Electrolyte-Induced Compositional Heterogeneity: A Novel Approach for Rate-Controlled Oral Drug Delivery

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Abstract □ In this work a new approach for in situ interactions between drug and electrolyte(s) is devised to control the release of highly water soluble drugs from oral hydrophilic monolithic systems. The model drug diltiazem hydrochloride (water solubility in excess of 50% at 25 °C), in conjunction with specific electrolytes, was principally employed in the design of swellable tablet formulations comprised of hydrophilic polymers such as hydroxypropylmethlcellulose (HPMC) or poly(ethylene oxide) (PEO). Electrolytes such as sodium bicarbonate or pentasodium tripolyphosphate were used to modulate intragel pH dynamics, swelling kinetics, and gel properties. Through in situ ionic interactions (an intragel matrix system composed of different chemical species that promote competition for water of hydration), a compositionally heterogeneous structure referred to as a "metamorphic scaffold" was established. It is shown that this latter structure results in the inhibition of drug dissolution, induction of a differential swelling rate, and attainment of "matrix stiffening" and axially provides a uniform gel layer. Presence of such phases in matrix structure and its influence on swelling dynamics enabled control of diltiazem hydrochloride release in a zero-order manner in different pH environments over a 24-h period. From kinetic analysis using the power law expressions [$M_t/M_\infty = k_1t^n$, $M_t/M_\infty = k_1t^n + k_2t^{2n}$] and Hopfenberg model [$M_t/M_\infty = 1 - (1 - k_1t)^n$], it became apparent that the dynamics of matrix relaxation and controlled erosion were major factors involved in the release mechanism, while the composite rate constant k_1 (in Hopfenberg model) decreased by approximately 2-fold in the presence of electrolyte(s). These findings indicated that the dynamics of swelling and gel formation in the presence of ionizable species within hydrophilic matrices provide an attractive alternative for zero-order drug delivery from a simple monolithic system.

Introduction

Controlled release drug delivery systems have received much attention in the past two decades with numerous technologically sophisticated products on the marketplace. Such advancements have come about by the simultaneous convergence of many factors, including the discovery of novel polymers, formulation optimization, better understanding of physiological and pathological constraints, prohibitive cost of developing new drug entities, and the introduction of biopharmaceutics in drug product design. The major benefits of these products lie in the optimization of drug input rate into the systemic circulation in order to achieve an appropriate pharmacodynamic response. This in turn should add to product safety and reduce the extent and incidence of major adverse drug reactions due to a more strict control of blood levels. Furthermore, with less frequent dosing, it is speculated that this should improve patient compliance and possibly maximize drug product efficacy in therapeutics.

Recently numerous hydrophilic polymers have been investigated and are currently used in the design of complex controlled release systems.[1−4] In many cases the formulator depends on the inherent rate-controlling mechanisms of the polymer to provide constant rate drug delivery. Among desirable features, the polymer should possess inherent physicochemical characteristics which provide for the attainment of high gel-state viscosity upon swelling, ability to maintain constant gel layer integrity over a prolonged period of time and hence low erosion rate, and complete dissolution of polymer upon exhaustion of drug release. Alternatively, a programmed system is sought for which swelling and erosion are the key factors in controlling drug liberation. The ideal polymer would permit these processes to operate synchronously, i.e., affording a balance between the principal processes of swelling, erosion, and dissolution. Among the most widely used polymers, such as the nonionic hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), poly(ethylene oxide) (PEO) types, the cationic chitosan types, and anionic alginate types, the attainment of high gel-state viscosity, maintenance of constant gel layer, or synchronous erosion−dissolution in a monolithic sense for linear drug release over a prolonged period of time is not easily achievable and still remains a challenge. Since the various dynamic phases in the rate processes of polymer relaxation, disentanglement, and/or erosion during dissolution are manifested in a nonconstant manner, realization of zero-order drug release from such monolithic devices is difficult.

This limitation of hydrophilic polymers may be circumvented through modification of the physical and chemical infrastructure of the polymeric gel system. In the present work a reliable process has been established for inducing in situ reactions between pharmaceutically acceptable electrolytes/acids and drug which influences the intragel swelling dynamics and relative physical integrity of the swollen matrix structure. Furthermore, this may produce heterogeneous domains within the swollen gel boundary referred to as "metamorphic scaffold" in this work (see Figure 1).

In the past, alkaline compounds or buffers have been included in solid oral formulations of several acidic drugs that undergo dissolution rate-limited absorption.[5−11] The same principle of addition of buffers, osmotically active agents, surfactants, or combinations thereof has also been utilized to control the swelling of hydrophilic polymers with different coating and inclusion techniques.[12] However, no specific strategy has been employed to apply the same principle to design a simple, directly compressible, monolithic, controlled-release system with provision of zero-order kinetics. In general, the application of buffers and ionizable

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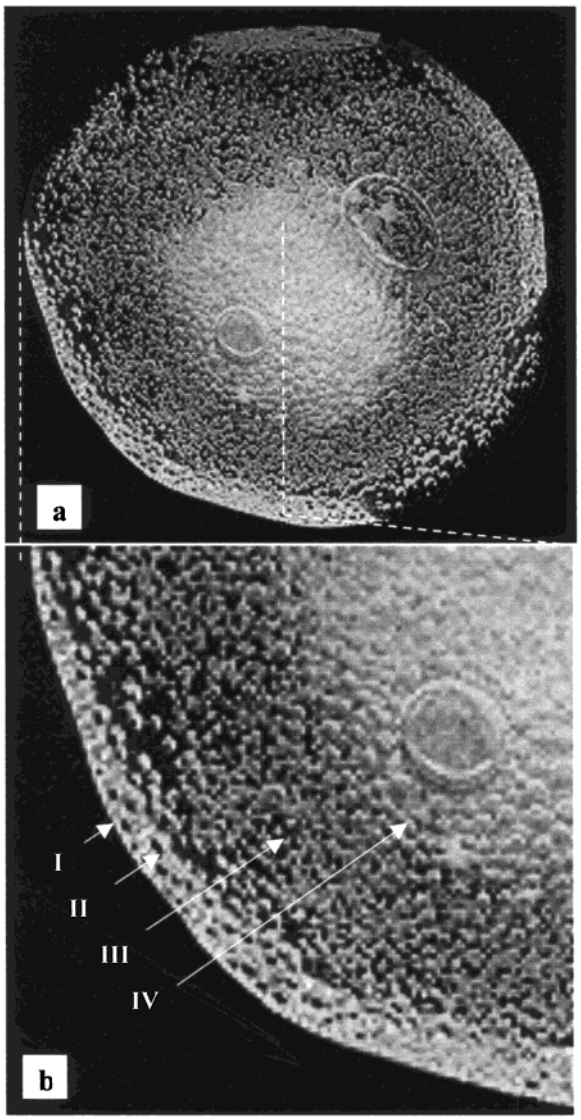

Figure 1—(a) Photomicrograph of swollen matrix (pH 1.5) of HPMC-based tablet containing 100 mg each of sodium bicarbonate and diltiazem hydrochloride, depicting the putative "metamorphic scaffold" and heterogeneous composition (magnification: ×7). (b) Magnified region of above swollen gelled matrix distinctly reflecting the proposed matrix transition phases (magnification: ×14): I) Water saturated diffusion front; II) Peripheral gel layer; III) Swollen infiltrated layer; and IV) Glassy swelling front. (For more detailed explanation see Figure 6c).

compounds in dosage form design has essentially been limited to the minimization of localized gastrointestinal tract adverse effects and the pH-solubility dependency of poorly soluble compounds.[5,6,13,14]

The aim of this work was to provide and expand on a means to design, formulate, and develop a novel oral monolithic, controlled-release tablet dosage form for drugs of various solubility that may be tailored to provide zero-order or quasi-steady-state drug release over a 24-h period.[15] The model drug employed in this work was diltiazem hydrochloride, which has a water solubility in excess of 50% at 25 °C. The rationale behind the mechanisms and dynamics of electrolyte-induced matrix stiffening and modulation of intragel pH changes for the provision of controlled drug release will be elucidated.

Experimental Section

Materials—Hydroxypropylmethylcellulose (HPMC K4M, Dow Chemical Company, Midland, MI) and poly(ethylene oxide) (PEO 4 million molecular weight, Union Carbide, CT) were employed in tablet production. Diltiazem hydrochloride (Seloc AG, Switzerland) was use as a model compound. The following electrolytes/acids used were of analytical grade: sodium bicarbonate (Ruger Chemical Co., NJ), potassium bicarbonate, magnesium carbonate (Fischer Scientific Co., NJ), calcium carbonate (E.M. Science, NJ), dibasic sodium phosphate as the 12-hydrate crystal (J. T. Baker Inc., NJ), sodium carbonate, pentasodium tripolyphosphate, sodium deoxycholate from parent 7-deoxycholic acid, maleic acid, adipic acid, and L-(+)-tartaric acid (Sigma Chemical Co., St. Louis, MO).

Methods—*Preparation of Tablets*—A typical monolithic formulation consisted of polymer, drug, and electrolyte. The ratio of drug:polymer was always maintained at the 1:2 level (i.e., 100 mg:200 mg), while the electrolyte content was varied. For example, a single tablet would be composed of 200 mg of HPMC K4M or PEO 4M, 0−100 mg of electrolyte, and 100 mg of drug. Pure and drug-loaded compacts of polymer were used as control indicators. The powder mixture was blended in a V-blender for 15 min prior to compression at 4000 lbs in an 11.5 mm diameter die using the Carver Press (Model C, Fred S. Carver, IN) and flat-faced punch. To minimize processing variables, all tablets were produced under identical conditions.

Drug Release and Matrix Erosion Studies—Dissolution studies on each formulation were performed in a calibrated six station dissolution test apparatus (VK 7000, Vankel Industries Inc., Edison, NJ) using the USP 23 Apparatus 2 in USP-recommended buffers (pH 1.5, 2.6, 4.1, 5.4, 6, 6.4, 6.8; 900 mL, 37 ± 0.5 °C, 50 rpm). All studies were conducted in triplicate ($N = 3$) using an automated sampling procedure. Drug release was analyzed by ultraviolet spectroscopy (HP Diode Array) at 238 nm.

The erosion properties for the above-described HPMC and PEO tablets were studied in pH 1.5 using Apparatus 2 in order to simulate actual dissolution conditions. At predetermined time intervals, tablets were removed, dried to constant weight under vacuum at 40 °C, and thereafter weighed.

Diltiazem Free Base Formation—Diltiazem hydrochloride (1.5 g) was solubilized in deionized water (10 mL) and transferred to a separatory flask. This solution was alkalinized with sodium bicarbonate (0.5 g) to precipitate the drug as the free base. The free base was extracted with ether (20 mL) and recrystallized on a rotavap (Rotavapo-R, Buchi) at 35 °C over a period of 30 min. The solvent residue was completely removed by drying under vacuum over a further 30-min period through an acetone−dry ice reservoir maintained at −178 °C.

Intragel pH Measurements—Transitions in the intragel pH (i.e., within the tablet gel matrix) were monitored with aid of a flat surface polymer combination electrode having a 5 mm contact area (Accumet, Fischer Scientific). The electrode, attached to a pH meter (Accumet pH meter 25, Fischer Scientific), was used for pH measurements of gel at the periphery and within the swollen matrix in both the axial and radial planes at predetermined time intervals on tablet formulations exposed to dissolution medium pH 1.5. Various inwardly depths were exposed for pH measurements by excisions with a scalpel. Furthermore, a continuous pH measurement of the external matrix interface was performed by having the perforated guard and the flat surface of the pH electrode in constant contact with the tablet during a dissolution study in buffer medium pH 1.5. pH titration methods were also adopted on plain HPMC solutions with and without drug to evaluate the influence of electrolyte content on concurrent pH changes and interaction with drug.

Sample Treatment and Force−Displacement Profiling by Textural Analysis—Textural analysis was performed on different tablet formulations in order to determine the electrolyte-related effects on structural alteration of the gelled scaffold and swelling dynamics. One planar base as well as the entire lateral surface of each tablet was sealed off with an organic coating consisting of 20 g of Eudragit PO in a mixture of 50 mL of acetone and 50 mL of 2-propranol. This coating rendered these surfaces impermeable to penetration by buffer medium. These steps ensured (i) prevention of interfacial deformation of core/gel structure during probe advancement, and (ii) confinement of swelling in the axial direction. When radial measurements were undertaken, both planar surfaces of the tablet were coated. Triplicate samples were then placed in dissolution vessels containing 900 mL of buffer medium pH 1.5 at 37 °C during separate tests. The paddle speed was set at 50 rpm to simulate the actual tablet dissolution process. At

predetermined time intervals individual tablets were removed and subjected to textural analysis in a similar manner described in recently published work.[16]

In summary, the Texture Analyzer instrument (TA XT2*i*, Stable Micro Systems, England) which has the ability to capture stress–strain profiles with a high degree of accuracy was used. Data were captured at a rate of 200 pps via the Texture Expert for Windows software, Version 1.20. A flat-tipped steel probe, 2 mm in diameter, was connected to a force transducer within the analyzer that measured the force of resistance encountered by the probe during advancement into the sample. During a typical test, the probe was advanced at a predetermined velocity into the sample in accordance with the following parameters: Pretest speed = 1 mm/s, test speed and post-test speeds = 0.2 mm/s, maximum compression force = 40 N, and an auto trigger using 0.5*g* as the trigger force.

Furthermore, the influence of stepwise pH changes on matrix structure was also evaluated in Apparatus 2 by periodically moving the tablets into different pH environments (i.e., pH 1.5, 3, 5.4, 6, 6.4, 6.8) and then evaluating their textural properties.

Data Treatment for Analysis of Release Kinetics and Deconvolution of Texture Profiles—To precisely determine the nature of release mechanism in the presence and absence of electrolyte, application of kinetic modeling for analysis of release profiles is necessary. Such analysis was performed on formulations comprised of HPMC K4M in the absence and presence of 100 mg of sodium bicarbonate. The kinetics of drug release (buffer medium pH 1.5) were analyzed using WinNonlin, Version 1.0 (SCI Software). In all least squares analyses, the Gaussian-Newton (Levenberg–Hartley) approach was adopted. The power law expression (eq 1) and its geometry-independent form (eq 2) were considered for data analysis.[17–20] In addition, the Hopfenberg model, a geometry-dependent equation (eq 3), was also employed for determination of release kinetics[21] (see below).

With reference to textural analysis, the predetermined maximum compression force of 40 N was established over a series of tests, such that after deconvolution of raw data, based on computed gradient changes within the matrix, distinct matrix phase transitions could be identified. By running Texture Expert macros, triplicate data from each experimental formulation was used in the calculation of time-related parameters associated with the diffusion layer, peripheral gel phase, swollen infiltrated gel phase, and glassy swelling fronts. These include changes in force, phase thickness, swelling gradients in axial and radial planes (determined from up-curving force–displacement changes), and associated resistance to probe penetration. The rationale behind the establishment of the above-mentioned phases will be discussed.

Results and Discussion

Drug Release Potential as a Function of Electrolyte Content and Release Kinetics—By incorporation of sodium bicarbonate into hydrophilic monolithic tablet matrices, it was possible to progressively reduce the release rate of diltiazem hydrochloride (water solubility in excess of 50% at 25 °C) over a 24-h period. Distinct evidence of this phenomenon is provided with application of a typical nonionic hydrophilic polymeric material such as poly(ethylene oxide), 4 million molecular weight (PEO 4M) (Figure 2a). With an increase in electrolyte concentrations (from 0 to 100 mg), the release rate of diltiazem hydrochloride tended to slow, indicating greater inhibition in release in comparison to the control formulation (i.e., in the absence of electrolyte). This electrolyte-induced, controlled release phenomenon was also observed with other polymeric materials such as HPMC, chitosan, and sodium alginate. To further illustrate the utility of the electrolyte effect typical release profiles for HPMC K4M-based matrix and diltiazem hydrochloride is provided (Figure 2b). The distinctive feature in the case of HPMC formulations is that an increase in the linearity of the release profiles was evident as the electrolyte content increased from 10 mg to 100 mg, with corresponding correlation coefficients of 0.7499 to 0.9836 (Figure 2b). Based upon this latter observation, all other testing procedures were conducted on the HPMC-based matrices. In addition, HPMC has good compactibility behavior and is widely used within the pharmaceutical industry. Under the given experimental conditions, the formulation containing 100 mg of sodium bicarbonate was considered optimal. On exposure of this electrolyte-containing HPMC formulation to different pH environments, a minimal burst effect (<10% of total dose) and linear drug release for up to 24 h was achieved (see Figure 2c). It is apparent that the delivery system has potential to function in a relatively pH-independent manner and is able to control the release of a highly soluble drug such as diltiazem hydrochloride (solubility >50% in water at 25 °C).

As an initial test to confirm that the process of electrolyte inclusion within the swelling matrix was not purely a catalyst for free base formation but was also involved in fundamental structural changes in gel boundary, the hydrochloride form of diltiazem was converted into its free base and incorporated into a HPMC-based tablet dosage form in the presence of acidic and basic electrolytes and thereafter evaluated its drug release potential in pH 1.5 and 6.8 buffer media (Figure 3a,b). As expected from pH-solubility theory, the free base displayed a higher solubility

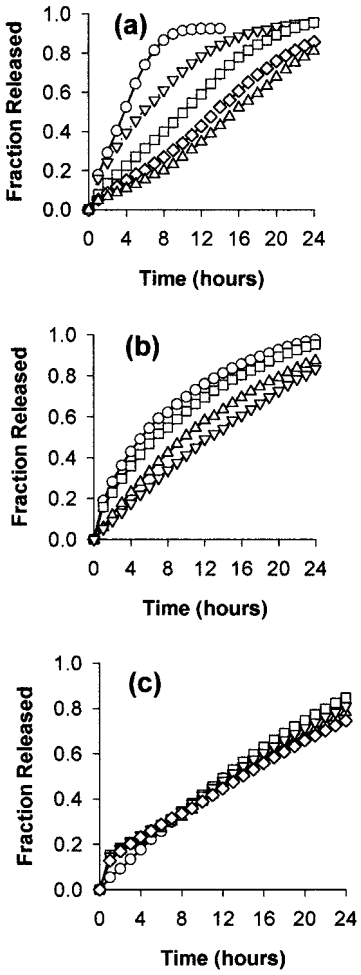

Figure 2—(a) Release of diltiazem hydrochloride from PEO 4 million formulations containing different quantities of sodium bicarbonate in buffer medium pH 1.5: 0 mg (○), 10 mg (▽), 50 mg (□), 75 mg (◇), 100 mg (△). (b) Release of diltiazem hydrochloride from HPMC K4M formulations containing different quantities of sodium bicarbonate in buffer medium pH 1.5: 0 mg (○), 10 mg (□), 50 mg (△), 100 mg (▽). (c) Influence of different bulk pH media on the release of diltiazem hydrochloride (100 mg) from formulation containing 100 mg of sodium bicarbonate: pH 1.5 (○), pH 5.4 (□), pH 6 (△), pH 6.4 (▽), pH 6.8 (◇).

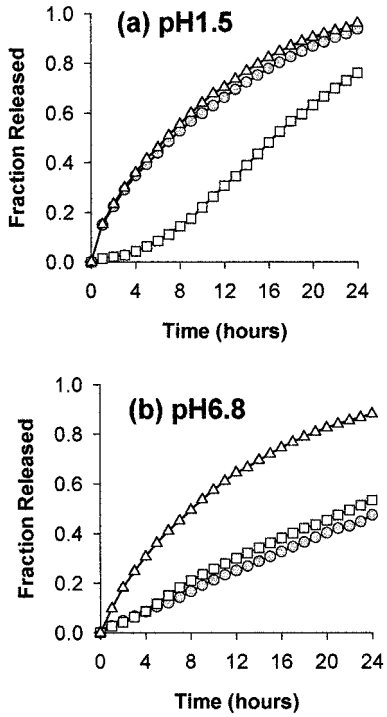

Figure 3—(a) Release of diltiazem free base in pH 1.5 from HPMC-based control (i.e., no electrolyte) and formulations containing sodium bicarbonate (100 mg) or tartaric acid (100 mg): control (gray ○), sodium bicarbonate (□), tartaric acid (△). (b) Release of diltiazem free base in pH 6.8 from control (i.e., no electrolyte) and formulations containing sodium bicarbonate (100 mg) or tartaric acid (100 mg): control (gray ○), sodium bicarbonate (□), tartaric acid (△).

in strongly acidic media (Figure 3a) as opposed to higher pH or weakly acidic media (Figure 3b). However, the overall release profile in this case was significantly different from that of the hydrochloride form shown in Figure 2c. The incorporation of tartaric acid in the free base-containing formulation did not alter drug release in acidic environment such as pH 1.5 (Figure 3a), but release was enhanced at higher pH values such as pH 6.8 (Figure 3b). It appears that the presence of sodium bicarbonate was crucial in controlling the release process (see Figure 3a). Even though the profiles for free base and free base mixed with sodium bicarbonate are comparable in pH 6.8, the extent of release is not acceptable (only 45−50% of drug is released in 24 h, Figure 3b). Therefore it is postulated that the incorporation of electrolyte into the tablet might essentially inhibit the dissolution of diltiazem hydrochloride through intragel pH-control and subsequent induction of textural variations in the swollen matrix. On substitution of sodium bicarbonate by other electrolyte types (e.g., sodium carbonate, calcium carbonate, magnesium carbonate, potassium bicarbonate, pentasodium tripolyphosphate, sodium phosphate (dibasic), or sodium deoxycholate), it appears that electrolyte solubility and formation of a buffer threshold within the matrix plays an essential role in effective interaction with drug and textural changes as shown in Figure 4 and Table 1 (based on extent of constant drug release and corresponding correlation coefficients).

Detailed consideration will be given to the rationale of these postulated mechanisms in following sections.

In general, drug release from simple swellable systems may be described by the power law expression:[17]

$$M_t/M_\infty = k_1 t^n \qquad (1)$$

where M_t and M_∞ are the amounts of drug released at time

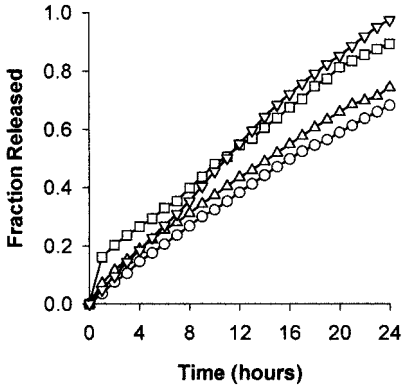

Figure 4—The influence of different electrolytes (100 mg) on the release of diltiazem hydrochloride–HPMC matrices in buffer media pH 1.5 using magnesium carbonate (○), potassium bicarbonate (▽), pentasodium tripolyphosphate (□), sodium carbonate (△).

t and the overall amount released respectively, k_1 is a release constant, and n is a release exponent indicative of the release mechanism. Classically, $n = 0.5$, $0.5 < n < 1$, or $n = 1$ for a slab, is indicative of Fickian release, anomalous transport, or Case II transport kinetics, respectively. However, the n values may change with the matrix geometry. Particularly in the case of a cylinder (as considered in this work), zero-order release is indicated by an n-value of 0.89, instead of 1.

Irrespective of dosage form geometry, various authors[18−20] have reported on the evaluation of contributions provided by Fickian diffusion and matrix relaxation/dissolution through the use of the following equation:

$$M_t/M_\infty = k_1 t^n + k_2 t^{2n} \qquad (2)$$

where k_1 is the Fickian kinetic constant and k_2 is the relaxational/erosion rate constant.

Additionally, release from systems with surface erosion and varying geometries also have been analyzed by Hopfenberg,[21] where a model applicable to a slab, cylinder, or sphere showing heterogeneous erosion is proposed (eq 3):

$$M_t/M_\infty = 1 - (1 - k_1 t)^n \qquad (3)$$

In this equation, k_1 is equal to $k_0/C_0 r_0$, k_0 is the erosion rate constant, C_0 is the uniform initial concentration of drug in the matrix, and r_0 is the initial radius for a sphere or cylinder or the half-thickness for a slab. In eq 3 the n values are as follows: $n = 1$ for a slab, $n = 2$ for a cylinder, and $n = 3$ for a sphere. The model assumes that time-dependent diffusional resistances internal or external to the eroding matrix do not influence the release kinetics. Furthermore, the contribution of the secondary surfaces to the release process is not considered, as discussed by Katzhendler and co-workers.[22]

From model fitting, it was observed that the simple power law expression (eq 1) provided an n-value of 0.837 for the electrolyte-containing formulation, confirming the closeness to attainment of ideal zero order drug release. The control formulation (i.e., without electrolyte) produced an n-value of 0.466, indicating a Fickian release mechanism. However, on the basis of the application of the geometry-independent expression (eq 2), it becomes apparent that through separation of the release constant into Fickian and relaxational components, matrix relaxation is predominant both in the presence and absence of electrolytes (without electrolyte $k_1 = 1.8 \times 10^{-5}$, $k_2 = 0.232$; with electrolyte $k_1 = 1.2 \times 10^{-5}$, $k_2 = 0.059$). Using an n-value of 2 in the Hopfenberg model (eq 3) produces a k_1 of 0.045

Table 1—Physicochemical Properties and Influence of Various Electrolytes on Drug Release

electrolytes	water solubility (wt %)[a]	pK_a[a]	pH of 1% in deionized water $T = 21$ °C	pH of 1% in deionized water $T = 37$ °C	induced intragel pH[b]	release and associated characteristics[d]	R^2 [e]
sodium bicarbonate	9.32[23]	6.37, 10.33[26]	8.159	8.069	7.037	constant throughout (0–24 h)	0.9836
sodium carbonate	23.5[23]	6.37, 10.33[26]	11.298	10.891	9.742	constant throughout (0–24 h)	0.9929
calcium carbonate	3.36×10^{-9} (K_{sp})[23]	6.37, 10.33[26]	10.041	9.561	5.674	constant middle phase (8–16 h)	0.8811
magnesium carbonate	6.82×10^{-6} (K_{sp})[23]	6.37, 10.33[26]	10.297	10.085	6.375	constant throughout (0–24 h)	0.9883
potassium bicarbonate	26.6[23]	6.37, 10.33[26]	7.96	8.132	6.841	burst; constant from 1.5–24 h	0.9235
pentasodium tripolyphosphate	16.67[24]	–	9.142	9.162	6.531	constant throughout (0–24 h)	0.9686
sodium phosphate	48.68[23]	2.12, 7.21, 2.67[26]	9.167	9.072	1.530	curved	0.6932
sodium deoxycholate	24.81[24]	6.58[24]	8.212	7.979	1.448	constant in latter phase (11–24 h)	0.8141
maleic acid	44.1[25]	2, 6.26[26]	1.739	1.638	8.842[c]	induces pH-independent release	0.9328
tartaric acid	58.16[25]	2.98, 4.34[24]	2.258	2.113	7.174[c]	does not assist pH-independent release	–
adipic acid	1.42[24]	4.41, 5.28[24]	2.778	2.522	9.287[c]	effective counterion for sodium deoxycholate	–

[a] Source of solubility data and pK_a values are shown as superscripts. All data reported at 25 °C except for sodium deoxycholate (15 °C), tartaric acid (20 °C), and adipic acid (20 °C). Due to the practically insoluble nature of calcium carbonate and magnesium carbonate in water, the solubility products (K_{sp}) are reported at 25 °C. [b] Measured using approach described in Methods section ($N = 3$, SD < 0.1). [c] Each of maleic acid and tartaric acid were used in combination with sodium carbonate to develop a system with pH-independent release. [d] The phase at which constant release is initiated is in part also an indication of the degree of reactivity of the electrolyte within the matrix and reflects an existence of a pH threshold value for the attainment of constant release. [e] Intercept set to zero.

in the absence of electrolyte while 0.024 in the presence of electrolyte. As k_1 incorporates the erosion rate constant k_0, it is evident that through drug–electrolyte interaction and related mechanisms of textural stiffening, the electrolyte-containing formulation experiences a 2-fold reduction in matrix erosion. On the basis of erosion studies (data not provided here), it became apparent that control formulations (i.e., without electrolyte) demonstrated a linear decrease in matrix weight. In this case 49.19% and 96.27% weight reduction was observed after 16 h for HPMC and PEO, respectively. However, in the case of the electrolyte-containing formulations, matrix weight reduction followed square root of time kinetics with 67.04% and 61.93% weight reduction observed at equivalent time (16 h) for both HPMC and PEO.

Determination of Intragel pH Changes in Swellable Matrices and Drug–Polymer Solutions—Specific physicochemical data extracted from the literature and experimentally determined values with respect to solubility, acid–base dissociation, solution pH, and intragel pH-control by the above-mentioned electrolytes and some acids to be evaluated are presented in Table 1.

pH measurements in the axial and radial planes were performed on swollen tablet formulations with and without sodium bicarbonate. Typically from axial plane pH measurements on control formulations (i.e., without sodium bicarbonate) at different depths, it became evident that the internal matrix essentially maintained a pH value that was the same as that of the surrounding dissolution medium (pH ≈ 1.5). This may be regarded as the baseline pH as shown in Figure 5a (broken line). On the other hand, the formulation containing sodium bicarbonate had the ability to maintain a relatively constant pH level >8 within the swollen matrix at similar depths to that of the control (Figure 5a). In the axial plane, the pH tended to stabilize at a depth of 5 mm. The constant pH value seen in the case of control on the gel surface interface in contact with the flat end of the pH electrode may be attributed to the predominance of the dissolution medium at this interface. Diltiazem hydrochloride has been reported to possess pH-independent solubility when studied with respect to buffer solutions.[27] In addition, when the solubility study was undertaken in our lab using USP-recommended buffers in the range from pH 1.5–10, no significant differences in drug solubility were observed. This may be due to the fact that the ionic strength of the electrolytes in the buffer systems has not reached the required threshold to induce marked changes in diltiazem hydrochloride solubility. Such levels of ionic strength might be achievable within a restricted gel structure. Hence, the ionic strength achieved with sodium bicarbonate within the swollen matrix tablet might be sufficiently high to produce this intragel pH effect on drug solubility.

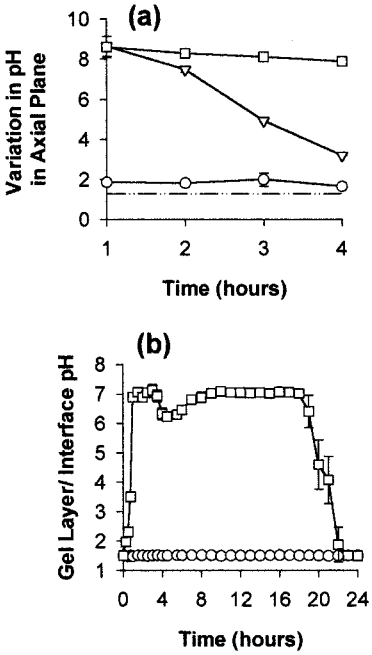

Figure 5—(a) Relationship between time and pH variation obtained by examination of swollen HPMC matrixes with and without sodium bicarbonate (100 mg), after exposure to buffer medium pH 1.5 for different time periods: Axial depth measurements: 0 mm, i.e., surface (○), 2 mm (▽), 5 mm (□). (b) Illustration of time–pH profile for diltiazem hydrochloride–HPMC K4M tablet formulations without (○) and with (□) sodium bicarbonate (100 mg) attached to the pH electrode during a typical dissolution study in buffer medium pH 1.5.

From the investigation on simultaneous transitions in intragel pH and drug release (i.e., tablet attached to electrode), it was found that approximately after 1 h, a maximum surface/gel layer pH of ≈7 was attained in the formulation containing sodium bicarbonate, as opposed to the control tablet formulation which essentially maintained a pH value equivalent to the dissolution medium (Figure 5b). This constant intragel pH was maintained for up to ≈20 h, upon which a rapid decrease in pH was noted possibly due to the exhaustion of sodium bicarbonate and dominance of the penetrated dissolution medium to the matrix core.

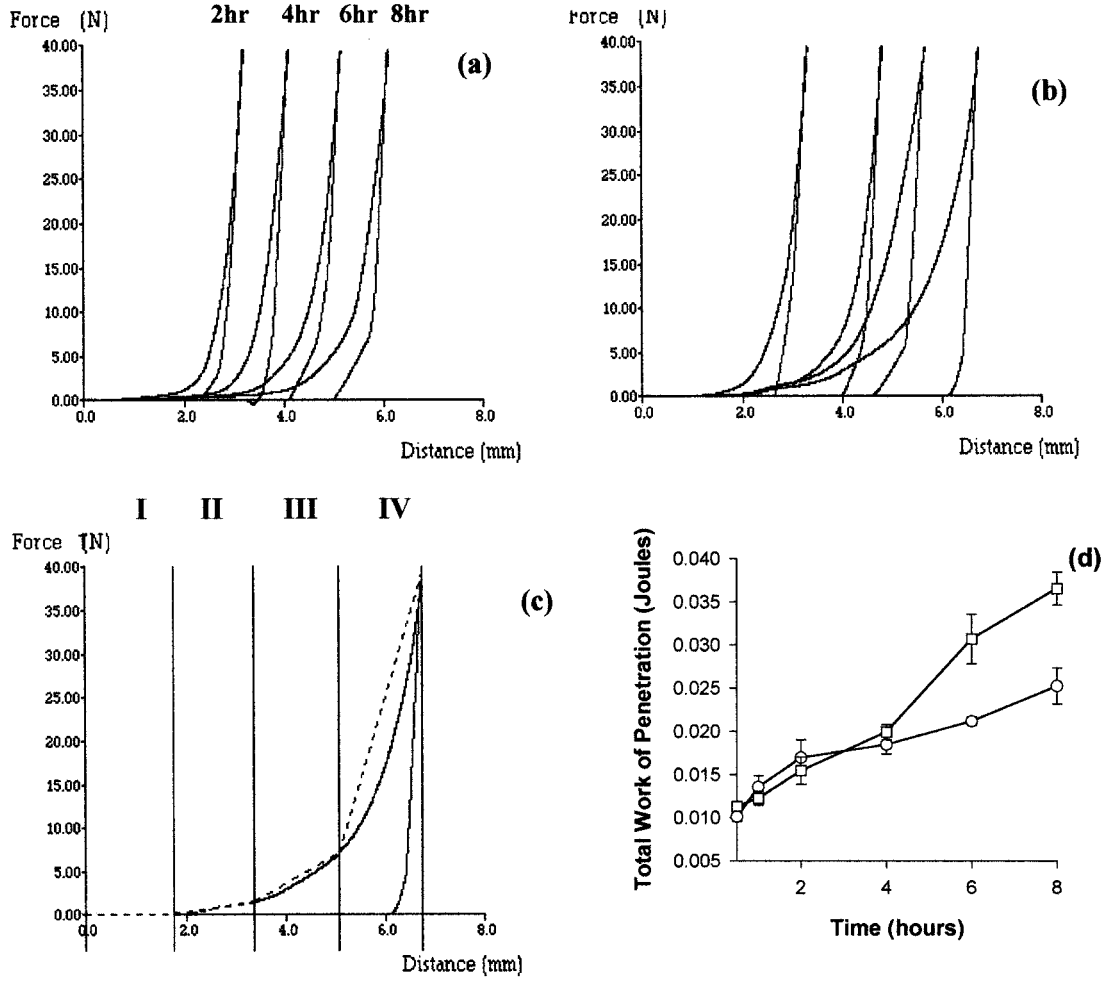

Figure 6—(a) Force–displacement (F–D) profiles for drug-loaded, control HPMC K4M compacts exposed for different time periods to buffer medium pH 1.5. (b) Similar profiles for electrolyte-containing formulation. (c) Details of typical F-D profile for electrolyte containing formulation after 8 h of exposure to buffer medium pH 1.5: (I) water-saturated diffusion front; (II) peripheral gel layer; (III) swollen infiltrated layer; and (IV) glassy swelling front. (d) Profiles depicting compositional heterogeneity within the polymer matrix as manifested through total work of probe penetration.

Through pH-titration studies in the presence and absence of drug-loaded polymeric solutions, it was established that drug−electrolyte interaction is effectively initiated at pH ≈ 6.4. This phenomenon may be used to develop a rationale on which constant release of diltiazem hydrochloride from the swollen gel system might be attainable. Table 1 effectively demonstrates that all electrolytes used in this study are able to maintain a basic pH in solution. However, this does not exclusively apply within the polymeric gel system (i.e., variable water availability), as some electrolytes appear to have a poor buffer threshold when confronted by the acidic penetrant (buffer medium pH 1.5) and hence are unable to maintain basicity, e.g., calcium carbonate (practically water-insoluble, pH-drop from 9.561 to 5.674), sodium phosphate (pH-drop from 9.072 to 1.530), and sodium deoxycholate (pH-drop from 7.979 to 1.448). The other electrolytes such as sodium bicarbonate, sodium carbonate, magnesium carbonate (practically water-insoluble), potassium bicarbonate, and pentasodium tripolyphosphate are able to maintain an intragel pH in excess of ≈6.4, a threshold above which drug−electrolyte interaction is likely to occur. Through this intragel pH-control, significant drug−electrolyte interaction was anticipated, which may lead to variable textural properties in the gel structure and suppression of drug release. Knowing that the pK_a of diltiazem hydrochloride is 7.7,[28] the degree of ionization and hence solubility will be affected in this pH threshold. Such effects may also affect the degree of polymer relaxation and swelling leading to formation of the putative metamorphic scaffold (see Figure 1).

Evaluation of Gel Strength and Time-Dependent Phase Transitions—To measure any transitions in gel matrix structure and alteration in swelling behavior in the presence of electrolytes, textural analysis was undertaken. By application of the texture analyzer instrument, it was possible to obtain the compressive force−displacement profiles for monolithic tablets containing (i) HPMC and drug, and (ii) HPMC, drug, and interacting electrolyte (such as sodium bicarbonate).

Figure 6a illustrates typical force−displacement profiles for compacts comprised of HPMC and drug (e.g., controls) exposed to buffer medium (pH 1.5) up to an 8-h period. The common feature presented in these profiles is a sharp, smooth, up-curving region followed by a rapid decline associated with the probe retraction. The overall features of these profiles reflect the formation of a relatively uniform gel boundary in different stages of hydration. On inclusion of sodium bicarbonate (100 mg) within the matrix system and measuring the profile under identical conditions, there are systematic increases in swelling as well as up-curving force after the initial 2 h of the experiment. Values computed for the maximum increase in matrix swelling (using the control as reference) corresponding to 0.5, 1, 2, 4, 6, and 8 h of exposure to buffer media are typically represented by −4.79%, −25.99%, −4.55%, 6.11%, 5.55%, and 5.34% (negative % indicates the value by which

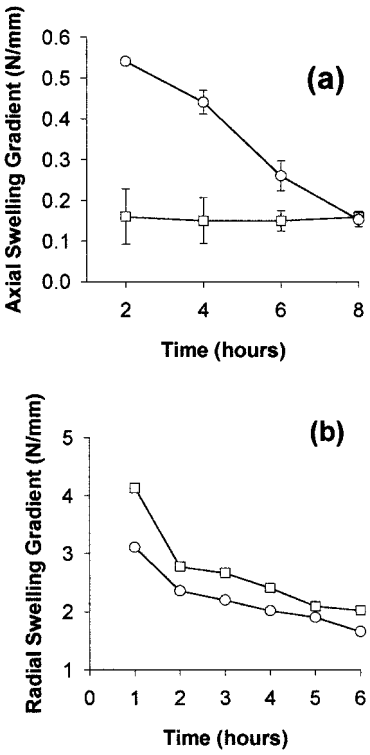

Figure 7—(a) Depiction of the attainment of constant average gradients of axial swelling for diltiazem hydrochloride–HPMC K4M formulations containing 100 mg of sodium bicarbonate (□) and control formulations, i.e., without electrolyte (○) in buffer medium pH 1.5. (b) Changes in the average gradients of radial swelling for HPMC-based formulations containing 100 mg of sodium bicarbonate (□) and control, i.e., without electrolyte (○) in buffer medium pH 1.5.

swelling of the electrolyte-containing formulation is lower than that of the control). In addition, the presence of increased resistance to probe penetration, as seen in the nonlinear rise in the initial stages of force–displacement in Figure 6b, reflects the more heterogeneous nature of the electrolyte-containing matrix. On the basis of the trend that was observed in force–displacement in both controls and in the presence of electrolyte, it was possible to identify and classify four distinct transition phases/regions (see Figure 1 and Figure 6c), namely:

- Phase I: Water saturated diffusion front;
- Phase II: Peripheral gel layer where initial interaction between sodium bicarbonate (or other electrolyte) and diltiazem hydrochloride is observed;
- Phase III: Swollen infiltrated layer where the electrolyte-induced effects are fully manifested; and
- Phase IV: Glassy swelling front.

The sharp increase in the total work associated with probe penetration (Figure 6d) in the case of the electrolyte-containing formulation is indicative of two phenomena, namely higher matrix swelling and greater resistance of the swollen structure to probe penetration, reflecting the heterogeneous structure induced through electrolyte interactions. This is contrasted by the uniform and linear trend in the work changes associated with the control formulation. Further work on this aspect is presently underway.

Differential Swelling Characterization of Matrices—As shown in Figure 7a, the constant peripheral gel phase observed to the depth of 1.5 mm through measurement of the axial gradient developed during matrix swelling of formulations containing sodium bicarbonate in buffer medium pH 1.5 essentially indicates the formation of a constant gel layer thickness, a phenomenon not seen in the absence of electrolyte.

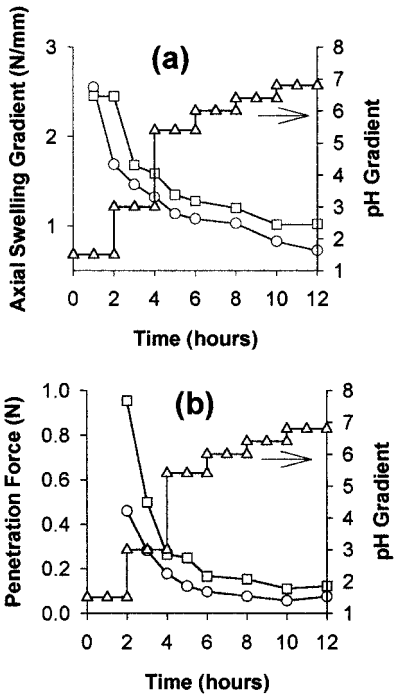

Figure 8—Influence of stepwise pH variation on (a) average gradients of axial swelling, and (b) penetration force in the axial plane for diltiazem hydrochloride–HPMC K4M formulations without (○) and with (□) 100 mg sodium bicarbonate. pH variation follows the order of 1.5, 3, 5.4, 6, 6.4, and 6.8 with both formulations being exposed for 2 h in each environment.

One of the important aspects revealed in this work is that the degree of swelling in the axial direction appears to be greater than that in the radial plane (i.e., for both controls and electrolyte-containing formulations). Apart from actual measurements, this was also apparent from the fact that the lower resistance to penetration in the axial plane (Figure 7a) as opposed to the radial plane (Figure 7b) is indicative of greater matrix infiltration and hence more swollen gel network in the axial plane. For example, from actual measurements on the electrolyte-containing formulation, it was shown that axial expansion occurred up to ≈5.75 mm in 6 h as opposed to ≈2.35 mm in the radial plane during the same time period. This swelling differential represents the nonuniform gel structure, and it is apparent that gel formation is relatively more rigid diametrically (Figure 7b).

Additional investigation conducted under different pH conditions demonstrated the sensitive nature of the electrolyte-containing gel matrix in terms of swelling gradients (determined from up-curving F–D profiles) and resistance to probe penetration (Figure 8a). From Figure 8a it can be seen that in spite of the lack of formation of a constant and uniform peripheral gel layer during stepwise pH changes, it may still be possible to attain constant drug release in these various pH environments (see Figure 2c). It has been postulated that attainment of zero-order drug release in these different pH environments may be attributed to associated textural changes in the swollen matrix, namely, an increase in the stiffness of the gelled structure induced through drug–electrolyte interactions as opposed to formulations without electrolyte (Figure 8b).

Release Modulation and Mechanisms—On the basis of the above data supporting electrolyte-induced compositional heterogeneity in intragel pH-control and proposed metamorphic scaffold structure, the following mechanisms may prevail during the period of drug release in a controlled, constant manner.

As the penetrant enters the periphery of the tablet, there is a rapid electrolyte–water interaction with significant

chemical reactivity through electrolyte solubilization and subsequent events that may lead to both initial suppression and later enhancement of polymer swelling. During this infiltration process, chemical species likely to be present within the gelled boundaries include sodium bicarbonate, sodium chloride formed via the interaction between the former electrolyte and hydrochloride species of the drug, ionized diltiazem, and possibly existence and formation of a free drug base. Diltiazem hydrochloride has a pK_a of 7.7,[28] and since the measured intragel pH is >7 but <pK_a, it is expected that drug species would not entirely exist in a precipitated base form. However, limited formation of the base form of drug may precipitate within the polymeric matrix and may result in hindrance of the relaxation process. Employing a modified concept of Schott,[29] the passive and actively formed electrolyte species within the gelled polymeric HPMC matrix would compete for water species at the outset and hence bind part of the water of the gelling polymer in order to become hydrated. This initial competition for water of hydration "dehydrates" the polymer molecules, leading to suppression of initial swelling, as seen up to 2 h where the formulation containing 100 mg of sodium bicarbonate is maximally inhibited in the range of ≈4−25% in overall swelling when compared to control tablet. However, once sufficient water has been attracted by electrolyte species into the polymer matrix the solubilized species will diffuse out, creating a capillary network for more water penetration after which an enhancement of swelling in comparison to controls is observed. Such possible alterations in physical polymeric configuration are manifested as a textural effect shown by the increased resistance to probe penetration resulting in "matrix stiffening" (see Figures 6d and 7b). The degree of matrix stiffening consistently decreases toward the center of the matrix core in a time-dependent manner over a long period (e.g., 24 h). Through these mechanisms and dynamics of intragel changes, it seems possible to inhibit drug dissolution and enhance polymer swelling to an extent, both of which would significantly contribute to achieving zero-order kinetics. This inhibition in dissolution may also be a time-dependent phenomenon, since as more penetrant enters the gel matrix layer-by-layer (i.e., sequentially), the electrolyte(s) content and their byproducts (such as sodium chloride) are diluted and any drug base may revert to its hydrochloride form and is subsequently released. An additional parameter that requires a more in-depth analysis is the influence of osmotic pressure and its impact on both swelling dynamics and diffusion mechanism.

Electrolyte Effects for Establishment of pH-Independent System—In an attempt to develop a pH-independent system, the sodium bicarbonate was replaced by sodium carbonate since it displays a less vigorous and delayed effervescent reaction in the presence of acidic electrolytes (Figure 9). Furthermore, to counteract the strong interaction between drug and sodium carbonate in higher pH environments, an opposing electrolyte was added to the system, namely maleic acid. Maleic acid essentially served to reduce the intragel pH at higher external pH conditions. PEO 4 million molecular weight was selected as the polymer for its ability to display greater free volume changes than HPMC, hence ensuring drug release in less acidic pH environments. Adipic and tartaric acids were also evaluated, but did not prove successful in providing comparable release in acidic and basic media. This may be due to the relatively lower and higher solubility of each acid within the gel system (see Table 1) and the dynamic structural changes during polymer infiltration and associated swelling conditions.

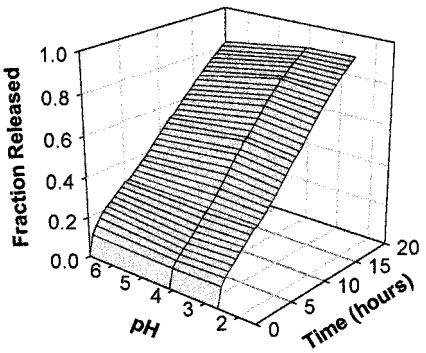

Figure 9—Release plot for diltiazem hydrochloride from a designed pH-independent system containing 100 mg of sodium carbonate and 50 mg of maleic acid in buffer media pH 1.5, 4, and 6.8.

Conclusions

This work has provided a novel simple approach to formulate an oral, swellable, monolithic, controlled-release delivery system designed for delivery of highly soluble, ionizable drugs over a long time period. An important feature of this system is the potential for generating constant drug release, a trend highly desirable for many pharmaceutical agents such as cardiovasculars, antiasthmatics, antihistamines, and narrow therapeutic index drugs. Through careful selection of electrolyte(s) and drug, an *in situ chemical interaction* within the gelled structure may be induced for the alteration of matrix-swelling dynamics and inhibition of drug dissolution. On the basis of textural analysis, peripheral axial front synchronization and greater radial matrix stiffening was observed to occur. This directional discrepancy in operating swelling mechanisms may be related to the fact that the degree of axial expansion of HPMC compacts was greater than radial expansion. In addition, the presence of electrolyte in the formulation clearly contributed to the formation of a more heterogeneous gel structure referred to as "metamorphic scaffold" in this work. The delivery system was also shown to be versatile in that it was neither electrolyte- nor polymer-limited, and specific formulation design can lead to release that is independent of variation in pH.

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