Effect of Hydrophobic Polymers on the Gastro Retention Time and *In vitro* Release of Ciprofloxacin HCl from Co-matrix Tablets

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ABSTRACT: The present study was conducted to investigate the effect of different polymers on the release profile and bio-adhesive strength of a water soluble drug, ciprofloxacin HCl from different percentages of Eudragit RS PO and Kollidon SR based co-matrix tablets. Matrix formulations were prepared by direct compression method. 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 Eudragit RS PO based co-matrix tablets release greater percentage of active drug and that bio-adhesive strength of Kollidon SR and xanthan gum based co-matrix tablets were significantly better. 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, Eudragit RS PO, Kollidon SR, 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 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] 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.

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The second class represents hydrophobic and water insoluble materials, which are potentially erodible.[4]

There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. The release of drug from the tablet matrix depends on the nature of polymer.[5] Polymers belonging to hydrophobic matrix systems control the drug release from and the liquid penetration into the center of the matrix system, that increase the retention time on mucosal surfaces and may lead to adhesive interaction.[6] The present study is designed to study the capacity of hydrophobic polymers as release retarding ingredients 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. Povidone K-30, sodium bicarbonate, 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 slaughter-house in Dhaka, Bangladesh. 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 mass of tablets was 1000 mg. The required amount of active drug and polymers were weighted separately, mixed thoroughly in a drum blender. The blend is then compressed with a constant compression pressure at specified weight using 16-station Manesty compression machine. 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 (pH 1.2) under sink condition. Sample solution was analyzed for ciprofloxacin HCl at 276 nm[7] by an UV-XXII spectrophotometer (Shimadzu, Japan). The amount of drug present in the sample tablets was calculated upon appropriate calibration curve constructed from reference standards. The average percent release of drug was then plotted against time.

Bio-adhesive testing by *in vitro* wash-off method. 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 onto wet, rinsed tissue specimen and immediately thereafter 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 in a 1 liter vessel.[8]

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 [9] and Higuchi equations [10] [equation (1)-(2) respectively].

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

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

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 Korsmeyer kinetic equation [11] 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 diffusion 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 the zero-order. In this case, the drug release is dominated by the erosion and swelling of the polymer.[12-13] Mean dissolution time (MDT) was calculated from dissolution data according to Mockel and Lippold [9] using the following equation:

$$MDT = \left(\frac{n}{n+1}\right) k^{-\frac{1}{n}} \quad \ldots \ldots \ldots \ldots \ldots (4)$$

RESULTS AND DISCUSSION

To investigate the effects of polymer and their content level on drug release eight formulations were prepared (Table 1). Formulations F-1, F-2, F-3 and F-4 fit with Korsmeyer kinetic model (R^2 = 0.985 ~ 0.998) (Table 2). The values of release exponent (n) for the above mentioned formulations were 0.711 ~ 0.756 which indicates anomalous transport mechanism (coupling of the diffusion and erosion mechanism).[11] Formulations F-5, F-6, F-7 and F-8 also followed Korsmeyer model (R^2 =0.9900 ~ 0.9977) (Table 2). The values of release exponent (n) were 0.722 ~ 0.793 which indicate that the drug was released by anomalous transport (coupling of the diffusion and erosion mechanism).[11]

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. MDT values for all the eight formulas are listed in Table 2. It was found that, MDT values were larger for those formulations which contained highest percentage of polymer.

Table 1. Formulations of ciprofloxacin HCl 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
Ciprofloxacin HCl	582	582	582	582	582	582	582	582
Eudragit RS PO	50	80	110	140	-	-	-	-
Kollidon SR	-	-	-	-	50	80	110	140
Povidone K 30	50	50	50	50	50	50	50	50
Xanthan gum	100	70	40	10	100	70	40	10
Citric acid	20	25	30	35	20	25	30	35
Sodium bicarbonate	50	45	40	35	50	45	40	35
Avicel PH 102	130	130	130	130	130	130	130	130
Aerosil	10	10	10	10	10	10	10	10
Magnesium stearate	8	8	8	8	8	8	8	8
% of polymer (Eudragit RS PO/Kollidon SR, xanthan gum)	5,10	8,7	11,4	14,1	5,10	8,7	11,4	14,1
Total weight (mg)	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-Pappas		Mean Dissolution Time (MDT) (hrs)
		K_o	R^2	K_H	R^2	n	R^2	
F-1	98.204	11.89	0.9698	36.46	0.9802	0.7112	0.9980	2.947
F-2	87.430	10.83	0.9700	33.07	0.9739	0.7250	0.9955	3.460
F-3	81.228	10.06	0.9734	30.61	0.9684	0.7280	0.9918	3.912
F-4	73.327	9.26	0.9777	27.94	0.9574	0.7563	0.9848	4.593
F-5	79.468	9.37	0.9838	28.22	0.9598	0.7330	0.9916	4.435
F-6	68.692	7.93	0.9798	24.03	0.9662	0.7220	0.9900	5.426
F-7	56.108	6.94	0.9768	20.55	0.9763	0.7374	0.9977	6.646
F-8	49.835	5.97	0.9875	17.94	0.9584	0.7929	0.9966	8.110

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 onto the gastric wall. The GRT was also found to be dependent on the polymer content and polymer nature. The gastro retention time for all the eight formulations are listed in Table 3.

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	13.14	0.2	19.21	9.00	7.50	0.08	2.900
F-2	14.20	0.1	19.25	8.99	7.25	0.08	2.725
F-3	14.38	0.3	19.26	8.89	7.56	0.04	2.375
F-4	15.76	0.2	19.25	8.57	7.70	0.09	2.050
F-5	14.84	0.3	19.12	8.89	7.97	0.07	3.500
F-6	15.45	0.1	19.12	8.90	7.26	0.00	2.775
F-7	16.40	0.2	19.13	8.65	7.57	0.06	2.550
F-8	16.51	0.3	19.35	8.27	7.68	0.02	2.375

Effect of Eudragit RS PO on the release and bio-adhesive strength of ciprofloxacin HCl loaded co-matrix tablets. Figure 1(a) shows the effect of different concentrations of Eudragit RS PO on drug release characteristics of ciprofloxacin HCl. A significant difference in release pattern was observed among the formulations of F-1, F-2, F-3 and F-4 which contain 50, 80, 110 and 140 mg of Eudragit RS PO and 100, 70, 40 and 10 mg of xanthan gum respectively. The average percentage of drug release was 98.2, 87.4, 81.2 and 73.3 after 8 hours of dissolution period. No formulation exerted any initial burst release. It is clearly evident that drug release was decreased with the increase in polymer loading. Bio-adhesive strength was determined using *in vitro* wash-off method. Formulations F-1, F-2, F-3 and F-4 retained on the mucosa for 2.900, 2.725, 2.375 and 2.050 hours respectively. As the amount of Eudragit RS PO increases and amount of xanthan gum decreases, the bio-adhesive strength of corresponding formulation decreases, possibly due to the less concentration in the gel layer.

Effect of Kollidon SR on the release and bio-adhesive strength of ciprofloxacin HCl loaded co-matrix tablets. Figure 1(b) elaborates the effect of different concentrations of Kollidon SR on drug release characteristics of ciprofloxacin HCl co-matrix tablets (F-5, F-6, F-7 and F-8) with 50, 80,

110 and 140 mg of Kollidon SR and 100, 70, 40 and 10 mg of xanthan gum respectively. The average percentage of drug release was 79.5, 68.7, 56.1 and 49.8 after 8 hours of dissolution period. In case of Eudragit RS PO loaded co-matrix tablet F-4 containing highest amount (14%) of Eudragit RS PO, drug release was 73.3% after 8 hours of dissolution whereas with Kollidon SR drug release was 49.8% after 8 hours. As Eudragit RS PO has comparatively less viscosity at short retention period, Kollidon SR exerted a very high retention time compared to Eudragit RS PO, possibly due to its more viscous gel layer.

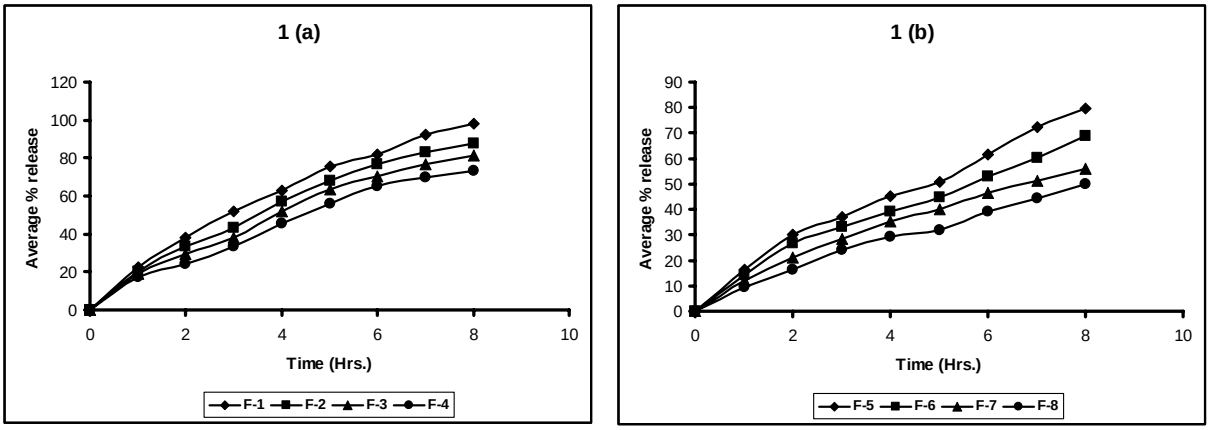

Figure 1. Zero-order release profile showing effect of polymers on ciprofloxacin HCl release from (a) Eudragit RS PO (b) Kollidon SR based co-matrix tablets.

Formulations F-5, F-6, F-7 and F-8 retained on the mucosa for 3.500, 2.775, 2.550 and 2.375 hour respectively. As the amount of Kollidon SR increases and amount of xanthan gum decreases, the bio-adhesive strength of corresponding formulation decreases, possibly due to the less concentration in the gel layer.

CONCLUSION

Bio-adhesive and subsequent release profiles were used 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 the one that possesses strong bio-adhesive property (drug is dissolved before dosage form leaves mucosa), sufficient release retarding capacity that provides a release profile that meets USP specification. Eudragit RS PO with xanthan gum has been proved eligible to be used in bio-adhesive sustained release dosage form with above properties, whereas Kollidon SR possesses sustaining property with moderate bio-adhesive characteristics. Judicial selection of the mentioned hydrophobic polymers 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 the dosage form. Scopes using X-ray and gama scintography should be explored to find the real bio-adhesion in animals. The *in vitro- in vivo* correlation should also be performed to assess the efficacy of the muco-adhesive dosage form.

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