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Effect of Microenvironment pH of Swellable and Erodable Buffered Matrices on the Release Characteristics of Diclofenac Sodium

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ABSTRACT

The aim of this work is to design pH-dependent swellable and erodable-buffered matrices and to study the effect of the microenvironment pH on the release pattern of diclofenac sodium. Buffered matrix tablets containing diclofenac sodium, physically mixed with hydrophilic polymer (hydroxypropyl methylcellulose [HPMC]) and pH-dependent solubility polymer (Eudragit L100-55) were prepared with different microenvironment pHs. The release of diclofenac sodium from the buffer matrices was studied in phosphate buffer solutions of pH 5.9 and 7.4. The swelling and erosion matrices containing only HPMC and Eudragit L100-55 were studied in phosphate buffer solution of pH similar to the microenvironment pHs of the matrices. Drug release from matrices was found to be linear as a function of time. Amount of drug released was found to be higher in the medium of pH 7.4 than that of pH 5.9. The rate of drug release increased with the increase of the microenvironment pH of the matrices as determined from the slope. The pattern of drug release did not change with the change of microenvironment pH. The swelling and erosion occurred simultaneously from matrices made up of HPMC and Eudragit L100-55. Both extent of swelling and erosion increased with increase of the medium pH. It was concluded from this study that changing the pH within the matrix influenced the rate of release of the drug without affecting the release pattern.

KEYWORDS: controlled release, buffered matrix, swelling, erosion, sustained release

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INTRODUCTION

Hydrophilic matrices are commonly used in formulating extended release dosage form. Cellulose ethers such as hydroxypropyl methylcellulose (HPMC) are commonly used as gel-forming agents, which are usually termed swellable matrix tablets.[1,2]

Water-insoluble inert carriers have been used for preparing sustained release dosage forms of various water-soluble and short-acting drugs. An example of such water-insoluble carriers is Eudragit, which is a group commercially available in anionic, cationic, and zwitterionic forms.[3,4] Eudragit Ll00-55 is an anionic copolymer of methacrylic acid and methyl methacrylate. The ratio of free carboxyl group to the ester is approximately 1:1. It has a pH-dependent solubility and is readily soluble in neutral to weakly alkaline conditions and forms salts with alkalis.[5] This polymer is commonly used in tablet coating as an enteric coating polymer.[6] Also, there have been some reports demonstrating that Eudragit L100-55 can be used as a sustained release carrier. Erosion is the main mechanism of release of drug dispersed in the polymer.[7,8] In addition, Eudragit L100-55 has been used as a colon-targeted drug delivery system[9] and to improve site-specific intestinal drug absorption.[10]

Matrix erosion and dissolution systems can provide means of overcoming the well-known advantage of a purely diffusion control system. Synchronization between erosion and diffusion fronts has been identified to produce zero order drug release.[7,11]

Buffered matrices have been employed in pharmaceuticals for different purposes. A compressed buffered aspirin matrix has been prepared to enhance the physical and chemical stability of the drug in the formulation.[12] Buffered ocular insert matrix containing timolol has been demonstrated to increase the rate of timolol released from the matrix and its ocular bioavailability.[13]

In the present work, several buffered matrices of different microenvironment pHs have been prepared using

Table 1. Composition and Calculated Microenvironment pHs of the Formulas of Matrix Tablets*

Formula No.	pH	Diclofenac Sodium (mg)	HPMC (mg)	Eudragit L100-55 (mg)	Na_2HPO_4 (mg)	NaH_2PO_4 (mg)	NaCl (mg)	Total Weight (mg)
1	6.2	100	323.4	40.4	5	45	36.23	550
2	7.1	100	336.7	42.1	25	25	21.26	550
3	7.6	100	345.0	43.1	37.5	12.5	11.90	550
4	8.1	100	350.0	43.7	45	5	6.28	550
5	8.3	100	351.3	43.9	47	3	4.78	550

*HPMC indicates hydroxypropyl methylcellulose.

gel forming swellable hydrophilic polymer, HPMC, and an erodable pH-dependent solubility polymer, Eudragit L100-55. Therefore, the release pattern was synchronized to obtain a zero order release of the model drug diclofenac sodium. The effect of microenvironment pH within the matrix on the drug release characteristics has been evaluated.

MATERIALS AND METHODS

Diclofenac sodium was donated by Dar Al-Dawa (Amman, Jordan). Methocel K100M (HPMC) was purchased from Dow Chemical (Midland, MI). Eudragit L100-55 was purchased from Rohm America (Piscataway, NJ). Disodium hydrogen orthophosphate anhydrous and sodium dihydrogen phosphate anhydrous were obtained from Scharlau Chemie (Barcelona, Spain). Sodium chloride was purchased from Frutarom Ltd (Kettering, UK). Only distilled deionized water was used. The materials used in the preparation of the matrices were allowed to pass through a sieve of 120-mesh size.

The following instrumentation was used: Cintra 5 UV/Vis spectrophotometer, GBC Scientific Equipment (Dandenong, VIC, Australia); Roell & Korthaus, RKM50 (Haan, Germany); Erweka DT60 dissolution apparatus type II (Heusenstamm, Germany); Metler Toledo analytical balance, AT261 (Greifensee, Switzerland); vacuum oven, model 19, Precision (Winchester, VA); and custom-made small V-shaped mixer.

Five different formulas of matrix tablets were prepared. The composition of each formula is presented in **Table 1**. The ratio between HPMC and Eudragit L100-55 was kept constant for the 5 formulas. The formulas differ in the amounts of the phosphate buffer components in an attempt to control the microenvironment pH of the matrix. Microenvironment pH is the pH within the matrix tablet after hydration and dissolving of phosphate species. According to the amounts of phosphate buffer component in each formula, the microenvironment pH was calculated using Henderson-Hasselbalch equation.[14] The values of the calculated microenvironment pHs are also listed in **Table 1**. Sodium chloride was added to the formula to maintain constant ionic strength of tablet as it was found that ionic strength effects matrix erosion and drug release.[15,16] The ionic strength was calculated for all buffer species and sodium chloride present within the matrix of each formula. The constituents of each formula were mixed in a small V-shaped mixer for 15 minutes. The tablets were prepared by direct compression method. The formulas were compressed using Roell & Korthaus machine in double flat one-half-inch tablet die. The tablet weight was kept constant at 550 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.

Drug release was evaluated on 3 tablets of each formula in 900 mL phosphate buffer solution of pH 5.9 and 7.4 at 37°C using Erweka dissolution apparatus. Paddle method was used at rotational speed of 100 rpm. The ionic strength of the buffer solution was kept constant at 0.25. Samples of 5mL were withdrawn and replaced with 5mL fresh phosphate buffer according to following time scheme: 0.5, 1, 2, 3, 4, 6, 8, and 12 hours. The samples were filtered using 0.45 μm Millipore filter (Waterloo, Belgium). The concentration of the model drug (diclofenac sodium) was determined using UV/Vis spectrophotometer at wavelength of 275nm.

Tablets composed only of 400 mg of HPMC and 50 mg Eudragit L100-55 were prepared and compressed as described. Swelling and erosion experiments were conducted on the prepared tablets using Erweka disso-

lution apparatus II at rotational speed of 100 rpm. The swelling and erosion medium used was phosphate buffer of constant ionic strength of the following pHs: 6.1, 7.2, 7.6, 8.1, and 8.3, which are the same microenvironment pHs calculated within the matrices. The design of this experiment using matrices containing HPMC and Eudragit L100-55 only aims to differentiate between polymer swelling and erosion from the solubility of the drug, NaCl, 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 a vacuum 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, where *S* is the weight of the matrix after swelling and *R* is the weight of the eroded matrix:

$$\% \ Swelling = \frac{S}{R} \times 100 \quad (1)$$

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

$$\% \ Erosion = \frac{T - R}{T} \times 100 \quad (2)$$

RESULTS AND DISCUSSION

Drug Release

Diclofenac sodium release profile of the 5 prepared matrices subjected to dissolution studies at pH 7.4 are shown and compared in **Figure 1**. All matrices showed continuous drug release for 12 hours. The extents of drug release during the testing period were between 40% and 65% for all formulas. The drug release profiles were dependent on the microenvironment pH because the drug release continuously increased with the increase of the pH. The rates of diclofenac release for the 5 different formulas at pH 7.4 were determined from the slope of the drug release profile by linear regression. **Table 2** presents values of the rates of drug release as a function the microenvironment pH. Square correlation coefficients (R^2) are also presented in **Table 2** indicating a linear drug release profile during the testing period for the 5 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. It has been shown by many researchers that increasing the pH of the dissolution media will increase the erosion[8,17] as well as the swelling[18-20] of controlled release systems containing polymethacrylic acid polymer. Presence of the high molecular weight and hydrophilic HPMC 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 5 matrices indicates zero order drug release profiles. The zero order release profile was maintained with the change in the microenvironment pH.

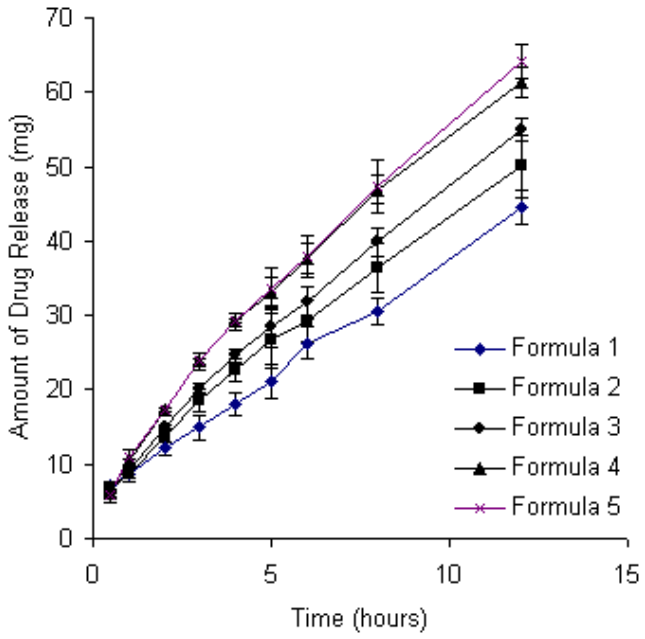

Figure 1. Release of diclofenac sodium from the different matrix formulations in phosphate buffer of pH 7.4 at 37°C.

Figure 2 shows the relationship between the rates of drug release as a function of the microenvironment pH. It was found that as the microenvironment pH increased, the rate of drug increased in a linear relationship ($R^2 = 0.973$). The effect of the microenvironment pH on the rate of drug release was evaluated statistically using analysis of variance (ANOVA) at $\alpha = 0.05$. Analysis results showed that the microenvironment pH significantly affects the rate of release of diclofenac sodium from the matrices. This behavior can be attributed to the increase in the solubility of Eudragit with

Table 2. 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	3.25	0.997
2	7.1	3.75	0.993
3	7.6	4.18	0.992
4	8.1	4.76	0.981
5	8.3	4.96	0.987

*R^2 indicates square correlation coefficients.

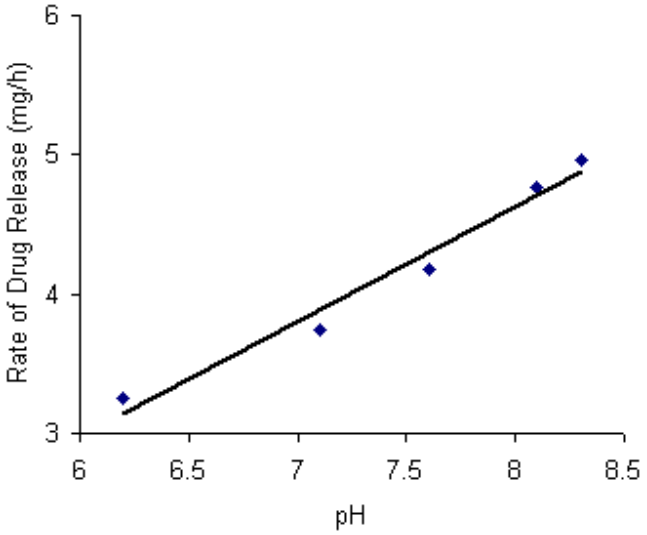

Figure 2. Effect of calculated microenvironment pH on the rate release of diclofenac sodium from buffer matrix tablet in dissolution medium of pH 7.4 at 37°C.

increasing the pH of the matrices as well as erosion. It has been demonstrated that matrix tablets containing Eudragit L100 provide rapid release of theophylline at pH of 7.4 due to the increase in the solubility of the polymer at this pH.[21] Matrix tablet containing Eudragit L100 or Eudragit S100 underwent gradual erosion at pH values exceeding the threshold of polymer ionization, which controlled prednisolone release.[17] Another factor to be considered is the effect of the microenvironment pH on the drug solubility. As the microenvironment pH increases, the solubility of diclofenac sodium increases which might increase drug release.[22]

In order to study the effect of the dissolution medium pH on the drug release pattern, drug release was studied in phosphate buffer of pH 5.9. **Figure 3** presents the amount of drug release as a function of time for the 5 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 by 40% to 60%. 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.[23]

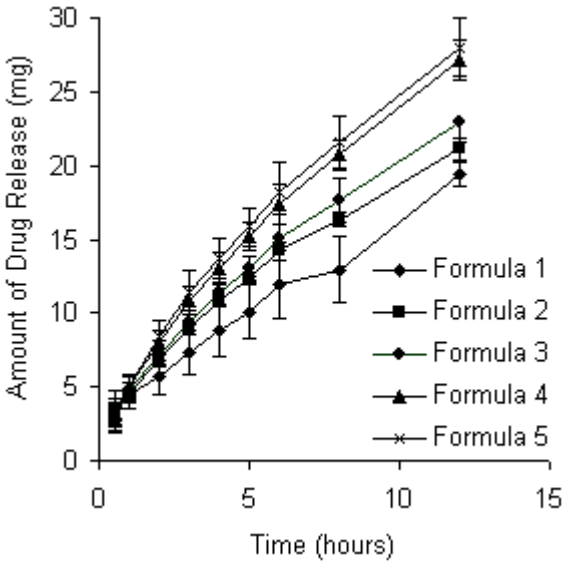

Figure 3. Release of diclofenac sodium from the different matrix formulations in phosphate buffer of pH 5.9 at 37°C.

Swelling and Erosion

On exposure of matrices to aqueous fluid, the tablet surface becomes wet and starts to hydrate to form a viscous gel layer. The release of the drug from the matrices can be governed by the diffusion and its subsequent erosion. In order to understand the influence of

the polymer system on drug release, swelling and erosion study on matrices containing the polymers only (HPMC 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. The percentage of matrix erosion ranged from 5.02% at pH 6.2 to 7.13% 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 310% at pH 6.2 to 377% 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 L100-55.[17] This creates electrostatic repulsion forces between Eudragit polymer chains, which disrupt the matrix and increase both swelling and erosion as the pH increases.

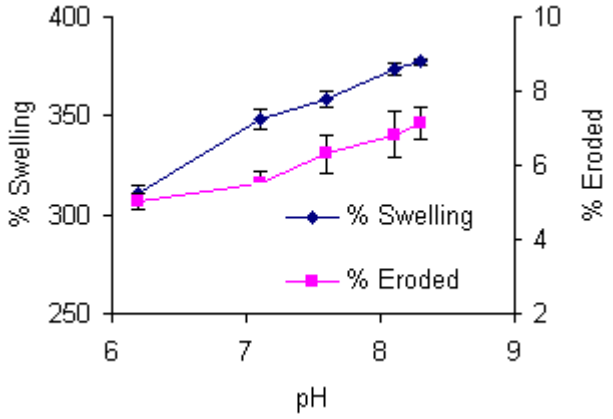

Figure 4. Percentage swelling and percentage erosion of the polymeric matrix tablet in phosphate buffer of different pHs at 37°C.

Since both swelling and erosion occurred simultaneously in the matrix, zero order release can be obtained in such types of matrices.[24,25] 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. Overall a constant diffusion path length is maintained.

In agreement with the effect of the microenvironment pH on matrix erosion and swelling, the release behavior of diclofenac sodium from buffered matrices made up of HPMC and Eudragit L100-55 can be also be explained. **Figure 5** demonstrates that the drug release from the matrices is directly related to percentage swelling and percentage erosion, which indicates that drug release and swelling and erosion occur simultaneously.

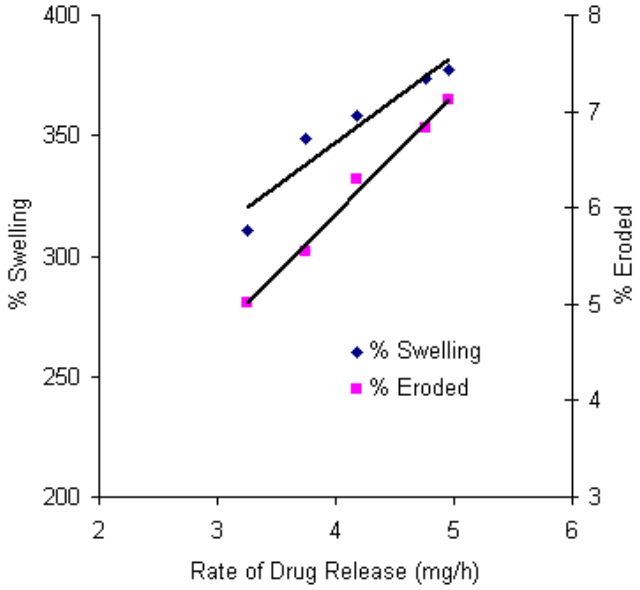

Figure 5. Correlation of matrix erosion (percentage eroded) and matrix swelling (percentage swelling) with rate of drug release in dissolution medium of pH 7.4.

CONCLUSION

For the formulation system investigated in this study, both matrix swelling and erosion can control drug release. In this regard, the microenvironment pH was found to be the key controlling 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.

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