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Research Article

THE DUAL ROLE OF A CARBOXYMETHYLATED STARCH IN MONOLITHIC POLYMERIC MATRICES OF CIPROFLOXACIN

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ABSTRACT

The effects of low level primogel on the release profile of ciprofloxacin hydrochloride from tablet matrices of ethylcellulose (EC), eudragit l-100 (EU), hydroxyethyl cellulose (HE) and hydroxypropyl methyl cellulose (HP) were investigated. Primogel was used at 0, 4 and 8 % w/w concentrations and the granules were prepared by wet granulation method with ethanol as the granulating solvent. Results show that, primogel exhibits a dual character of enhancing or retarding drug release from the polymer matrices depending on the type of polymer used. Primogel in the hydrophobic polymers was found to be an effective disintegrant causing a release of over 90 % of drug in just 30 min. It was however, found to be a good retardant in the hydrophilic polymers where drug release was sustained for more than 8 h. Primogel had an appreciable effect on drug release mechanism changing it from fickian to anomalous and vice versa also depending on the polymer type. Primogel, a carboxymethylated starch may be a useful additive in monolithic polymeric matrices of ciprofloxacin when immediate or sustained release oral dosage forms are intended.

Keywords: Primogel, Hydrophilic and hydrophobic polymers, Ciprofloxacin, Tablets

INTRODUCTION

Oral drug delivery continues to be the preferred route of drug administration and the use of hydrophilic matrices in achieving this has increased tremendously in the last three decades [1-6]. However, the prohibitive cost of both synthesis of new polymeric materials and their safety, is a major reason scientists have recently focused on investigating the use of polymer blends of pharmaceutically approved polymeric materials as matrix functional excipients to enhance single polymer performance [7-10].

From a practical point of view, the permeability of drugs within the macromolecular networks can effectively be adjusted over a wide range by simply varying the polymer blend ratio. Amighi and Moes[11, 12] investigated the effects of Eudragit® RL:Eudragit® RS blend ratio on the resulting drug release kinetics from coated theophylline matrix pellets and concluded that, the desired drug release profiles can easily be achieved by adjusting the polymer:polymer blend ratio. Rowe [13] found that drug release from ethylcellulose:HPMC (90:10) – coated pellets significantly increased with decreasing molecular weight of the ethylcellulose. This was attributed to the decreasing mechanical stability of the polymeric films, facilitating the formation of cracks and flaws within the film coatings through which the drug could rapidly diffuse out.

Blends of GIT-insoluble and enteric polymers have provided drug release profiles that are triggered by the pH of the surrounding environment along the GIT [14-16]. In the stomach (at low pH), both polymers are insoluble, whereas in the intestine (at high pH), the enteric polymer is soluble and might (at least partially) leach out from the matrix. This can lead to significant, dynamic changes in the physicochemical properties of the matrix during the GIT transit (e.g., increased permeability) and, thus, to altered drug release kinetics. Amighi et al [17] used blends of GIT-insoluble polymer Eudragit® NE and the enteric polymer Eudragit® L in order to achieve pH-independent release of a weakly basic model drug. In this study, one single polymer failed to provide pH-independent drug release (the release rate was too slow at high pH). However, blends of Eudragit® NE: Eudragit® L 70:30 produced a pH-independent release in the range of pH 1–7. In another study, Dashevsky et al [18] blended Kollicoat® SR and Kollicoat® MAE [aqueous dispersions of poly (vinyl acetate) and methacrylic acid:ethyl acrylate copolymer 1:1)] to coat verapamil-HCl-layered sugar cores. In a related study, Dashevsky *et al* [18] reported that pellets coated with the enteric polymer dispersion Kollicoat® MAE 30DP alone, lost their enteric properties upon compression into tablets because of the brittleness of the film coatings. However, when blended with 30% of the highly flexible polymer Kollicoat® EMM, the flexibility of the latter was sufficiently enhanced, and severe film damage during compression was avoided.

Polymer blends which are sensitive to the surrounding environment may also be of particular interest for many applications, for instance colon targeting.

Usually when polymers of varying physicochemical properties are blended, they do not interact in the same way with water and drug molecules, resulting in different mobility for water and drug within the polymeric networks [19-21]. Polymer blends which are sensitive to the surrounding environment may be of particular interest for many applications [19-23]. The use of high gelling polymers like carbopols or hydrophobic polymers such as ethylcellulose in drug delivery, especially in sustained release formulations may sometimes require other additives on account of high drug release retardant effect encountered with the polymer [23]. These additives are capable of interacting with the polymer to attenuate release of the incorporated active drug [10]. Ciprofloxacin is a broad spectrum fluoroquinolone antibiotic used to treat various infections. Due to its small molecular size, it penetrates tissue readily and leads to high tissue accumulation and systemic toxicities thus necessitating the formulation of the sustained release forms [24]. Thus, sustained release dosage forms of ciprofloxacin can provide desirable serum concentrations for prolonged periods without frequent dosing thereby providing patient compliance.

In a study by Emeje et al [10] blending a natural polysaccharide with carbopol 71G at the ratio of 2:1 was found to reduce the excessive thickening of the former while suitably controlling the release of zidovudine in the uncoated tablets. Ethyl cellulose however, is a polymer used to prepare sustained release medication of various types. Although it is insoluble, it can take up water. This can be explained on the basis of the hydrogen bonding capability of the polymer with water. Sodium carboxymethylcellulose on the other hand, is an anionic water soluble polymer derived from cellulose. It acts as a thickener, binder, stabilizer, protective colloid, suspending agent and rheology control agent due to these properties it has a broad application in the food and pharmaceutical industries. For example, Lecomte et al reported that, if applied as a film coating

material, ethylcellulose perfectly formed membranes which resulted in very low drug release rates because ethylcellulose is poorly permeable for most drugs. To overcome this restriction, some researchers investigated the effect of adding water-soluble polymers such as polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC) to ethylcellulose coatings. They were of the opinion that upon contact with aqueous media, these water soluble polymer additives hydrate and leach out from the polymeric membranes, resulting in more permeable films and increased drug release rates.

The present paper reports the findings of the study on the influence of low level primogel on the sustained release of ciprofloxacin from tablet matrices of four different polymers; Ethylcellulose, Hydroxyethylcellulose, Hydroxypropyl methylcellulose, and Eudragit L-100. Ciprofloxacin hydrochloride (CFH) a fluoroquinolone is a broad spectrum antibiotic used in the treatment of urinary and gastro intestinal tract infections in the dose range of 250 – 500 mg three times daily. Due to its small molecular size, it penetrates tissue readily and leads to high tissue accumulation and thus systemic toxicities [21]. Hence its choice as a model drug in this study.

MATERIALS AND METHODS

Ciprofloxacin hydrochloride (Jawa Int., India), primogel® (Generic Chem., USA), ethylcellulose, hydroxyethylcellulose and hydroxypropyl methylcellulose (Fluka, Germany), Eudragit L-100 (Rohm Pharma, Italy). Other chemicals used were of analytical grade and used as obtained from the manufacturers.

Methods

Preparation of matrix tablets

The wet granulation method of massing and screening using hydro alcoholic solution was used to prepare the granules. The constituent of each batch (Table 1) was weighed and triturated using a mortar and pestle. The dry mix was then moistened with a dispersion of the polymer in ethanol to form a damp mass. The wet mass was then screened through sieve number 10 (1.7 mm) and dried in a hot air oven at 55oC for 60 minutes. The dried granules were rescreened through sieve number 16 (1.0 mm) and lubricated with talc and magnesium stearate prior to compression with a single punch tabletting machine (Manesty model F3, England) fitted with 17 mm concave punches.

Table 1: Composition of matrix tablets of ciprofloxacin containing different polymers and varying concentrations of primogel

Ingredients (mg)	Batches											
	EC1	EC2	EC3	EU1	EU2	EU3	HE1	HE2	HE3	HP1	HP2	HP3
Drug	500	500	500	500	500	500	500	500	500	500	500	500
EC	150	150	150									
EU				150	150	150						
HE							150	150	150			
HP										150	150	150
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Mgst	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Primogel	0	20	40	0	20	40	0	20	40	0	20	40

Drug, ciprofloxacin HCl; EC, ethylcellulose; EU, eudragit L – 100; HE, hydroxyethyl cellulose; HP, hydroxypropyl methylcellulose; MgSt, magnesium stearate

Evaluation of Tablet properties

Hardness

Ten tablets were randomly selected from each batch and the hardness determind with standard Mosanto hardness tester (Erweka, Germany).

Friability

The friability of 20 randomly selected tablets was detrmined using Erweka model friabilator. The dedsuted tablets were put in the friabilator and set at the speed of 25 rotations per minute for four minutes and the percentage change in weight calculated.

Weight variation

Weight of 20 randomly selected tablets was taken with a metler electronic balance of readability 0.001 g. The mean and standard deviation were noted for each batch.

In vitro release studies

In vitro release of ciprofloxacin from the matrices was determined in 0.1N HCl (pH 1.5) by using standard USP XXII rotating paddle (method II) apparatus, Erweka, Germany. A 900 mL volume of the dissolution medium was used to ensure sink conditions and the paddle was maintained at 50 rotations per minute at 37 ± 1.0oC. At predetermined time intervals, 5 mL of the sample was taken and replaced with fresh dissolution medium. The samples were diluted appropriately and the absorbance determined at 278 nm as in drug content determination.

Drug content

Twenty tablets were randomly selected and ground in a mortar to a fine powder and weight equal to the average weight of one tablet was dissolved in 0.1N HCl. The filterate was then diluted appropriately and the absorbance taken in a Unico spectrophotometer at 278 nm.

Statistical analysis

Statistical analysis was carried out using Microsoft Excel software (SPSS), which included mean, standard deviations, variances and analysis of variance (ANOVA, F-test). At 95% confidence interval, P-values less than or equal to 0.05 were considered significant.

RESULTS AND DISCUSSION

Physical characterization of the matrix tablets

Physical appearance, tablet hardness, friability, weight variation, and drug content uniformity of different formulations of the four polymers were found to be satisfactory as can be seen from Table 2. Tablet hardness varied between 6.42 to 9.60 KgF and friability was less than 0.5 % w/w. The prepared tablets exhibited low weight variation and a high degree of drug content uniformity indicating that the hydro-alcoholic wet granulation method is acceptable for preparing good quality matrix tablets of ciprofloxacin.

Release rate studies

Most commonly, the results of dissolution tests are expressed in terms of the time required to release some percentage of labeled amount of the drug from the dosage form. This approach is reported to be particularly useful for quality control purposes once the dissolution characteristics of a drug and dosage form are understood. The dissolution of ciprofloxacin from the tablets was evaluated using the above concept. The time taken for 50 % of the drug to be released ($t_{50\%}$) and the maximum amount of drug released at the end of dissolution time, 10 h (C_{max}) were adopted to characterize the release of ciprofloxacin from the tablets. These parameters are shown in Table 3. Results in Fig. 1 show the effect of polymer type (without primogel) on the release profile of ciprofloxacin from matrix tablets containing 30 % w/w of each polymer. Generally, formulations containing eudragit exhibited faster rate of drug release than the other three polymers. The order of drug release retardation from the polymers is HP > EC > HE > EU. After 10 h of dissolution, the different formulations containing EC, EU, HE and HP released 46.32, 63.63, 65.8 and 50.19 % of their drug

content respectively. These results indicate excessive retardation of drug release, implying that these formulations would require additives such as channeling, wetting agents, or release enhancers. Drug release from the four polymers differed significantly ($p < 0.05$) from each other and these variation could be attributed to the nature (weakly acidic to weakly basic) and solubility differences of these polymers. Figs. 2 - 5 show the drug release profiles of the different formulations containing primogel as indicated in Table 1. Complete drug release was not achieved within the 10 h of dissolution study in any of the formulations. Drug release from all batches was sustained beyond 8 h. Tablets containing ethylcellulose (EC1 – EC3) retarded drug release to a larger extent than the other polymers. The presence of primogel significantly ($P < 0.05$) enhanced drug release from the two hydrophobic polymers; EC and EU, while having little or no effect on the ciprofloxacin release from tablets containing the hydrophilic polymers; HP (HP 1 – HP3) and HE (HE1 – HE3). It is important to note here that, this dual effect of primogel is depended on both the nature of the polymer and the concentration of primogel. Primogel being a hydrophilic starch derivative may have created some channels in the hydrophobic polymers resulting in the leaching of the drug. But due to its hydrophilic nature, it may have hydrated and gelled together with the hydrophilic polymers resulting in a more swollen matrix that entrapped drug within its matrix while having to cross the extended solvent front developed due to higher swelling. This observation is similar to those of Emeje *et al* [20] and Ofoefule and Chukwu [23] who suggested that there is considerable potential for polymer – polymer interaction depending on the type of polymers blended and that this may influence the formation and properties of the gel layer and ultimately, drug release. Values of $t_{50\%}$ in Table 3 indicate that, primogel enhanced the dissolution of the drug from EC and HP tablets. The effect of the additive on EC tablets was observed to be independent of the concentration used, suggesting that, when primogel is to be used as an additive in EC formulations containing ciprofloxacin, concentrations above 4.0 % may offer no additional advantage. Similar trend was noticed with formulations containing HE as matrix agent. In contrast to these observations however, primogel retarded drug release from tablets containing EU and HP as matrix polymers. The dissolution tests show that primogel had both enhancing and retardation effect on drug release, the extent of which depends on the type of polymer. Modified starches have been used both as disintegrants to enhance tablet disintegration and dissolution and as matrixing agent to retard drug release in modified dosage preparations [25-35]. The implication of these observations is that, primogel can serve as a drug release enhancer or retardant depending on the matrix system in which it is being used.

In vitro release mechanism

The most probable mechanism of ciprofloxacin release from EC and HE tablet matrices in the absence of primogel (EC1 and HE1 respectively) appeared to be by Fickian diffusion, while release from EU and HP (EU1 and HP1 respectively) matrices was by anomalous diffusion of the drug from the matrix base into the dissolution medium through swelling and erosion of the polymers. The presence of primogel in EC and HE formulations, irrespective of the concentration resulted in tablets of very fast disintegration; essentially converting the system to immediate release tablets, making it impossible to determine the mechanism of drug release. However, the presence of primogel did not have any appreciable effect on the drug release mechanism from EU and HP tablet matrices. The values of k, n, C_{max} and $t_{50\%}$ as obtained from the dissolution data for the four polymers are given in Table 3. The values of n for these formulations ranged from 0.37 to 0.71 in the absence of primogel, and 0. 49 to 0.79 in the presence of primogel. The release rate of ciprofloxacin from EU formulation containing 8.0 % primogel (EU3) was the slowest, with a K value of 7.21 % h^{-1} and $t_{50\%}$ greater than 10 h, whereas the release rate from HE formulation containing 0 % primogel (HE1) was found to be the fastest with a K value of 25.29 % h^{-1} and $t_{50\%}$ of 5.72 h. Generally, the K values in Table 3 show that, primogel actually decreased the rate of release of ciprofloxacin from all the formulations, except the HP formulation containing 4 % primogel where release rate was decreased. Although the rate of drug release from EU tablet matrices was decreased, the effect of primogel was not significant. Furthermore, the $t_{50\%}$ of the sustained release formulations for all the polymers was affected by the presence of primogel in the formulations. However, only HE formulations (HE1 – HE3) were highly significant with the $t_{50\%}$ values decreased by approximately 17-fold in comparison to the formulation without primogel (HE1).

Table 2: Pharmaco technical properties of matrix tablets of ciprofloxacin containing different polymers and varying concentrations of primogel

Batch code	Hardness (kgf) n = 10	Weight ± SD (mg) n = 20	Drug content ± SD (mg) n = 3	Friability (%) n = 10
EC1	7.90 ± 0.45	659.25 ± 7.95	111.7 ± 1.04	0.241
EC2	7.12 ± 0.23	675.93 ± 9.48	95.63 ± 1.06	0.245
EC3	6.84 ± 0.24	691.54 ± 7.34	97.06 ± 1.28	0.241
EU1	9.60 ± 0.04	659.90 ± 7.38	96.98 ± 0.95	0.246
EU2	8.06 ± 0.82	672.15 ± 8.52	96.26 ± 2.16	0.304
EU3	7.33 ± 0.34	699.24 ± 9.78	100.21 ± 0.42	0.320
HE1	7.45 ± 0.47	661.2 ± 6.57	102.14 ± 0.61	0.212
HE2	8.24 ± 1.02	680.06 ± 10.22	101.44 ± 4.64	0.278
HE3	6.56 ± 0.22	694.87 ± 5.11	97.56 ± 0.63	0.356
HP1	7.05 ± 0.21	661.65 ± 6.53	91.47 ± 0.53	0.274
HP2	7.05 ± 0.24	668.72 ± 7.01	96.52 ± 1.36	0.440
HP3	6.42 ± 0.36	692.12 ± 6.20	95.99 ± 2.82	0.216

EC, ethylcellulose; EU, eudragit l-100; HE, hydroxyethylcellulose; HP, hydroxypropyl methylcellulose formulations

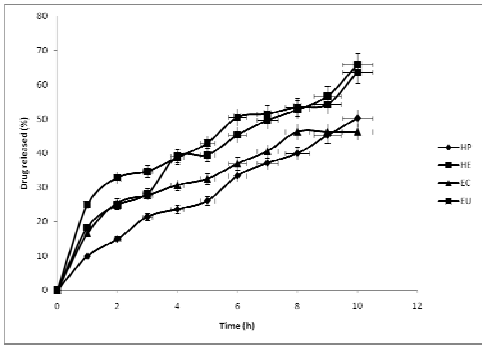

Fig. 1: Effect of polymer type on the release profile of ciprofloxacin from matrix tablets

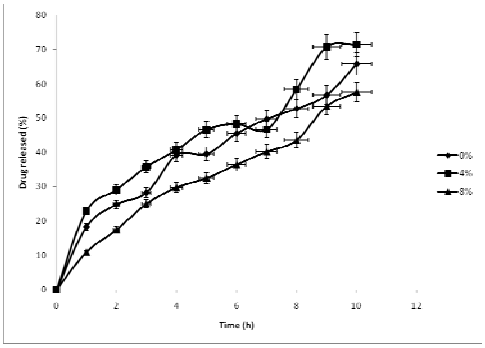

Fig. 2: Effect of concentration of primogel on the release profile of ciprofloxacin from HE matrix tablets

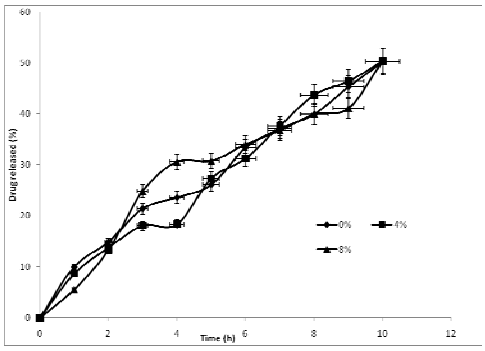

Fig. 3: Effect of concentration of primogel on the release profile of ciprofloxacin from HP matrix tablets

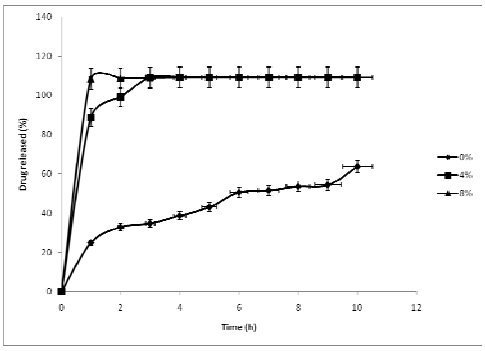

Fig. 4: Effect of concentration of primogel on the release profile of ciprofloxacin from EU matrix tablets

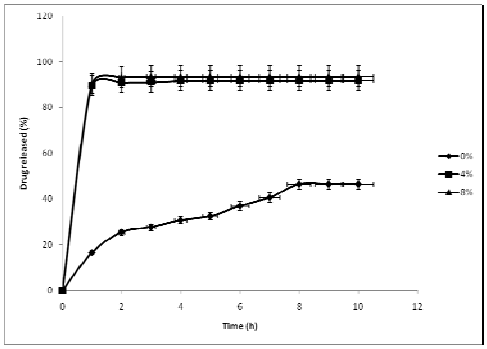

Fig. 5: Effect of concentration of primogel on the release profile of ciprofloxacin from EC matrix tablets

Table 3: Release parameters of matrix tablets of ciprofloxacin containing different polymers and varying concentrations of primogel

Batch code	Primogel content (%)	Polymer concentration (%)	T50% (min)	Cmax (%)	Korsemeyer values	
					n	K (h-1)
EC1	0	30	------	46.32	0.45	16.94
EC2	4	30	34.28	91.74	-----	-----
EC3	8	30	34.28	93.53	-----	-----
EU1	0	30	528.27	63.63	0.71	9.24
EU2	4	30	------	109.17	0.79	7.74
EU3	8	30	------	108.99	0.75	7.21
HE1	0	30	343.17	65.80	0.37	25.29
HE2	4	30	20.43	71.44	-----	------
HE3	8	30	20.57	57.60	-----	------
HP1	0	30	429.70	50.19	0.55	17.14
HP2	4	30	446.66	50.38	0.49	21.26
HP3	8	30	506.67	50.38	0.71	10.86

EC, ethylcellulose; EU, eudragit l-100; HE, hydroxyethylcellulose; HP, hydroxypropyl methylcellulose formulations

CONCLUSIONS

The results presented here show that low level primogel affected the release behavior of ciprofloxacin from all the polymer matrices, the extent of which depends principally on the type of polymer used. High concentration of primogel did not show any advantage over low concentration. It is therefore concluded that appropriate preformulation studies of primogel use with these polymers are necessary before scale up production.

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