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Effect of Microenvironment pH on Drug Release from Matrix Formulation

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Absorption and dissolution are well explained by pH-partition hypothesis. Major limitation to this is microenvironment pH existing at formulation surface and affecting drug release. Hence, studies on release pattern of formulations without considering microenvironment pH will be incomplete. Present study on effect of microenvironment pH within the matrix on drug release and to study interference of polymer and drug solubility on this phenomenon. Four buffered matrices of different microenvironment pH were prepared using HEC and Eudragit S-100 and compressed in tablet with Diclofenac as model drug. Drug release was evaluated in phosphate buffer solution of pH 5.9 and 7.4. Swelling and erosion experiments were carried out to study interference of polymer and drug solubility. Formulation containing HEC: Eudragit in 40:60 proportions was selected for studies due to close resemblance to zero-order release. As the microenvironment pH increased, rate of drug release increased in linear relationship. It was found that % swelling also increased in linear relationship with % erosion for polymer-only tablets. Drug release from all matrices was directly related to percentage swelling and erosion, indicating simultaneous occurrence of drug release with swelling and erosion. Change in microenvironment pH influenced drug release rate without affecting the release pattern.

KEYWORDS: Microenvironment pH, pH-partition hypothesis, Zero-order drug release.

INTRODUCTION

In vitro dissolution has been recognized as an important element in drug development. Under certain conditions it can be used as a surrogate for the assessment of bioequivalence[1, 2]. Drug absorption is key factor in successful pharmacotherapy. Dissolution also governs the drug absorption process. The processes of absorption and dissolution are well explained by pH-partition hypothesis. It is stated that absorption and dissolution are dependent on the pH of fluids in gastrointestinal lumen. Based on this concept, an infinite number of studies have been performed worldwide in various areas like Pharmaceutics, Biopharmaceutics, Pharmacokinetics, Analysis etc[3].

But one major limitation to pH-partition hypothesis is that a virtual pH, also called as microenvironment pH, different from the luminal pH exists at the formulation surface and affects drug release. This virtual membrane pH determines the extent of drug ionization and hence drug dissolution and absorption[3]. Thus, the concept of microenvironment pH strongly questions the basics of pH-partition hypothesis. Hence, studies on release pattern of conventional, controlled release and targeted formulations like colon specifics without considering microenvironment pH will be incomplete.

The aim of this work is to study the effect of microenvironment pH on drug release pattern from tablet formulation. Zero-order drug release system was chosen so as to nullify the interference due to concentration effect on drug release. This task is achieved by incorporating matrix erosion and dissolution systems in formulation. Synchronization between erosion and diffusion fronts act to keep diffusional path length constant and hence produce zero-order drug release[4].

Diclofenac sodium was selected as drug candidate. Hydrophilic matrices like cellulose ethers are commonly used as gel-forming agents. Here, Hydroxy Ethyl Cellulose (HEC) is used as swelling polymer[2, 5]. Water-soluble inert carrier Eudragit S-100 is an anionic copolymer of methacrylic acid and methyl methacrylate. The ratio of free carboxyl group to the ester is approximately 1:2[6]. Erosion is the mechanism of release of drug dispersed in this polymer[7, 8].

In the present work, several buffered matrices of different microenvironment pHs have been prepared using gel forming, swellable, hydrophilic polymer HEC and an erodable

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solubility polymer Eudragit S-100. The effect of microenvironment pH within the matrix on the drug release has been evaluated.

MATERIALS AND METHODS

Diclofenac sodium was a gift sample from CIPLA ltd, Mumbai. Hydroxy Ethyl Cellulose (HEC), Eudragit S100, Disodium hydrogen orthophosphate anhydrous, Sodium dihydrogen phosphate anhydrous, Sodium chloride was purchased from Loba Chemie, Mumbai. Only triple distilled water was used. The materials used in the preparation of the matrices were passed through a sieve of 120-mesh size.

The following instrumentation was used: UV-VIS Spectrophotometer Shimadzu 1700 (Pharmapec, Japan); USP dissolution apparatus type II (LabIndia 2000, India); Single Pan Digital balance HR200, (A&D Mumbai); pH meter (LI 613), Elico. KBr press (Techno search Instruments, India)

1. Optimization of Proportion of Polymers:

Proportions of polymers to be used in the formulations were optimized in order to get controlled release of Diclofenac sodium most close to zero order by keeping the diffusion path length constant during drug release by balancing matrix erosion with matrix swelling. For this matrix tablets with varying proportions of polymers were prepared. (Table No.1)

Tablets were prepared using KBr press. The tablet weight was kept constant at 200 mg by adjusting the amount of polymeric material used in each formula. The pressure applied during compression was kept at 100 ± 5 N/mm^2 for all tablets. Dissolution studies were performed in phosphate buffer of pH 7.2.

2. Preparation of matrix tablets:

Four buffered matrices of microenvironment pH 6.2, 7.1, 8.1, 8.3 have been prepared by keeping HEC: Eudragit S100 ratio constant at 40:60. Henderson-Hasselbalch equation was used to measure the microenvironment pH and it was determined from phosphate buffer components in the formula. The composition of each formula is presented in Table 2.

The formulations differ in the amounts of the phosphate buffer components in an attempt to control the microenvironment pH of the matrix. Sodium chloride was added to the formula to maintain constant ionic strength of tablet as it was found that ionic strength affects matrix erosion and drug release[9, 10]. The tablets were prepared by direct compression method using KBr press. The tablet weight was kept constant at 250 mg by adjusting the amount of polymeric material used in each formula. The pressure applied during compression was kept at 100 ± 5 N/mm^2 for all tablets.

3. Evaluation of Drug Release:

Drug release was evaluated from 3 tablets of each formulation independently in 900 mL phosphate buffer solution of pH 5.9 and 7.4 at 37°C using USP dissolution apparatus. Paddle method was used at rotational speed of 100 rpm. Samples of 5mL were withdrawn and replaced with 5mL fresh phosphate buffer at time intervals of 1, 2, 3, 4, 6, 8,---- hours. The samples were filtered using Whatmann filter paper of pore size 0.45µm. The concentration of the model drug (Diclofenac sodium) was determined using UV/Vis spectrophotometer at wavelength of 275nm.

4. Swelling and Erosion Studies:

Tablets composed only of 40 mg of HEC and 60 mg Eudragit S-100 were prepared and compressed as described above. Swelling and erosion experiments were conducted on the prepared tablets using USP dissolution apparatus type II at rotational speed of 100 rpm. The medium used was phosphate buffer of constant ionic strength of pH 6.1, 7.1, 8.1, and 8.3 similar to that of microenvironment pH calculated within the matrices. This study was described only to differentiate between polymer swelling and erosion from the solubility of the drug, Sodium chloride and buffer components within the formula. The volume of the medium was 900 mL. The temperature was maintained at 37°C. Three tablets were tested in each buffer medium for 4 hours. The tablets were removed using a small basket and swollen weight of each tablet was determined. To determine matrix erosion,

swollen tablets were placed in oven at 40°C for 48 hours then the tablets were removed and weighed. The percentage of swelling was calculated according to the following formula,

$$\% \text{ Swelling} = S/R \times 100$$

Where, S is the weight of the matrix after swelling and

R is the weight of the eroded matrix:

On the other hand, the percentage erosion was calculated according to the following formula,

$$\%\text{Erosion} = T\text{-}R/T \times 100$$

Where, R is the weight of the eroded matrix

T is the initial weight of the matrix:

5. Statistical Analysis

Data obtained was processed **s**tatistically using one way analysis of variance (ANOVA) to determine significance of difference between groups.

RESULTS AND DISCUSSION

Diclofenac sodium release profile of the 4 formulations prepared and subjected to dissolution studies at pH 7.2 are shown and compared in Figure 1. Formulation 3 containing HEC and Eudragit S100 in 40:60 proportions was selected for further studies since release profile closely resembles to zero-order controlled release. Formula 4 shows slow release behavior, hence rejected.

Diclofenac sodium release profile of the 4 prepared matrices subjected to dissolution studies at pH 7.4 are shown and compared in figure 2. All matrices showed continuous drug release for 9 hours. The extents of drug release during the testing period were between 80% and 95% for all formulas. Drug release was calculated from the slope of the drug release profile. Slope was calculated using Microsoft excel software. The drug release profiles were dependent on the microenvironment pH because the drug release continuously increased with the increase of the pH. It is confirmed by using statistical software ezanova for calculating analysis of variance ($p>0.01$).

Table 3 presents values of the rates of drug release as a function of the microenvironment pH. Square correlation coefficients (R^2) are also presented in Table 3, indicating a linear drug release profile during the testing period for the 4 formulas.

The linear behavior in these types of matrices can be explained by keeping the diffusion path length constant during drug release as that matrix erosion was balanced with swelling of the matrix. Researchers had shown that increasing the pH of the dissolution media will increase the erosion[11] as well as the swelling[12] of controlled release systems containing polymethacrylic acid polymer. Presence of the high molecular weight and hydrophilic HEC inside the matrices maintained the shape and the integrity of the matrices tablet during dissolution and is mainly responsible for the swelling characteristics of the matrices.

The linearity shown in the release profiles of Diclofenac sodium from the 4 matrices indicates zero order drug release profiles. The zero order release profile was maintained with the change in the microenvironment pH. It was also found that as the microenvironment pH increased, the rate of drug release increased in some linear relationship (R^2 =0.829).

But, this behavior may be the result of

A) Increased solubility of Eudragit with increase in pH of the matrix as well as erosion[11].

B) As the microenvironment pH increases, the solubility of Diclofenac sodium increases which might increase drug release[13].

But, we were interested in effect of microenvironment pH on the prepared matrix system. In order to avoid interference due to above mentioned factors, swelling and erosion experiments were carried out on tablets prepared only of HEC and Eudragit.

In order to study the effect of the dissolution medium pH on the drug release

Table 1-Composition of formulas of matrix tablet for optimization

No.	Diclofenac sodium (mg)	HEC (mg)	Eudragit S100 (mg)
1	100	20	80
2	100	30	70
3	100	40	60
4	100	50	50

Table 2-Composition and microenvironment pH of formulations of the matrix tablets

Formula No.	pH	Drug (mg)	HEC (mg)	Eudragit S-100 (mg)	Na_2HPO_4 (mg)	NaH_2PO_4 (mg)	NaCl (mg)
1	6.2	100	35	52.50	5	45	12.5
2	7.1	100	37.5	56.15	25	25	6.25
3	8.1	100	38.5	57.85	45	5	3.75
4	8.3	100	39.0	58.50	47	3	2.5

Table 3 -Rate of Diclofenac sodium release from matrix tablets in phosphate buffer of pH 7.4 Calculated by linear regression

Formula No.	Microenvironment pH	Rate of drug release(mg/h)	R^2
1	6.2	8.39	0.979
2	7.1	8.45	0.997
3	8.1	9.57	0.992
4	8.3	11.45	0.997

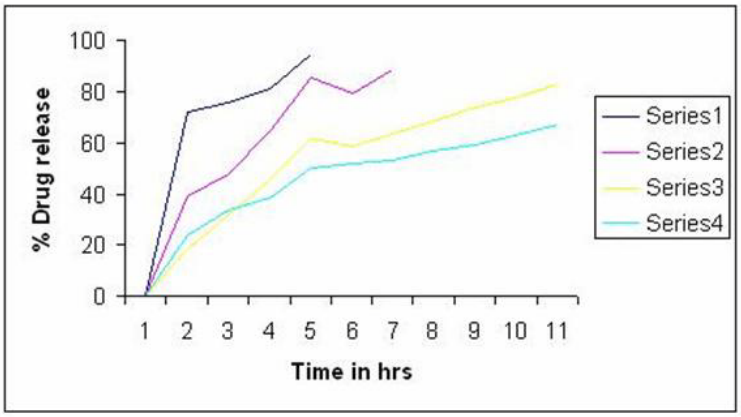

Figure 1 -Release of Diclofenac sodium from formulations in phosphate buffer of pH 7.2

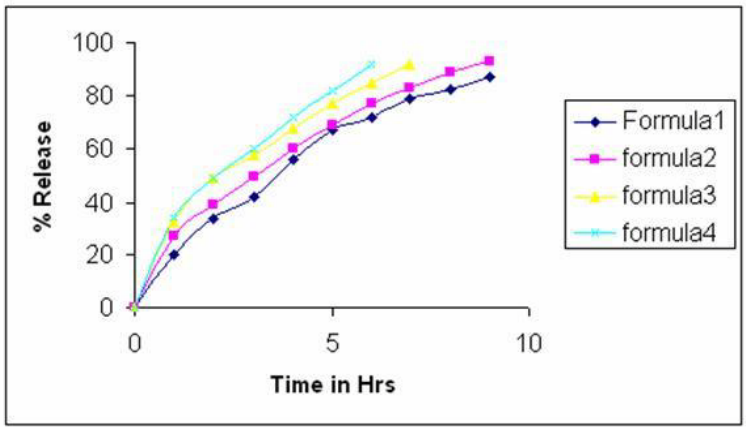

Figure 2 -Release of Diclofenac sodium from formulations in phosphate buffer of pH 7.4 at 37° C

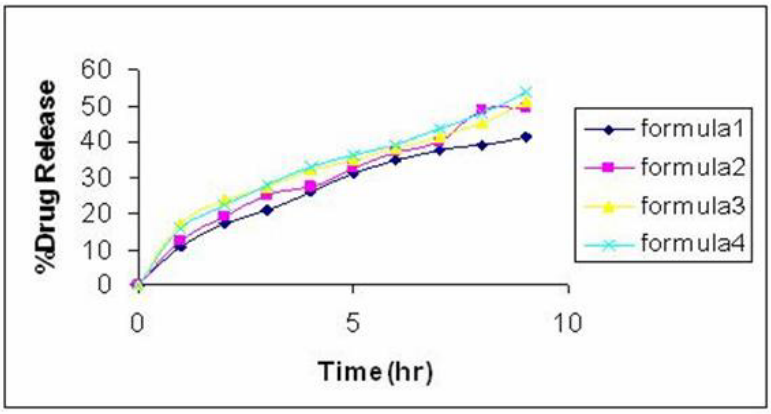

Figure 3 -Release of Diclofenac sodium from formulations in phosphate buffer of pH 5.9 at 37° C

pattern, drug release was studied in phosphate buffer of pH 5.9. Figure3 presents the amount of drug release as a function of time for the 4 formulas.

The release profile of Diclofenac sodium from the matrices increased continuously with time, and the amount of drug release increased as the microenvironment pH of the matrices increased. Rates of release of the 5 different formulas followed the same pattern as that of pH 7.4. The cumulative amount of drug release is higher at pH 7.4 than that of pH 5.9. This decline in drug release at pH 5.9 can be attributed to the effect of dissolution medium pH on the matrices and decreased drug solubility at this pH[14].

Swelling and Erosion

In order to understand the influence of microenvironment pH on the polymer system and thereby drug release, swelling and erosion study on matrices containing the polymers only (HEC and Eudragit) was evaluated. Figure 4 presents the percentage of matrix erosion as well as percentage swelling as a function of pH.

It is clear that the matrices underwent both swelling and erosion at the same time as it was placed in the dissolution media. The pH of the media influenced both matrix erosion and swelling. It was found that as the % swelling increased, % erosion increased in a linear relation-ship (R^2 = 0.996). The percentage of matrix erosion ranged from 5.04% at pH 6.2 to 7.26% at pH 8.3. This indicates that as the pH of the media increased, the percentage eroded increased. This verifies that as the microenvironment pH increased, erosion of the matrix containing Diclofenac sodium increased, thereby increasing the rate of drug release. On

the other hand, the percentage of matrix swelling as a function of pH ranged from 304.02% at pH 6.2 to 353.99% at pH 8.3 (Figure 4). This demonstrates that matrix swelling depends on the pH of the media. As the pH of the media increases, swelling of the matrix increases. The increase in matrix erosion and swelling with increase of the pH is due to the increase in ionization of methacrylic acid moiety present in Eudragit S100.

Thus, both swelling and erosion occurred simultaneously in the matrix. This behavior is responsible for maintaining zero order release in which the increase in diffusion path length due to swelling is balanced with the decrease in the diffusion path length due to matrix erosion[15]. Overall a constant diffusion path length is maintained. Figure 5 demonstrates that the drug release from the matrices is directly related to percentage swelling and percentage erosion, which indicates that drug release also occur simultaneously with swelling and erosion.

CONCLUSION

The microenvironment pH was found to be the key factor in controlling swelling and erosion and thus drug release. It can be concluded that changing the pH within the matrix influenced the rate of release of the drug without affecting the release pattern.

The reason behind unaffected drug release pattern is the linear correlation between swelling and erosion.

REFERENCES

1. US FDA, CDER. Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In vitro/In vivo Correlations. 1997
2. Chien YW, Fundamentals of rate-controlled drug delivery; In: Novel Drug Delivery Systems. Edn 2. Marcel Dekkar; New York, 1992, 43-137.
3. Bramhankar DM, Jaiswal SB, Biopharmaceutics and Pharmacokinetics: A Treatise, Edn 5, Vallabh Prakashan; Delhi, 1998, 32-39.
4. Lee P.I; J Memb Sci. 1980, 7, 255-275.
5. Tiwari S.B., Rajabi-Siahboomi A.R.; Meth. Molec. Biol. 2008, 437, 217-243.
6. Wade A., Weller P.J; Handbook of Pharmaceutical Excipients, Pharmaceutical Press London, 1994, 362-366.
7. Ching A. L, Liew C. V., Chan L. W., Sia Heng P. W.; Eur J Pharm Sci., 2008, 33, 4-5, 361-370.
8. Vyas S.P., Khar R.K; Controlled Drug Delivery: Concepts and Advances, Delhi, India, Vallabh Prakashan; First Edition: section-I, 2002, 1-51.
9. Abrahamsson B., Alpesten M., Bake B., Larsson A., Sjogren J; Eur J Pharm Biopharm. 1998; 46:69-75.
10. Sheu M., Chou H., Kao C., Liu C., Sokoloski T; Int J Pharm. 1992; 85: 57-63.
11. Mehta K.A., Kislalioglu M.S., Phuapradit W., Malick A.W., Shah N.H; Int J Pharm. 2007; 213: 7-12.
12. Bettini R., Colombo P., Peppas N.A; J Control Release. 1995; 37:150-111.
13. Avdeef A., Berger C.M., Brownell C; Pharm Res. 2000; 17:85-89.
14. Sarjeev C., Saha R.N; Drug Dev Res. 2001; 53:1-8.
15. Padmalatha D.K., Ranga Rao K.V., Baveja S., Fathi M., Roth M; Pharm Res. 1989; 6: 313-317.