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MODULATION OF THE MICRO-ENVIRONMENTAL PH AND ITS INFLUENCE ON THE GEL LAYER BEHAVIOR AND RELEASE OF THEOPHYLLINE FROM HYDROPHILIC MATRICES

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ABSTRACT

The specific aim of this study was to develop a pH independent controlled release system for the basic drug, theopylline. The release of the drug was investigated *in vitro* from hydrophilic swellable matrices composed of hydroxyethyl cellulose and Eudragit S-100. The micro-environmental pH of the hydrated gel layer of the matrices was manipulated by the addition of fumaric acid. It is expected that the solubility of theophylline and release form matrices, without controlled micro-environmental pH, will decrease as the matrix tablets travel down the GIT which may lead to incomplete solubility and release of the drug, and hence, low bioavailability. Incorporation of fumaric acid in the matrix formulation was found to control the micro-environmental pH of the hydrated gel layer and resulted in pH independent release of the drug irrespective of the dissolution medium and its pH. Thus, efficient and predictable drug release is expected from such matrices.

KEYWORDS:Micro-environmentalpH,pH-independentdrug release,Hydrophilic matrices,Theophylline,Fumaric acid

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INTRODUCTION

Several physiological variables in the gastrointestinal tract (GIT) are expected to alter and affect the *in vivo* drug release performance of controlled release systems. Such variables include pH of different segments in the GIT, gastric residence time, intestinal motility, and the contents of the GIT. Some drugs demonstrate pH dependent solubility profiles based on their ionazable groups. Therefore, drug release rate from controlled release matrices may vary as the matrix formulation travels down the various segments of the GIT. Thus, significant and high intersubject variabilities and incomplete drug delivery are expected[1]. Since dissolution affects the drug absorption, the processes of dissolution and absorption are well explained by the pH partition concept or hypothesis. The dissolution and absorption are dependent on the pH of the fluids along the GIT lumen[2]. A virtual pH, called the micro-environmental pH, constitutes a major limitation to the pH partition hypothesis. This term has been used with solid formulations although the concept of pH does not apply to solids. The micro-environmental pH is different from the luminal pH of the GIT and expected to exist at the surface of the formulation and affect drug release. The micro-environmental pH has been recognized as a factor influencing drug degradation of solid dosage forms in addition to dissolution behavior and hence the bioavailability of many drugs, especially weak bases[3,4]. However, this concept is not well defined with no availability of well established techniques to measure it. Therefore, studies on drug release patterns from conventional or controlled and targeted release formulation, such as colon targeted formulations, without considering the effect of micro-environmental pH are assumed to be incomplete.Several studies have been performed in different approaches to investigate the effect of the micro-environmental pH on drug release patterns. Some studies were based on the incorporation of acidic excepients in the matrix. This will keep the pH within the system as well as the solubility of ionizable drugs constant. This approach proved efficient drug release irrespective of the dissolution medium. Papaverine HCl showed pH independent release from cellulose acetate and bees wax inert matrices in the presence of an organic acid[5]. Addition of citric acid to HPMC matrices containing vinopocetine showed a linear relationship between the release rate and the proportion of citric acid added[6]. Tatavarti et al. incorporated acidic polymers to modulate the micro-environmental pH and demonstrated that the release of papaverine HCl is dependent on the concentration of the acidic polymer[7]. The approach of incorporation of acidic excepients was shown to be a useful approach for basic drugs because their solubility decreases significantly with increase in the pH, and thus, may precipitate as the matrix proceeds down the intestine leading to incomplete drug release and absorption. In addition, since the release rate from the matrix is a function of drug solubility, it will fall as the matrix reaches a higher pH range leading to variability[8-10].Other approaches to investigate the effect of the micro-environmental pH used buffered matrices of hydrophilic polymers. A study by Al-Taani and Tashtoush showed that changing the pH within a hydrophilic matrix affected the release rate of diclofenac sodium without affecting its release pattern where the release rate increased linearly with increasing the micro-environmental pH[11]. This approach has also been used to prepare buffered matrix aspirin tablets[12]. Finne et al. has shown that the release rate and ocular bioavailability of timolol have been increased by using buffered ocular inserts[13].Formation of a gel layer on the matrix surface is a characteristic of swellable hydrophilic matrices. Gel layer formation, and consequently, drug release rate are controlled by water penetration, polymer swelling, drug dissolution, diffusion, and matrix erosion[14]. The polymer dissolution rate is an important process in drug release. It depends on the matrix shape, dimension, type of the dissolution medium and the polymer itself[15, 16]. A swelling and erosion front is formed during the swelling process. When the drug has a finite solubility, a layer of undissolved drug is detected in the gel layer[17]. The position of this layer is called the diffusion front and it is highly dependent on the conditions of the media.

Drugs with high pH dependent solubility will have complex gel behavior while the matrix moves down the GIT. Differences in the gelation of the polymers due the pH of the medium will also complicate the drug release process.This investigation was an attempt to understand the effect of the GIT physiological pH on the gel layer formation and its dynamics, and consequently, its effect on the release characteristics of a basic drug. Theophylline was used as a model basic drug in this study. We also investigated the influence of manipulating the micro-environmental pH of the hydrated swollen gel layer on the drug release characteristics. A zero-order release system was chosen to perform this study. This system will nullify the interference which could be due to concentration effect on drug release. This was achieved by combining matrix erosion and dissolution systems in the matrix formulation. Synchronization between erosion and diffusion fronts will keep the diffusional path length available for the drug constant, and thus, produce a zero-order drug release fashion.Hydrophilic polymers like cellulose ethers are usually used as gel forming agents and they are also known as swellable polymers[18]. In this study, hydroxyethyl cellulose (HEC) was used as a swelling polymer. The water soluble inert polymer, Eudragit S-100 was used as the erodable polymer. Eudragit S-100 is an anionic copolymer of methacrylic acid and methyl methacrylate. Several matrices were prepared using HEC and Eudragit S-100 as the swellable and erodable polymers, respectively. The micro-environmental pH was manipulated by incorporation of fumaric acid in the matrix tablets and its influence on the gel layer dynamics, and consequently, the release of theopylline was evaluated.

MATERIALS AND METHODS

Materials

Theophylline was a generous gift from Riyadh Pharma (Riyadh, Saudi Arabia) and its original supplier was Ranbaxy Fine Chemical Ltd. (India). HEC, fumaric acid, and magnesium stearate were obtained from Sigma Chemical Company (USA). Eudragit S-100 was obtained from Evonik Industries (Germany). Lactose was obtained from FMC Corp., (USA). Freshly distilled and de-ionized water was used in all experiments. All materials were of pharmaceutical grade and were used as supplied without any further treatment.

Methods

Solubility of theophylline

The solubility of theophylline was determined in simulated gastric fluid (SGF) without enzymes (pH 1.2), pH 6.8 phosphate buffer and pH 10.2 phosphate buffer. It was determined by adding excess of the drug to the media and equilibrating on a shaking water bath at 37 °C. The equilibrium time was determined according to preliminary solubility studies and it was found to be 24 hrs. Samples were withdrawn and filtered through 0.45 µm membrane filter (Millipore, USA) and the concentration of theophylline in the filtrate was measured spectrophotometrically at 270 nm.

Optimization of the proportion of polymers in the matrix tablets

The proportions of the polymers (HEC and Eudragit S-100) to be used in the matrix tablets were optimized in order to get controlled release of theophylline that is most close or near zero order. That was achieved through preliminary studies by selecting different proportions from the polymers and keeping the mass of the drug in the matrix tablets constant and then running dissolution studies to examine the release pattern.

Preparation of matrix tablets of different micro-environmental pH

After selecting the most suitable ratios of the polymers to achieve zero order release of the drug, the tablets were made to contain a constant amount of theopylline and varying proportions of the polymers and fumaric acid. Magnesium stearate was used as a lubricant in the tablets and lactose was used as a filler.The adequate components of the drug and the polymers were thoroughly mixed in a tumbler mixer for 15 min. Magnesium stearate was passed through a 0.25 mm sieve and then mixed with the initial mixture in the tumbler mixer for 10 min. The blends were compressed by the direct compression method using a single station tablet press (TP60 CAPPLUS

Technologies, USA) under a compression force of 2 ton ($2X10^3$ kg). The matrix tablets were compressed in the form of double flat faced tablets using 8 mm diameter flat faced die and punches. The hardness of the tablets was adjusted to be in the range of 12 -14 Kp (TBH20, Erweka Instruments, CT, USA) and the weight of each tablet was 200 ± 3 mg. Sufficient batch size (200 tablets) from each formulation was produced for further investigation.

Drug release studies

The dissolution of theophylline from different matrix tablets was carried out *in vitro* on a USP dissolution apparatus at an operating speed of 100 rpm. The media were 500 ml of SGF (pH 1.2) or phosphate buffer (pH 6.8) maintained at 37 °C. At predetermined time intervals, the progress of the dissolution process was monitored by withdrawing samples of suitable volume then filtration through a 0.45 µm membrane filter (Millipore, USA) and assaying spectrophotometrically for the content of theophylline at 270 nm. After sampling, the same volume of the sample was immediately replaced by the dissolution medium. The average values of six measurements were used for the characterization of the release profiles of theophylline. The drug release data were analyzed and interpreted with the simple power law expression:

$$M_t/M_\infty = Kt^n$$

Where M_t/M_∞ is the fraction of drug released at time *t*, *K* is the kinetic constant, and *n* is the release exponent that characterizes the drug release mechanism. This law can best describe the kinetics of drug release from swellable hydrophilic matrices[19].

Swelling and erosion studies

Tablets composed of only the suitable ratios of the polymers (as determined according to the optimization process) were prepared without the drug and compressed. They were subjected to swelling and erosion studies using type II dissolution apparatus at a rotational speed of 100 rpm. These studies were conducted in SGF of pH 1.2 and in phosphate buffer of pH 6.8 which are the same media that were used for investigation of the drug release. A suitable number of tablets were studied for a suitable time in a dissolution medium of 900 ml maintained at 37 °C. At predetermined time intervals, the tablets were removed from the dissolution medium using a small manual basket, lightly patted with tissue paper, and weighed. In order to determine matrix erosion, the swollen tablets were placed in a vacuum oven for 48 hrs at 40 ºC and then were removed and weighed. After removal of the tablets from the medium and weighing, the percentages of swelling and erosion were determined according to the following formula, respectively:

$$\%Swelling = (S/R)\ X\ 100$$
$$\%Erosion = (T - R/T)\ X\ 100$$

Where: S is the weight of the matrix after swelling; R is the weight of the eroded matrix; and T is the initial weight of the matrix.

RESULTS AND DISCUSSION

Theophylline is a xanthine derivative used mainly in the chronic control of bronchial asthma and it has a narrow therapeutic index that requires suitable formulation strategies to maintain a plasma concentration of the drug within the therapeutic range[20]. There are several sustained release oral formulations for theophylline, however, the bioavailability of theophylline form these formulations may be incomplete and variable. Due to these observations, there is a constant search for new and effective controlled delivery formulations for this drug[21,22].Theophylline is a weakly basic drug with pKa of 8.81 and it has showed a pH dependent solubility in the pH range of the GIT. Our solubility study showed that the solubility of theophylline at pH 1.2 was found to be 645 ± 23 mg/ml, 72.6 ± 5 mg/ml at

pH 6.8, and 0.023 ± 0.0012 mg/ml at pH 10.2. These results indicated pH dependent solubility with an exponential decline in the solubility of theophylline between pH 1.2 and pH 10.2 and they are in agreement with the results reported in the literature[23].Proportions of the polymers to be used in the formulations were optimized by preparing different matrix formulations containing varying proportions of the polymers. The compositions of these matrix tablets intended for optimization are shown in Table 1. They have been prepared by selecting different proportions from the polymers and keeping the mass of the drug in the matrix tablets constant.

Table 1
Composition of matrix tablet formulations prepared for optimization

Formulation	Theophylline (mg)	HEC (mg)	Eudragit S-100 (mg)
F1	100	20	80
F2	100	30	70
F3	100	40	60
F4	100	50	50

Dissolution studies were performed on these matrix tablets in order to examine the release pattern of the drug from them. The release profiles of theophylline from these matrices were examined at pH 7.2 and are shown in Figure 1. Among them, formulation F3 has shown a release profile that is close or near zero order. The extent of drug release from F3 was approximately 70% over the test period of 8 hrs. This formulation contains HEC and Eudragit S-100 in a ratio of 40:60. It has been decided upon this formulation (F3) to be selected for further experiments in our study. Formulations F1 and F2 showed faster release while formulation F4 showed slow and erratic release behavior over the test period. In this study, it is important to ensure synchronization between the erosion and the diffusion fronts in the matrix system to keep the diffusional path length constant, and thus, maintain a zero order drug release pattern.

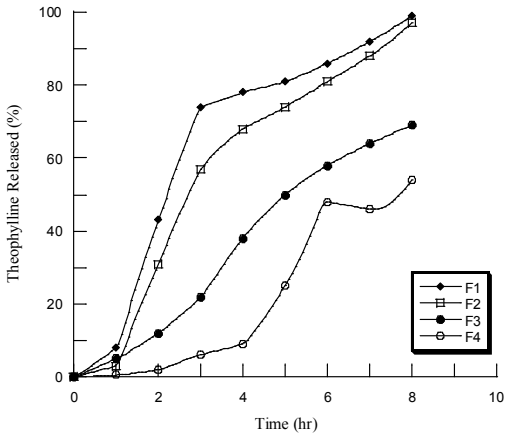

Figure 1
Release profiles of theophylline from the matrix tablet formulations prepared for optimization at pH 7.2 and 37 °C (n = 3).

Based on these results, the tablets formulations were made of 100 mg theophylline, HEC and Eudragit S-100 (constant ratio of 40:60), fumaric acid (either 5% or 10%), 1% magnesium stearate, and a quantity sufficient of lactose as a filler. The release of theophylline from these hydrophilic matrices was investigated at pH 1.2 SGF and pH 6.8 phosphate buffer. The release patterns were also compared with fumaric acid free tablets in order to investigate the effect of fumaric acid in controlling the release of the drug in the acidic and basic pH. Figure 2 shows the release data of theophylline from the optimized formulation (F3) at pH 1.2 (SGF) and pH 6.8. Theophylline release at pH 1.2 was relatively faster and this could be due to the high solubility of theophylline at lower pH and/or pH dependent swelling and gel layer dynamics of hydrophilic polymers. The effect of the addition of fumaric acid was studied at pH 6.8 at two concentrations and these were 10% and 5%. The effect of the addition of fumaric acid is also shown in Figure 2. It can be seen that the used polymers controlled the release of theophylline at both pH values. However, fumaric acid has a significant effect on the release of theophylline when it was studied at pH 6.8 compared to fumaric acid free tablets studied at the same pH. A remarkable difference can be observed when 10% of fumaric acid was used at pH 6.8 buffer. The addition of 10% fumaric acid at this pH enhanced the rate and extent of release of theophylline to be comparable to the release profile of the drug at pH 1.2. The addition of 5% of fumaric acid enhanced the release of the drug but to a lesser extent compared to 10%. Therefore, the increase in the release was further found to be dependent on the amount added of fumaric acid. These results correlate well with the hypothesis that addition of organic acids maintains a constant micro-environmental pH in the gel layer of the matrices, thus, leading to high solubility and eventually high release of basic drugs like our model drug, theophylline.

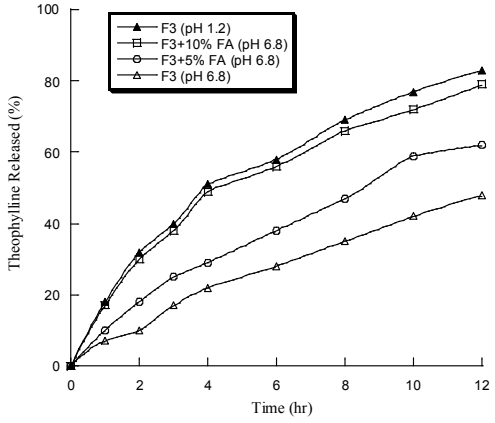

Figure 2

Effect of the pH of the dissolution medium and the addition of fumaric acid (FA) on the release of theophylline from the optimized formulation (F3) at pH 1.2 (SGF) and pH 6.8 (37 °C, n = 6).

Addition of organic acids to the formulation is expected to create a constant acidic environment inside the gel layer irrespective of the pH of the surrounding dissolution medium. Since the pH inside the gel layer is expected to be acidic, then the solubility of basic drugs in the gel layer will be high. This will lead to faster and usually complete release of the drug. Organic acids having high acidic strength and relatively low solubility at lower pH range are assumed to be suitable because they can provide low pH in the matrix for longer periods

of time even if they were used at low proportions. At high pH, organic acids can act as pore formers due to their high solubility in high pH range. Therefore, low proportions are always desirable to be used. Based on these fundamental requirements, fumaric acid was selected for this study. Fumaric acid has two pKa values of 3.03 and 4.54 and aqueous solubility of 6.3 mg/ml at 25 °C [24]. A lesser release of theophylline was observed from the matrices containing 5% fumaric acid. In this case, it is expected that the amount of fumaric acid available as the buffer migrates into the formulation may not be sufficient to maintain the microenvironmental pH to the same level as provided by 10% concentration. A study by Streubel et al. reported release of verapamil HCl from HPMC matrices that is independent of fumaric acid concentration[1]. However, the concentrations used in their study were much higher than those we have used in our study. The swelling and erosion studies are presented in Figure 3 where the percentage of swelling as well as the percentage of erosion are shown as a function of time. The data presented in Figure 3 were obtained by placing the matrices in SGF of pH 1.2. The results clearly show that the matrices underwent both swelling and erosion at the same time as they were placed in the dissolution medium. The swelling and erosion behaviors were also investigated at pH 6.8 (data not shown) and a similar behavior was also obtained as that presented in Figure 3 without any significant differences. These results also indicated that the dynamics of swelling and erosion are not affected by the pH of the surrounding dissolution medium. In both cases, the results indicated that there is a correlation and balance between the swelling and erosion dynamics which are expected to maintain a constant diffusional front for the release of the drug. The swelling and erosion studies have been carried out in attempt to correlate the release profiles to the polymers composition of the matrices. Since there were no significant differences, it was difficult to correlate the drug release to the polymers composition. However, the ratio of the polymers that has been selected (40:60) was found to be effective in maintaining a constant diffusional front in the gel layer available for the release of the drug in a fashion that is close to a zero-order process. Based on these results and the dissolution studies of the matrices containing fumaric acid we can verify that the release of the drug was mainly controlled by fumaric acid.

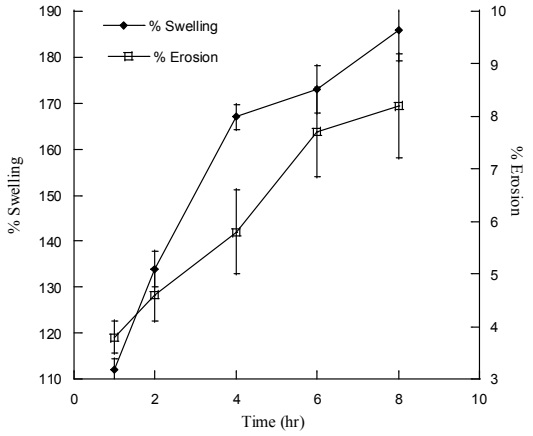

Figure 3
Swelling (%) and erosion (%) of the polymeric matrix tablets as a function of time at pH 1.2 (SGF) and 37 °C (n = 3).

CONCLUSION

We can conclude that the addition of fumaric acid to hydrophilic matrices has increased the release of theophylline to a significant extent in pH 6.8 phosphate buffer. This increase in the release was further found to be dependent on the amount added from fumaric acid. Our results have shown that the release profiles of the drug from matrices with 10% fumaric acid at pH 6.8 almost overlapped with the release from the matrices without fumaric acid at pH 1.2. This correlates well with the hypothesis that addition of organic acids maintains a constant micro-environmental pH in the gel layer of the matrices. Addition of fumaric acid to the formulation created a constant acidic micro-environment within the hydrated gel layer irrespective of the surrounding dissolution medium. Since the pH inside the gel layer is expected to be acidic then the solubility of the basic drug will be high. This will lead to faster and usually complete release of the drug. A similar approach was also utilized for acidic drugs by employing basic pH modifiers to provide complete and sustained drug release that starts in the stomach[25].

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