pH-independent release of propranolol hydrochloride from HPMC-based matrices using organic acids

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ABSTRACT

Background and purpose of the study: Propranolol HCl, a widely used drug in the treatment of cardiac arrhythmias and hypertension, is a weak basic drug with pH-dependent solubility that may show release problems from sustained release dosage forms at higher pH of small intestine. This might decrease drug bioavailability and cause variable oral absorption. Preparation of a sustained release matrix system with a pH–independent release profile was the aim of the present study.

Methods: Three types of organic acids namely tartaric, citric and fumaric acid in the concentrations of 5, 10 and 15 % were added to the matrices prepared by hydroxypropyl methylcellulose (HPMC) and dicalcium phosphate. The drug release studies were carried out at pH 1.2 and pH 6.8 separately and mean dissolution time (MDT) as well as similarity factor (f_2) were calculated for all formulations.

Results and discussion: It was found that incorporation of 5 and 10 % tartaric acid in tablet formulations with 30 % HPMC resulted in a suitable pH-independent release profiles with significant higher f_2 values (89.9 and 87.6 respectively) compared to acid free tablet (58.03). The other two acids did not show the desirable effects. It seems that lower pK_a of tartaric acid accompanied by its higher solubility were the main factors in the achievement of pH-independent release profiles.

Keywords: Propranolol HCl, pH-independent release, HPMC matrices. Organic acids

INTRODUCTION

Many active ingredients are weak bases and their salts show variable release from diffusion controlled dosage forms in different areas of gastrointestinal tract due to pH-dependent solubility. Penetration of intestinal juices may results a conversion of the more ionizable drug to a less soluble base which brings down the diffusion rate of the drug through the matrix (1-2). Different drug release rates could result in variable oral absorption and bioavailability problems. Therefore, preparation of a pH-independent sustained release dosage form is desirable for a reliable drug therapy (3).

Several attempts have been conducted to overcome pH-dependent solubility of weak basic drugs (3-8). The addition of pH-adjusters such as organic acids to the matrix tablet (3-5) and increase in the permeability of the dosage form to counteract the decrease in the solubility (6-8) are two principle approaches to overcome the pH-dependent drug release. Organic acids create a suitable micro-environmental pH and result in an advanced drug solubility at high pH. For the second approach, tablets composed of a hydrophilic polymer and an enteric polymer can be used. The enteric polymer is not soluble in acidic medium, and contributes to the retardation of the release phenomenon. In the intestinal fluids, this polymer dissolves and acts as a pore-former which increases the permeability of the dosage forms (5, 9). Also the enteric polymer can enhance drug release in basic medium by lowering micro-environmental pH (8).

For the preparation of pH-independent drug release system, various studies revealed that a variety of factors including drug pK_a and solubility, type and concentration of the organic acid as well as its solubility are important (4, 10).

Propranolol HCl ((±)-1-isopropylamino-3-(1-naphthyloxy) propan-2-ol hydrochloride) as a weak basic drug is widely used in the treatment of hypertension and cardiac arrhythmias (11). Its short elimination half life of 3 hours makes it an appropriate candidate for sustained delivery (12). Few studies have been carried out in order to achieve pH-independent sustained release of this drug, by using anionic polymers in polymeric

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matrices as release modifying agents (7) and to our knowledge the effect of incorporated organic acids on the release profile of propranolol HCl has not been reported. Therefore, the objective of the present study was to achieve pH-independent release behavior of propranolol HCl from HPMC-based matrix tablets by using different organic acids. Citric, tartaric and fumaric acids in different concentrations were used as acid components. HPMC, a cellulose ether, was employed in this study due to its safety of delivery systems (13)..

MATERIALS AND METHODS

Materials

The following chemicals were obtained from suppliers and used as received. Propranolol hydrochloride (Shaheed Razakani, Iran), citric, tartaric and fumaric acid, magnesium stearate (Merck, Germany), hydroxypropyl methylcellulose (HPMC K4M, Colorcon, UK), dicalcium phosphate (DCP; Fluka, Switzerland).

Preparation of tablet matrices

Propranolol HCl (100 mg) matrices were prepared using HPMC K4M as a polymer, dicalcium phosphate as a filler and magnesium stearate as a lubricant, by direct compression method. Organic acids including citric, tartaric and fumaric acids with the concentrations of 5, 10 or 15% were introduced separately in the matrix formulations (Table 1). All ingredients except the lubricant were passed through a 50 mesh sieve and mixed thoroughly for 15 min. Thereafter, 1% w/w magnesium stearate was added and blended for an additional 2 min. The final mixture was compressed into a tablet using a single punch tableting machine (Erweka, Germany) equipped with a flat-faced 9 mm die and punch set.

All tablets were examined for their hardness and friability which were 8.5 - 10 kP and ≤ 0.8 % respectively.

Drug release studies

In vitro drug release test was carried out using a USP type II dissolution apparatus (paddle method) of 90 rpm speed. Dissolution medium were 900 ml of 0.1 HCl (pH=1.2) and phosphate buffer solution (pH=6.8) maintained at 37 ± 0.5 ^{o}C were used as dissolution medium separately. Samples were withdrawn at predetermined time intervals, filtered and assayed by UV spectrophotometer (Shimadzu UV1201, Japan) at 292 and 291 nm for acidic and buffer media respectively. The mean of three determinations was used to calculate the drug release from the matrix tablets.

Release data analysis

The release profiles were compared to each other by calculation of the mean dissolution time (MDT) by the following equation (14):

$$MDT = \sum_{i=1}^{n} t_{mid}\,\Delta M \,/\, \sum_{i=1}^{n} \Delta M$$

Where i is the sample number, n is the number of dissolution sample time, t_{mid} is the time at the midpoint between i and i-1, and ΔM is the additional amount of the drug which was dissolved in the period of time between i and i-1. The MDT is a measure of the rate of the dissolution process. To assess the statistical significance between the MDT values, ANOVA was carried out.

For further evaluation of the release profiles in two dissolution medium with different pHs, the similarity factor (f_2) was determined by the following equation (15):

$$f_2 = 50 \times \log\left[\frac{1}{\sqrt{1+\frac{1}{n}\sum(R_t - T_t)^2}} \times 100\right]$$

In which R_t and T_t are the cumulative percent of drug dissolved from matrices for the reference and test samples at time t and n is the number of time points. The similarity between two profiles increases when the f_2 value approaches 100.

Kinetics evaluation

Two following models were used to study the release kinetics for all formulations (16, 17):

Zero order $Q_t = Q_0 + k_0.t$

Higuchi $Q_t = k_H.\sqrt{t}$

where Q_0 and Q_t are drug released at time 0 and t respectively and k_0 and k_H corresponds to the zero order and Higuchi release rate constants.

Furthermore, in order to characterize the release mechanism better, the Korsmeyer-Peppas semi-empirical model ($Q_t = k_{KP}.t^n$) was applied in which k_{KP} is a constant related to the structural and geometric characteristics of the device and n is the release exponent which indicates the mechanism of the drug release (18).

RESULTS AND DISCUSSION

Effect of pH of dissolution media

There was remarkable difference in the release of propranolol HCl from HPMC-based matrices containing no organic acid (F0) in 0.1 N HCl and buffer medium of pH 6.8 (Figure 1). It is evident that the drug releases decreased by increase in the pH of the media and after 5 hrs about 65.34 and 39.78 % of the drug at pH of 1.2 and 6.8 was released respectively. MDT values calculated for

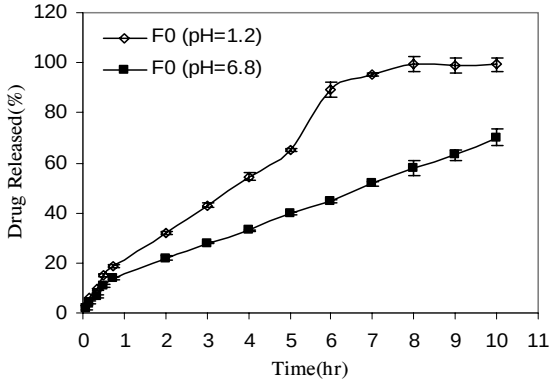

Figure 1. Release profiles of propranolol HCl from HPMC-based matrices without organic acids at two different pHs (Mean ± SD, n=3)

these profiles also showed a significant difference ($p < 0.01$) (Table 2). This phenomenon is due to different solubility of propranolol HCl as a weak basic drug at pH 1.2 (225 mg/mL) and pH 6.8 (130 mg/mL) (7). Lower similarity factor confirmed this matter.

From the Figure 1, it appears that the drug release rate at pH 1.2 was increased after about 5 hours when the dissolution experiment was started. It is probable that the hydrophilic matrix has been completely hydrated at that time and the glassy core has been disappeared. Therefore a sudden increase in matrix area occurs, which in turn enhances the rate of the drug release. It seems that matrix erosion become evident at this point (19). Regarding the dissolution profile at pH 6.8, this phenomenon might have happened at the late time of the release study, but it could not compensate the low solubility of propranolol HCl in order to increase the dissolution rate.

Effect of organic acids

According to the results, incorporation of 5 % tartaric acid in tablet formulations (F1) had a noticeable effect on the drug release behavior. The similarity between two profiles was improved (f_2 =89.09) and there was no significant difference between the calculated MDT values (Figure 2a, Table 2). For this formulation, the release rates of up to 60% of drug in two media were similar to each other. Incorporation of 10 % tartaric acid in the presence of 30 % HPMC (F3) also increased the similarity factor to 87.6 and showed a suitable pH-independent drug release behavior (Figure 2b). Using 5 or 10 % tartaric acid along with lower amount of HPMC (formulations F2 and F4) did not increase the similarity factor appropriately. Statistical analysis showed significant differences between the MDT values for these formulations ($p < 0.05$). Although the similarity factors for these tablets were more than the basic one (F0), by using lower concentration of HPMC, the drug released faster (due to a decreased gel layer) which was more observable for F4 (MDTs for F4 < F3).

Further increase in the percentage of tartaric acid in tablets up to 15 % (F5 and F6), resulted in decline of similarity factor which is possibly due

Table 1. The composition of tablets prepared with or without organic acids

Formulation* no.	HPMC (%)	DCP (%)	Tartaric acid (%)	Citric acid (%)	Fumaric acid (%)
F0	30	37	-	-	-
F1	30	32	5	-	-
F2	27.5	34.5	5	-	-
F3	30	27	10	-	-
F4	25	32	10	-	-
F5	30	22	15	-	-
F6	22.5	29.5	15	-	-
F7	30	32	-	5	-
F8	27.5	34.5	-	5	-
F9	30	27	-	10	-
F10	25	32	-	10	-
F11	30	22	-	15	-
F12	22.5	29.5	-	15	-
F13	30	32	-	-	5
F14	27.5	34.5	-	-	5
F15	30	27	-	-	10
F16	25	32	-	-	10
F17	30	22	-	-	15
F18	22.5	29.5	-	-	15

*: All formulations contain 100 mg propranolol HCl.

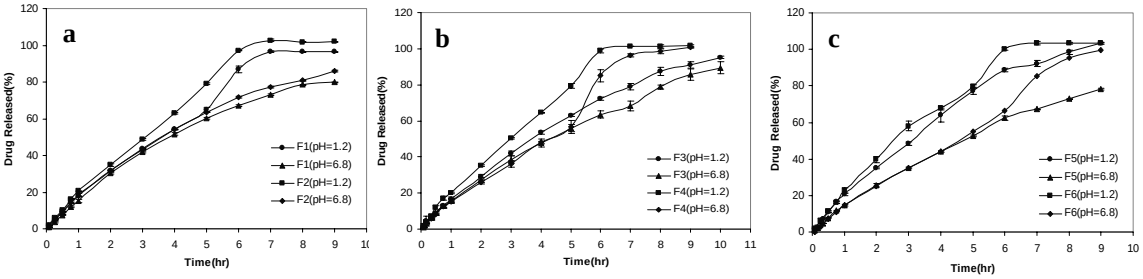

Figure 2. Release profiles of propranolol HCl from matrices containing tartaric acid with different concentrations (a: 5%, b: 10% and c: 15%) (Mean ± SD, n=3)

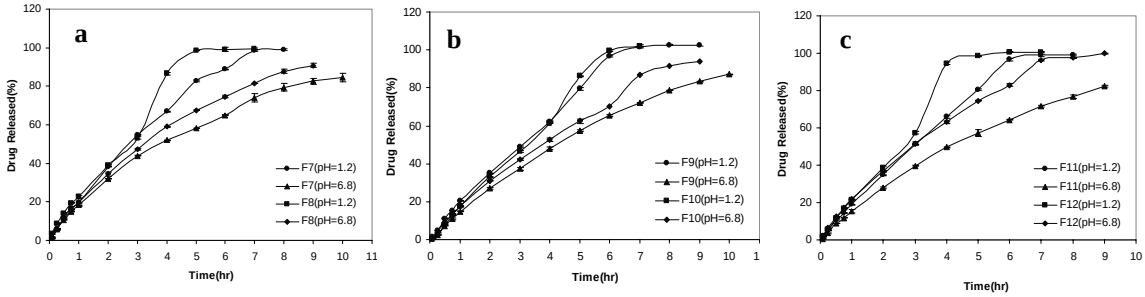

Figure 3. Release profiles of propranolol HCl from matrices containing citric acid with different concentrations (a: 5%, b: 10% and c: 15%) (Mean ± SD, n=3)

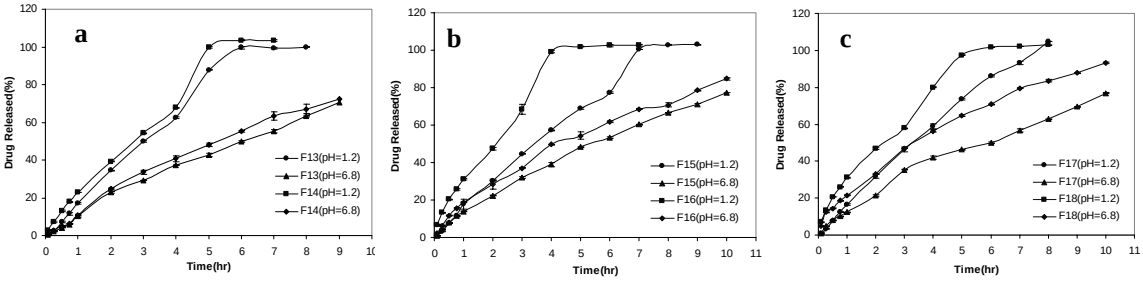

Figure 4. Release profiles of propranolol HCl from matrices containing fumaric acid with different concentrations (a: 5%, b: 10% and c: 15%) (Mean ± SD, n=3)

to the lower amount of HPMC (a swellable polymer) and dicalcium phosphate (an insoluble filler) and higher amount of tartaric acid (a soluble acid) which caused faster tablet erosion and drug dissolution (formulations F5 and F6, Figure 2c).

Figure 3 shows the release profiles of propranolol HCl from tablets prepared in the presence of 5, 10 and 15 % citric acid. Although the difference between the release profiles in acidic and buffer medium was mostly less than F0 (acid free formulation), the similarity factors for all tablets of this group were in the range of 51.35 - 60.32. It means that using different amounts of citric acid in the preparation of HPMC based propranolol matrices was not suitable for pH-independent drug release. This matter was verified by significant differences between MDT values of these profiles. As it was shown for tartaric acid containing tablets, decrease in the amount of HPMC in formulations resulted in higher drug release rate due to a decrease in the formation of gel layer around tablet.

The release profiles of propranolol from fumaric acid containing tablets are depicted in Figure 4. As it is shown, the differences in release rate between two profiles of each tablet in different pHs increased considerably by incorporation of fumaric acid in the formulations. In most cases the similarity factor was reduced compared to F0 and significant difference ($p < 0.01$) was observed between MDT values. Various concentrations of fumaric acid showed the same results. MDT values (table 2) were in accord with this fact that fumaric acid containing tablets showed slower release rate at buffer medium compared to tablets prepared in the presence of tartaric and citric acids.

Of three acids, tartaric acid was the best acid to achieve a pH-independent release profile for

Table 2. Similarity factors and MDT values obtained for different matrices and the squared regression coefficient based on various models

Formulation no.	pH of the Medium	MDT (hr) (n=3)	f_2	n*	r^2		
					Peppas model	Zero order	Higuchi model
F0	1.2	3.32±0.50	58.03	0.73	0.992	0.986	0.977
	6.8	3.66±0.14		0.69	0.987	0.983	0.988
F1	1.2	3.35±0.02	89.09	0.88	0.997	0.991	0.977
	6.8	3.27±0.03		1.01	0.986	0.989	0.989
F2	1.2	3.73±0.01	67.71	0.87	0.997	0.986	0.995
	6.8	3.38±0.05		0.96	0.983	0.985	0.894
F3	1.2	3.63±0.07	87.60	0.97	0.950	0.992	0.977
	6.8	3.86±0.31		0.93	0.975	0.985	0.988
F4	1.2	3.06±0.04	67.22	0.93	0.991	0.993	0.969
	6.8	3.69±0.10		0.78	0.995	0.974	0.919
F5	1.2	3.40±0.15	63.47	0.71	0.768	0.801	0.882
	6.8	3.71±0.06		0.93	0.992	0.993	0.985
F6	1.2	2.94±0.08	58.73	0.92	0.997	0.986	0.985
	6.8	3.27±0.02		0.93	0.903	0.995	0.894
F7	1.2	2.95±0.04	51.53	0.99	0.986	0.991	0.979
	6.8	3.37±0.05		0.86	0.976	0.971	0.995
F8	1.2	2.47±0.01	57.28	0.80	0.992	0.978	0.925
	6.8	3.30±0.08		0.89	0.988	0.988	0.990
F9	1.2	3.15±0.02	60.32	0.96	0.993	0.993	0.984
	6.8	3.70±0.02		1.09	0.977	0.991	0.990
F10	1.2	2.64±0.04	57.07	1.04	0.956	0.922	0.977
	6.8	3.65±0.03		1.05	0.969	0.992	0.926
F11	1.2	2.99±0.01	58.29	0.94	0.998	0.998	0.972
	6.8	3.61±0.04		1.02	0.970	0.985	0.989
F12	1.2	2.41±0.03	56.99	0.95	0.997	0.979	0.915
	6.8	3.24±0.01		0.86	0.997	0.990	0.986
F13	1.2	2.99±0.02	43.32	1.03	0.967	0.995	0.955
	6.8	4.63±0.04		0.82	0.932	0.996	0.963
F14	1.2	2.75±0.02	35.88	0.82	0.999	0.993	0.989
	6.8	4.93±0.01		0.75	0.938	0.995	0.969
F15	1.2	3.65±0.02	61.85	0.88	0.982	0.994	0.976
	6.8	4.21±0.02		1.05	0.994	0.989	0.988
F16	1.2	2.08±0.02	42.09	0.63	0.998	0.987	0.978
	6.8	3.95±0.04		0.76	0.991	0.978	0.989
F17	1.2	3.62±0.06	55.00	0.85	0.983	0.997	0.972
	6.8	3.99±0.06		1.12	0.990	0.972	0.989
F18	1.2	2.44±0.01	27.53	0.59	0.999	0.984	0.979
	6.8	3.66±0.01		0.60	0.985	0.983	0.991

*: Release exponent (n) was calculated according to Korsmeyer-Peppas model.

propranolol HCl which could be attributed to a variety of factors of which pK_a is one of the important factors. The pK_a of tartaric, citric and fumaric acid are 2.93, 3.13 and 3.03 respectively (20). The lower pK_a of tartaric acid can more reduce the pH of microenvironment and improve the solubility and dissolution of propranolol HCl at higher pH. This is in agreement with some previously reported investigations (5, 9), although, a pH-independent release of a weak basic drug from methacrylate coated tablets containing a higher pK_a organic acid has also been reported (21).

Solubility of the organic acids seems to be another factor in the achievement of desirable release profiles. The order of solubility for three organic

acids which were used in this study is tartaric acid > citric acid > fumaric acid (solubility of 1g acid in water: 0.75 mL, 1.7 mL and 158.7 mL respectively) (20). More soluble tartaric acid was the suitable organic acid in obtaining pH-independent release, while fumaric acid with lower solubility was not capable of keeping the micro-environmental pH in acidic range properly and enhancing the drug dissolution in buffer medium which is opposite to two reported data (9-10). It has been reported that succinic acid (moderately soluble) showed better results in providing pH-independent release than freely soluble citric and tartaric acids from inert non-swellable matrices. It has been reasoned that freely soluble compounds might diffuse very rapidly through the polymeric matrices, while fairly soluble acids diffuse out at relatively lower rate (10). It has also been showen that opposite to tablets made by other organic acids (adipic, glutaric and tartaric) incorporation of fumaric acid in tablets prepared by PVA/PVP (a poorly swellable mixture) released a weak basic drug in both high and low pH values similarly (9). Different results of this study could be attributed to the type of the polymer and additive used for matrix preparations. It seems that formation of a gel barrier around tablet after hydration of HPMC slows down the diffusion of dissolved organic acid towards out of the matrix system and keeps it inside the matrix core for a longer period of time. On the other hand, high quantity of soluble additives (such as lactose) of the other study (9) might result in formation of a pore following dissolution, which in turn increases the diffusion of soluble acid out of the matrix. Also, it might enhance the dissolution of less soluble organic acids. It has been emphasized that soluble additives create a more permeable hydrated gel layer, increase the porosity and rate of erosion of HPMC-based tablet, leading to faster solute release (22). In this investigation, dicalcium phosphate was used in the matrix preparation which is an insoluble additive and does not show the same effect as lactose during dissolution studies.

In order to clarify the mechanism of pH-independency, release matrix tablet based on HPMC containing pelanserin has been prepared (4) by using citric acid and it has been found that the drug release in acidic medium from formulation without citric acid was lower than the one containing citric acid. It has been concluded that increase in the porosity and loosening effect of citric acid in the matrix structure might be the main mechanism for pH-independent release of pelanserin. In this study, there was no significant difference between the MDT values of tablets (containing 30% HPMC) made in the presence of the organic acids and the basic one (without any acid) at pH 1.2 (Table 2). Therefore, the influence of acids on micro-environmental pH and modification of the drug solubility at higher pH seems to be the major pH-independent release mechanism. Pore forming and matrix loosening effects of the soluble organic acids might be observed at higher concentrations.

Kinetic study of all formulations showed that the drug release profiles of the most tablet matrices prepared with different organic acids in acidic and buffer medium up to 60% were best fitted with zero order (Table 2). In addition, most of the release exponents calculated by Korsmeyer-Peppas equation were close to unity indicating a Case II drug release mechanism, whereas an anomalous transport was shown for the drug release from acid free tablet (23). It seems that incorporation of organic acids especially tartaric and citric acids inside polymeric matrices, along with modification of drug release rate, has changed the release mechanism.

CONCLUSION

Addition of citric and fumaric acid to HPMC-based matrix tablets failed to achieve pH-independent release of propranolol HCl, whereas formulations F1 and F3 containing 5 and 10 % of tartaric acid in tablet formulations, respectively, improved the drug release in phosphate buffer (pH 6.8) sufficiently and were considered as the best tablet formulations. It seems that lower pK_a of tartaric acid results in a pH-independent drug release profile. The solubility of organic acid as well as the type of matrix former should also be considered as two other important aspects in achievement of appropriate results.

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