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Design of pH-independent controlled release matrix tablets for acidic drugs

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Abstract

The rate and extent of drug release from most controlled release systems are influenced by the pH of the dissolution medium for drugs with pH-dependent solubility. This dependency of drug release on pH may lead to additional inter- and intra-subject variability in drug absorption. In the present study, a pH-independent controlled release matrix system for acidic drugs was designed by incorporating release-modifiers in the formulation. Controlled release matrix tablets were prepared by compression of divalproex sodium, Methocel K4M and Eudragit E 100 or Fujicalin as the release-modifier. For formulations without any release-modifier, the extent and rate of drug release at pH 6.8 was much higher than that at pH 1.0. Formulations containing Eudragit E 100 provided drug release that was essentially independent of pH. This was achieved because Eudragit E 100 significantly increased the drug release in acidic medium and slightly decreased the release rate at higher pH. The increased release in the acidic medium can be attributed to the elevation of the micro-environmental pH in the swollen polymer gel layer. Formulations containing Fujicalin were less effective than those containing Eudragit E 100. This was attributed to the relative inability to elevate the pH and shorter residence time of Fujicalin in the matrix relative to Eudragit E 100.

Keywords: Acidic drugs; Matrix system; pH-independent controlled release

Due to the variable pH values observed in the gastrointestinal tract (GIT), the conventional controlled release matrices of ionizable drugs with pH-dependent solubility may give rise to intra- and inter-individual variabilities in bioavailability (Yamada et al., 1990; Kohri et al., 1989, 1992; Vashi and Meyer, 1988). Incorporation of pH-modifiers into controlled release matrix tablets seems to be an obvious approach but the selection of the modifier may not be as straightforward as it first appears. In the context of controlled release matrix tablets, an ideal pH-modifier needs to be one that provides the desired pH over an extended period of time. The ability of a modifier to alter the pH is dependent on its ionization constant and solubility whereas the residence time in the matrix is dependent on the diffusivity and solubility of the pH-modifier. The importance of these physicochemical properties on the dissolution of ionizable drugs and buffer components have been reported previously (Mooney et al., 1981; Thoma and Zimmer, 1990).

Divalproex sodium ($pK_a = 4.6$), has a solubility of 1 mg/ml at pH 1.0 and 200 mg/ml at pH 6.8. Depakote ER, the commercially available matrix tablet of dival-

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proex sodium showed pH-dependent dissolution. The purpose of this work was to design pH-independent hydrophilic matrices of acidic drugs by incorporating release-modifiers. Both Eudragit E 100 and Fujicalin were selected as the release-modifiers because they are soluble in acidic media and insoluble at neutral to alkaline pH. However, the relative effectiveness of the two materials to elevate and maintain the pH, molecular weights and therefore the diffusion coefficients are significantly different from each other. Fujicalin (Fuji Chemical Industries, Robinsville, NJ) is processed dibasic calcium phosphate anhydrous that may be used as a direct compression excipient. Eudragit E 100 (degussa (Rohm Pharma Inc.), Piscataway, NJ) is aminoalkyl methacrylate copolymers containing multiple tertiary amines. The pK_a of its functional group, ethyldimethyl amine, is approximately 8–9 (information provided by supplier, Rohm America, NJ). It is commonly used as a protective and taste-masking film coating agent and its application as a release-modifier hasn't been reported.

Previously, Delargy et al. (1989) used an anionic polymer, sodium alginate for the pH-independent release of a basic drug, verapamil hydrochloride from a hydrophilic HPMC-based matrix tablet. Although the reason for pH-independent release was not explained, sodium alginate may have altered the pH in the matrix tablet. The current work compares a "small molecule" pH-modifier with a polymeric modifier further emphasizing the importance of the residence time of the pH-modifier in the matrix tablet.

Divalproex sodium, Methocel K4M (Dow Chemical Co., Midland, MI), lactose (Foremost Farms USA, Baraboo, WI) and/or milled Eudragit E 100 or Fujicalin were blended manually in a bottle. All the materials were previously passed through a 100 mesh screen. Fine powder (mean = 52.4 μm) of Eudragit E 100 was obtained prior to use by milling with a jet mill. Four hundred milligrams of this physical mixture were then compressed into a tablet using a Carver hydraulic press at a pressure of 2000 lb for 5 s. All tablets contained 15% w/w divalproex sodium, 25% w/w Methocel K4M, 25% lactose and 35% w/w Fujicalin or Eudragit E 100. Control formulations without any release-modifiers were also prepared by using 15% w/w divalproex sodium, 25% w/w Methocel K4M and 60% lactose. Two kinds of dissolution tests were conducted in USP Paddle Apparatus 2 at 100 rpm, 37 °C and 900 ml of dissolution medium: (1) tablets were exposed to dissolution medium of constant pH values of 1 (0.1N HCl), 4.5 (0.05 M phosphate) and 6.8 (0.05 M phosphate); (2) tablets were placed in acidic medium (pH 1.0) before exposing them to medium at pH 6.8. The effect of gastric retention time (GRT) was investigated by varying the in vitro exposure time to acidic medium (0, 2 and 4 h). All dissolution tests were conducted for a total of 8 h. Samples from the dissolution studies were collected at regular intervals of time and analyzed for drug by a fluorescence polarization immunoassay using Abbott TDX (O'Connell et al., 1995).

Dispersions of Fujicalin and Eudragit E 100 were prepared by suspending 35, 70 or 140 mg in 1 ml of 0.1N HCl (pH 1.0). The pH value of each of these dispersions was determined using a pH meter (pHBoy-P2, Shindenger Electric Mfg. Co. Ltd., Tokyo, Japan).

Divalproex sodium release from the control formulation into dissolution media with different pH values of 1.0, 4.5 and 6.8 are shown in Fig. 1. As expected, the extent and rate of drug release at pH 6.8 was greater than that at pH 4.5 and 1.0. Drug release kinetics was also apparently different. The difference in drug release rates at different pH values is due to the pH-dependent solubility of the drug. Earlier, Tahara et al. (1996) pointed out that when the drug solubility was in large excess of the drug loading, medium infiltration or diffusion was the rate limiting step and when the solubility was low, the release rate was erosion-controlled. It is desirable to obtain an extended release hydrophilic matrix tablet of sodium divalproex that provides a pH-independent drug release.

Fujicalin-laden matrices (15% drug, 25% Methocel K4M, 35% Fujicalin, 25% lactose) also provided drug release at a slower rate at pH 1.0 than at pH 6.8 (Fig. 2). Compared to the control formulation, the release rate improved slightly at pH 1.0 but no apparent change in release rate was observed at pH 6.8. Fig. 3 shows the release from matrix tablets containing Eudragit E 100 (15% drug, 25% Methocel K4M, 35% Eudragit E 100, 25% lactose). Unlike Fujicalin, Eudragit E 100 significantly increased the release rate at pH 1.0. Drug release rate slightly decreased at pH 6.8. Thus, Eudragit E 100-laden matrices provided extended release of divalproex sodium that is essentially pH-independent.

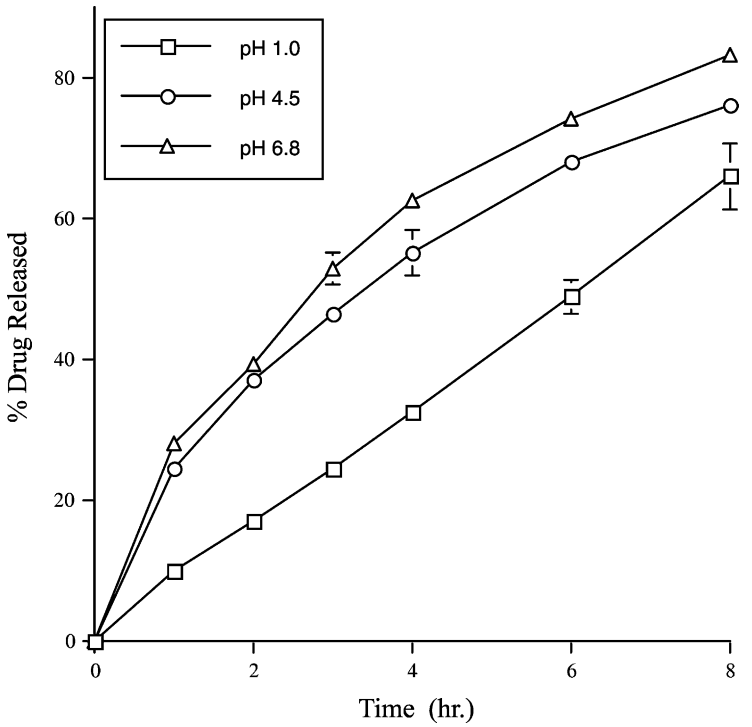

Fig. 1. Divalproex sodium release from 400 mg matrix tablets (drug: 15%, Methocel K4M: 25%, lactose: 60%) into dissolution media at different pH conditions.

At pH 6.8, both Fujicalin and Eudragit E 100 are expected to behave as insoluble and inert materials present in the hydrophilic matrix. In fact, matrix tablets with pH-modifiers showed slightly decreased release rate at pH 6.8 when compared with the control tablet. This is likely a direct result of physical presence of the insoluble excipient in the matrix that slows down drug diffusion and/or medium infiltration. However, in acidic conditions, Fujicalin and Eudragit E 100 presumably increased the "micro-environmental" pH in the swollen gel layer of the matrix tablet. In order to test this hypothesis different amounts of Fujicalin and Eudragit E 100 were dissolved in 1 ml of 0.1N HCl and the final pH of this solution was measured. Each tablet contains about 140 mg of the release-modifier. Table 1 shows the pH values obtained from aqueous dispersions of Eudragit E 100 and Fujicalin in 0.1N HCl. Eudragit E 100 provided much stronger pH-altering effect compared to Fujicalin. Additionally, Fujicalin (molecular weight = 136.06) is expected to have a higher diffusion coefficient than Eudragit E 100 (average molecular weight = 150,000) at pH 1.0.

Table 1
The effect of amount of release-modifier (Eudragit E 100 and Fujicalin) added to 0.1N HCl on the resultant pH

Amount of release-modifier (mg) added to 1 ml of 0.1N HCl	pH of the solution after addition of the release-modifier	
	Fujicalin	Eudragit E 100
140	3.8	6.7
70	3.7	6.2
35	3.7	5.7

Specific interaction between oppositely charged drug and polymer (Ford et al., 1991) can be ruled out as any such interaction would then lead to decreased drug release rate. Another possible mechanism that may be considered is that the release-modifiers dissolve much faster in the acidic conditions and therefore decrease the resistance to drug diffusion in acidic

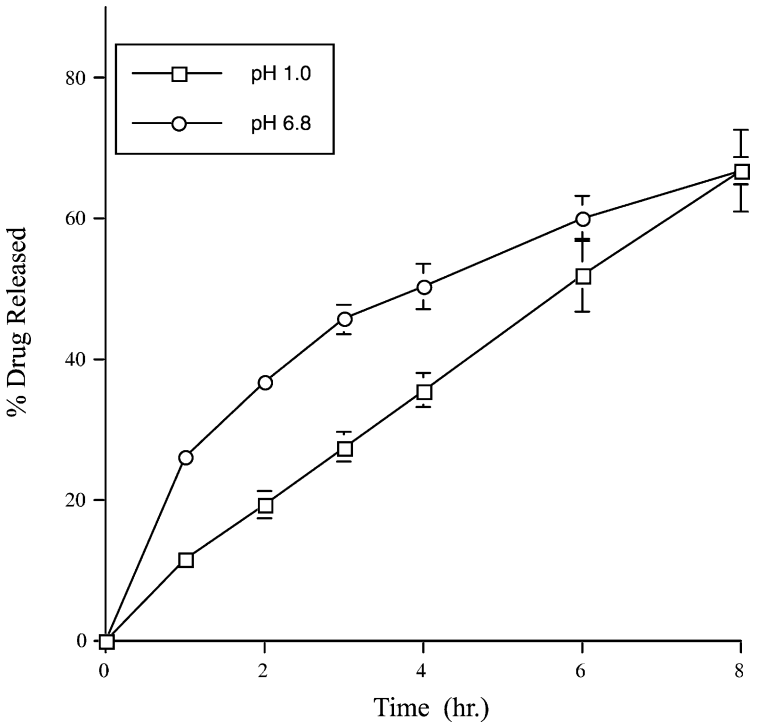

Fig. 2. Divalproex sodium release from 400 mg matrix tablets containing Fujicalin (drug: 15%, Methocel K4M: 25%, Fujicalin: 35% and lactose: 25%) into dissolution media at different pH conditions.

conditions. However, if this mechanism were operative, one would expect Fujicalin to perform better because of its higher solubility and diffusivity compared to Eudragit E 100. The present matrix tablet shows exactly opposite results suggesting that the mechanism for increased drug release in acidic conditions is the elevated micro-environmental pH provided by the dissolved Eudragit E 100 in the swollen gel layer which leads to an increase in driving force or solubility of the drug.

All release profiles were fitted to the following semi-empirical mathematical model (Ritger and Peppas, 1984) used to describe drug release for matrix devices:

$$\frac{M_t}{M_\infty} = Kt^n \tag{1}$$

where M_t and M_∞ are the drug released at time t and infinity, K the release rate constant and n is the diffusional exponent characteristic of the release mechanism. The mechanism-dependent parameter, n, obtained from the matrix tablets without any release-modifiers was 0.99 at pH 1.0 and 0.51 at pH 6.8 (Table 2). Based on this model it is difficult to

Table 2
Analysis of release data from matrix tablets with and without Eudragit E 100 based on Eqs. (1) and (2)

pH	Lactose (without Eudragit E 100)			Eudragit E 100		
	$K \times 100\,h^n$	n	MDT (h)	$K \times 100\,h^n$	n	MDT (h)
1.0	8.39 (±0.47)	0.99 (±0.03)	6.08 (±0.43)	17.38 (±0.68)	0.76 (±0.02)	4.32 (±0.32)
4.5	25.88 (±0.75)	0.53 (±0.02)	4.44 (±0.32)	25.99 (±0.53)	0.53 (±0.01)	4.40 (±0.19)
6.8	29.16 (±0.78)	0.51 (±0.02)	3.78 (±0.32)	26.69 (±0.37)	0.49 (±0.01)	4.87 (±0.17)

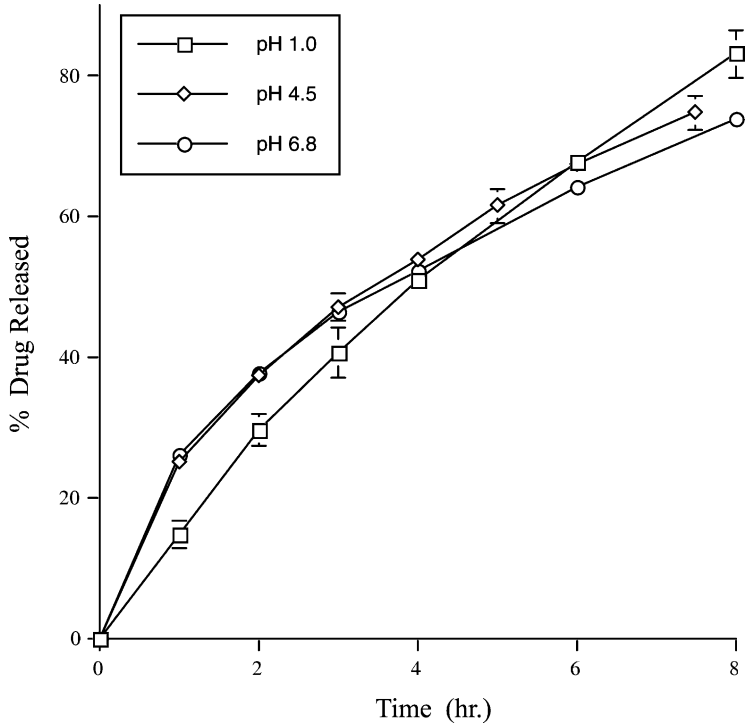

Fig. 3. Divalproex sodium release from 400 mg matrix tablets containing Eudragit E 100 (drug: 15%, Methocel K4M: 25%, Eudragit E 100: 35% and lactose: 25%) into dissolution media at different pH conditions.

compare the release profiles obtained from different tablets subjected to different dissolution conditions. Therefore, a model-independent mean dissolution time (MDT) was calculated as follows:

$$\mathrm{MDT} = \frac{n}{(n+1)(K^{(1/n)})} \quad (2)$$

Table 2 illustrates the values of K, n and MDT obtained for the drug release profiles from both control (lactose) and Eudragit E 100-laden matrix tablets. The MDT of the control tablets is dependent on the pH whereas tablets containing Eudragit E 100 provide drug release and MDT which are independent of pH.

Another determinant in the overall performance of a controlled release matrix of an ionizable drug could be the gastric residence (retention) time (GRT). This is especially very important for single-unit dosage forms as the transit time depends on the dosage size and the feeding state (Dressman et al., 1998). This GRT was simulated in vitro by exposing the tablets to acidic pH for various times followed by exposure to pH 6.8. Fig. 4 illustrates the effects of GRT on the in vitro MDT of the model ionizable (acidic) drug, divalproex sodium released from hydrophilic matrix tablets. These tablets when incorporated with Eudragit E 100, however, rendered drug release (or MDT) independent of the GRT.

In conclusion, a hydrophilic matrix system that provides controlled drug release essentially independent of pH and GRT was successfully designed for acidic drugs by incorporating a release-modifier. Eudragit E 100 was shown to be an effective release-modifier while dicalcium phosphate was found to be less useful, most likely due to its inability to alter the pH, limited buffering capability, smaller molecular weight and high solubility in acidic medium. Therefore, in designing this type of system for either weak acids or bases, it is very important to take the solubility, ionization constants and diffusion coefficient of both drug and the modifier into consideration. Other factors such as pK_a, solubility and the salt form of the drug are currently being investigated.

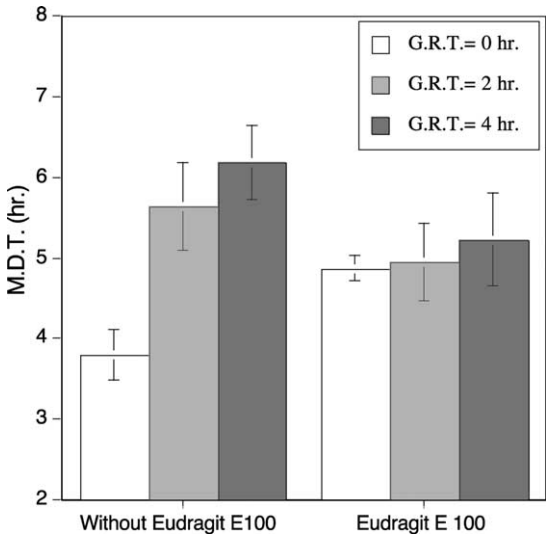

Fig. 4. In vitro effect of gastric residence time (GRT) on the mean dissolution time (MDT) of divalproex sodium from matrix tablets with and without Eudragit E 100. All tablets were of 400 mg containing 15% drug and 25% Methocel K4M. Tablets with Eudragit E 100 contained 35% Eudragit E 100 and 25% lactose whereas tablets without Eudragit E 100 contained 60% lactose.

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