placed on to wet rinsed tissue specimen and immediately there after the support was hung to the arm of the USP tablet disintegrating test machine. When the disintegrating machine was operated, the tissue specimen was given a slow, regular up and down movement in the gastric fluid (pH 1.2) at 37°C contained in a one liter vessel of the machine. Similar experiments were also cited.[6]

Kinetic modeling of drug release. After completing *in vitro* dissolution of all the batches for eight hours, the data were treated with zero order equation [7] and Higuchi equations [8] (equation 1-2 respectively).

$$M_t = M_0 + k_0 t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

$$Mt = M_0 - k_H t^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

In these equations, M_t is the cumulative amount of drug released at any specified time (t) and M_0 is the dose of the drug incorporated in the delivery system. k_0 and k_H are rate constants for zero order and Higuchi model respectively. These models failed

to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore the dissolution data were also fitted to well-known Korsmeyer kinetic equation [9] to ascertain the mechanism of drug release.

$$\log (M_t/M_\infty) = \log k + n \log t \ldots\ldots\ldots\ldots (3)$$

Where M_∞ is the amount of drug release after infinite time; k is the release rate constant which considers structural and geometric characteristics of the tablet; and n is the diffusional exponent or release exponent; indicative of the mechanism of drug release. For a tablet having cylindrical shape, when n is below 0.45, the Fickian diffusion phenomenon dominates, and n between 0.45 and 0.89 is an anomalous transport (non-Fickian diffusion), often termed as first-order release. After the n value reaches 0.89 and above, the release can be characterized by case II and super case II transport, which means the drug release rate does not change over time and the release is characterized by zero order. In this case, the drug release is dominated by the erosion and swelling of the polymer.[11-12] Mean dissolution time (MDT) was calculated from dissolution data according to Mockel and Lippold [7] using the following equation :

$$MDT = \left(\frac{n}{n+1}\right) k^{-\frac{1}{n}}$$

RESULTS AND DISCUSSION

To investigate the effects of polymer and their content level on drug release twelve formulations were prepared (Table 1). Formulation F-1, F-2 and F-3 fits with Korsmeyer kinetic model (R^2 =0.9767, R^2=0.9781 and R^2=0.9736 respectively) (Table 2). The values of release exponent (n) for the above mentioned formulations are 0.7335, 0.7605 and 0.8337 respectively which indicates anomalous transport mechanism (coupling of the diffusion and erosion mechanism).[9] F-4 (R^2=0.9667) has a value of release exponent (n) is 1.0074 which indicates case II and super case II transport, i.e. the drug release rate does not change over time and the release is characterized by zero order. In this case, the drug release is dominated by the erosion and swelling of the polymer.[10-11] Formulation F-5, F-6 and F-7 also followed Korsmeyer model (R^2 =0.9899, R^2 =0.9907 and R^2 =0.9780 respectively) (Table-2). The values of release exponent (n) for the formulation F-5, F-6 and F-7 are 0.8937, 0.9276 and 0.9464 respectively. Formulation F-8 (R^2=0.9786) has a value of release exponent (n) is 1.0772, which indicates the drug release is dominated by the erosion and swelling of the polymer. In the same manner formulations F-9, F-10, F-11 and F-12 best fit with Korsmeyer kinetic model (R^2 =0.9933, R^2 =0.9820, R^2 =0.9864 and R^2 =0.9735 respectively) (Table-2). The values of release exponent (n) for the formulation F-9, F-10, F-11 and F-12 are 0.6218, 0.6454, 0.6816 and 0.6652 respectively which indicate that the drug was released by anomalous transport

The mean dissolution time (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 of the polymer and vice versa. The MDT value was also found to be a function of polymer content and polymer nature. MDT values for all the twelve formulas are listed in Table 2. From the table, it was observed that, MDT values were larger for those formulations which contained highest percentage of polymer.

Again, gastro retention time (GRT) is used to characterize the muco-adhesive strength of the dosage form inside the stomach. A higher value of GRT indicates a higher dosage form retaining ability on to the gut wall and vice versa. The GRT was also found to be dependent up on polymer content and polymer nature. The gastro retention time for all the twelve formulations are listed in Table 3.

Effect of Methocel K4M on the release and bio-adhesive strength of Ciprofloxacin HCl loaded co-matrix tablets. Figure 1 (a) shows the effect of different concentration of Methocel K4M on drug release characteristics from Ciprofloxacin HCl. A significant difference in release pattern was observed among the formulations of F-1, F-2, F-3 and F-4. Ciprofloxacin HCl loaded F-1, F-2, F-3 and F-4 contain 50, 80, 110 and 140 mg of Methocel K4M

Table 1. Formulations of Ciprofloxacin HCl (CPX HCl.H_2O) monohydrate loaded co-matrix tablets prepared by direct compression method.

Ingredients	Formulation Code											
(mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12
Ciprofloxacin HCl.H_2O	582	582	582	582	582	582	582	582	582	582	582	582
Methocel K4M	50	80	110	140	-	-	-	-	-	-	-	-
Methocel K15M CR	-	-	-	-	50	80	110	140	-	-	-	-
Methocel K100LV CR	-	-	-	-	-	-	-	-	50	80	110	140
Povidone K 30	50	50	50	50	50	50	50	50	50	50	50	50
Xanthan gum	100	70	40	10	100	70	40	10	100	70	40	10
Citric acid	20	25	30	35	20	25	30	35	20	25	30	35
Sodium bi carbonate	50	45	40	35	50	45	40	35	50	45	40	35
Avicel PH 102	130	130	130	130	130	130	130	130	130	130	130	130
Aerosil	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	8	8	8	8	8	8	8	8	8	8	8	8
% of polymer (methocel, xanthan gum)	5,10	8,7	11,4	14,1	5,10	8,7	11,4	14,1	5,10	8,7	11,4	14,1
Total Weight	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000

Table 2. Kinetic parameters of Ciprofloxacin HCl release from different polymeric co-matrix tablets

Formulation code	% of drug release after 8 hrs	Zero Order		Higuchi		Korsmeyer		Mean Dissolution Time (MDT) (hrs)
		K_o	R^2	K_H	R^2	n	R^2	
F-1	90.136	10.79	0.9563	33.32	0.9821	0.7335	0.9767	3.314
F-2	83.294	10.20	0.9566	33.45	0.9788	0.7605	0.9781	3.680
F-3	77.924	9.93	0.9540	30.48	0.9673	0.8337	0.9736	4.037
F-4	73.136	9.72	0.9577	29.42	0.9445	1.0079	0.9667	4.587
F-5	75.541	9.36	0.9882	28.03	0.9543	0.8937	0.9899	4.775
F-6	66.20	8.27	0.9884	24.65	0.9452	0.9276	0.9907	5.598
F-7	55.633	7.03	0.9815	20.82	0.9252	0.9469	0.9780	6.906
F-8	41.536	5.76	0.9730	16.86	0.8986	1.0772	0.9786	8.475
F-9	97.772	11.57	0.9665	35.58	0.9841	0.6218	0.9933	5.819
F-10	92.720	11.02	0.9744	33.59	0.9743	0.6454	0.9820	6.559
F-11	87.583	10.28	0.9858	31.02	0.9647	0.6816	0.9864	7.547
F-12	80.423	9.38	0.9850	28.13	0.9535	0.6652	0.9735	8.905

and 100, 70, 40 and 10 mg of Xanthan gum respectively. The average drug released was 90.14, 83.29, 77.92 and 73.14% after 8 hours of dissolution period. No formulation exerted any initial burst release. The ability of hydroxy propyl methyl cellulose (HPMC) to prevent burst release was also claimed by Reza *et al*, 2002 [13]. It is clearly evident that drug release was decreased with the increase in polymer loading. Methocel K4M is a class of hydrophilic matrix system which when comes in contact with liquid dissolution medium, forms fast and strong viscous gel to control initial drug release [12]. While HPMC could potentially retard the release of a soluble drug, it could also facilitate the release of relatively insoluble drug due to its solubilizing effect [12]. The hydrated gel matrix formed by HPMC is involved in the phenomenon of bio-adhesion. Bio-

adhesive strength was determined using *in-vitro* wash-off method. Formulation F-1, F-2, F-3 and F-4 retained on the mucosa for 3.475, 3.810, 3.975 and 4.525 hours respectively. As the concentration of Methocel K4M increases and amount of Xanthan gum decreases, the bio-adhesive strength of corresponding formulation increases, possibly due to its more concentrated gel layer.

Table 3. Physical parameters and gastro retention time of Ciprofloxacin HCl loaded co-matrix tablets of different polymers

Formulation code	Average Hardness (Kg)	Friability (%)	Average Length (mm)	Average Width (mm)	Average Thickness (mm)	Weight variation (%)	Gastro retention time (hrs.)
F-1	11.11	0.3	19.12	8.85	7.52	0.02	3.475
F-2	11.37	0.1	19.11	8.86	7.30	0.01	3.810
F-3	12.90	0.2	19.16	8.81	7.26	0.02	3.975
F-4	12.93	0.3	19.19	8.45	7.21	0.01	4.525
F-5	13.72	0.1	19.19	8.81	7.30	0.07	4.815
F-6	14.77	0.3	19.17	8.86	7.52	0.08	5.000
F-7	14.93	0.4	19.97	8.46	7.70	0.02	5.525
F-8	15.86	0.3	19.89	8.80	7.65	0.04	5.975
F-9	9.19	0.5	19.11	8.53	7.14	0.07	2.810
F-10	10.04	0.6	19.15	8.53	7.52	0.03	2.575
F-11	10.92	0.4	19.16	8.25	7.26	0.06	2.425
F-12	11.88	0.3	19.11	8.59	7.30	0.09	2.150

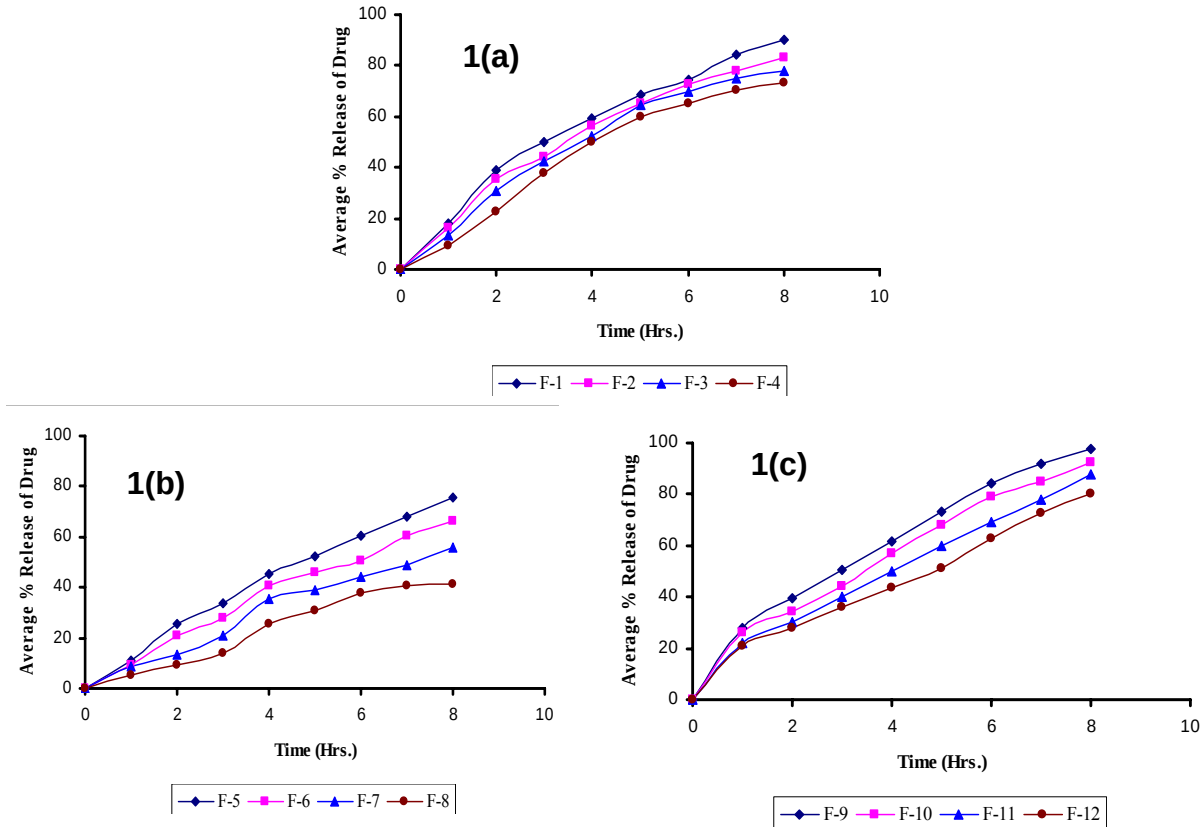

Figure 1. Zero order release profile showing effect of polymers on Ciprofloxacin HCl release from (a) Methocel K4M (b) Methocel K15M CR (c) Methocel K100 LV based co-matrix tablets.

Effect of Methocel K15M CR on the release and bio-adhesive strength of Ciprofloxacin HCl loaded co-matrix tablets: Figure 1 (b) elaborates the effect of different concentration of Methocel K15M CR on drug release characteristics of Ciprofloxacin HCl (CPX HCl) co- matrix tablets (F-5, F-6, F-7 and F-8) with 50, 80, 110 and 140 mg of Methocel K15M CR and 100, 70, 40 and 10 mg of Xanthan gum respectively. And the average drug released was 75.54, 66.20, 55.63 and 41.54% after 8 hours of dissolution period. In case of Methocel K4M loaded co-matrix tablet F-4 containing highest amount (14%) of Methocel K4M, drug release was 73.14% after 8 hours of dissolution where as with Methocel K15M CR drug release was 41.54% after 8 hours. Lower viscosity grade of HPMC, as they have comparatively less viscosity exerted more drug release with short retention period. Higher HPMC grade (Methocel K15M CR) exerted a very high retention time compared to Methocel K4M possibly due to its more viscous gel layer.

Effect of Methocel K100 LV on the release and bio-adhesive strength of Ciprofloxacin HCl loaded co-matrix tablets. The release profile of Ciprofloxacin HCl from Methocel K100 LV based co-matrix tablets is depicted in figure-1 (c). This polymer exerted initial burst release within 1 hour irrespective of polymer content. Povidone K-30, being highly soluble in aqueous environment, is leached slowly from the matrix generating numerous pores and channels through which the drug is released by diffusion process.[13] Moreover, Ciprofloxacin HCl is highly water-soluble drug with pKa value 6.09 and 8.62 [14]. Again Methocel K100LV CR has the lowest viscosity compared to Methocel K4M and Methocel K15M CR. All these effects contribute to the initial burst release. Retention capacity on gut wall was also less than those prepared with Methocel K4M and Methocel K15M CR.

CONCLUSION

Bio-adhesive and subsequent release profiles were performed to evaluate the performance of Ciprofloxacin HCl when formulated with varying concentrations of different rate retarding polymers. From pharmaceutical and biopharmaceutical viewpoint the most potential polymer should be one that possesses strong bio-adhesive property (drug is dissolved before dosage form leaves mucosa), sufficient release retarding capacity and provides a release profile that meets USP specification. Methocel K15M CR with Xanthan gum has been proved eligible to be used in bio-adhesive sustained release dosage form with above properties. Whereas Methocel K4M possesses sustaining property with moderate bio-adhesive characteristics and Methocel K100LV CR lacks both properties. Judicial selection of the mentioned hydrophilic polymer may lead to an optimum formulation with desirable distinctiveness. However, further studies in this context should be carried out to establish stability and reproducibility of this dosage form. Scopes using X-ray and Gama scintography should be explored to find the real bio-adhesion in animals. The i*n vitro- in vivo* correlation should also be performed to assess the efficacy of this muco-adhesive dosage form.

REFERENCES

1. Vyas, S.P. and Khar, R.K. 2002. Controlled Drug Delivery 1st eds. Jain, M.K., Published by CBS publishers, Delhi, p. 199.
2. Wilson, C.G. and Washington, N. 1989. Biological barriers to drug absorption. In: Physicological Pharmaceutics. Ellis Harwood, Chickestar.
3. Cardinal, J.R., Matrix systems, in Langer R. S. and Wise, D.L. 1984. Medical Applications of Controlled Release, Volume 1, Classes of Systems, Published by CRC Press, Boca Raton, FL, USA, pp. 41-67.
4. Lachman, L., Lieberman, H.A. and Kanig, J. L. 1990. *Sustained Release Dosage Forms*. In: The Theory and Practice of Industrial Pharmacy, 3rd edition, Varghese Publishing House, Bombay, pp. 453-454.
5. The United States Pharmacopoeia. 2006. 29th eds. pp. 520.
6. Chowdary, K.P.R. and Rao, Y.S. 2003. Design and In Vitro and In Vivo Evaluation of Muco-adhesive Microcapsules of Glipizide for Oral Controlled Release: A Technical Note. *AAPS PharmSciTech 2003,* **39.**
7. Mockel, J.E. and Lippold, B.C. 1993. Zero order release from hydrocolloid matrices. *Pharm. Res*. **10**, 1066-1070.
8. Higuchi, T. 1961. Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci*. **50**, 874-875.

9. Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A. 1983. Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm*. **15**, 25-35.

10. Peppas, N.A. 1985. Analysis of Fickian and non-Fickian drug release from polymers. *Pharm. Acta. Helv*. **60**, 110-111.

11. Chueh, H.R., Zia, H. and Rhodes, C.T. 1995. Optimization of sotalol floating and bioadhesive extended release tablet formulations. *Drug Dev. Ind. Pharm.* **21,** 1725-1747.

12. Lee, B.J., Ryu, S.G., and Cui, J.H. 1999. Formulation and release characteristics of Hydroxypropylmethylcellulose matrix tablet containing meletonin. *Drug Dev. Ind. Pharm*. **25**, 493-501.

13. Reza, S., Quadir, M.A. and Haider, S.S. 2002. Development of theophylline sustained release dosage form based on kollidon SR. *Pakistan J. Pharm. Sci.* **115**, 63-70.

14. Barbosa, J., Barrón, D., Jiménez-Lozano, E. and Sanz-Nebot. 2001. V. Comparison Between Capillary Electrophoresis, Liquid Chromatography, Potentiometric and Spectrophotometric Techniques for Evaluation of pKa Values for Zwirterionic Drugs in Acetonitrile-Water Mixtures. *Anal Chim. Acta, pp.* 437, 309.