A novel approach for constant rate delivery of highly soluble bioactives from a simple monolithic system

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Abstract

A novel monolithic drug delivery system for highly water-soluble bioactive agents to follow pH-independent zero-order kinetics is described. The system utilizes a hydrophilic gel-based swellable polymeric material (polyethylene oxide), a model drug (metoprolol tartrate, 100% water soluble at 25°C) and different electrolytes, such as sodium carbonate and/or pentasodium tripolyphosphate. Based on the induction of in situ intra-gel chemical reactions between different ionic species, drug and polymer, a heterogeneous structure manifested as ‘peripheral boundary stiffening,’ is accomplished. The consequence of these interactions essentially include the development of gradient-controlled matrix swelling as elucidated through textural profiling, which may contribute to inhibition of drug solubility and its outward diffusion. Analysis of textural profiles and photomicroscopy distinctly provides information on the disposition of peripheral boundary densification for the electrolyte-containing matrices. Electrolytic conductivity measurements performed with the simultaneous analysis of matrix swelling showed that sodium carbonate forms a highly reactive matrix within the first 3 h of medium penetration. On the other hand, larger molecules such as pentasodium tripolyphosphate maintain a constant conductivity level, which may be related to its lower solubility and diffusion in comparison to sodium carbonate. Based on model fitting and statistical analysis, it is shown that drug release kinetics were adequately described by $M_t/M_\infty = k_0t$, with zero-order release rate constant $k_0$ of 0.054 h$^{-1}$. This novel approach in formulation development could potentially be used for constant rate delivery of highly soluble bioactive agents over an extended period for specific biopharmaceutical needs. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

In general, designing monolithic controlled release drug delivery systems for providing 12 or 24 h zero-order release kinetics, especially for highly water-soluble agents, is often difficult and unsuccessful. This shortfall in delivery system design may essentially be attributed to three factors: (i) the high water solubility of the drug results in a burst effect; (ii) the lack of proper control over time-dependent processes of polymer relaxation/disentanglement in relation to drug dissolution and diffusion; and (iii) compensation for an increase in the diffusional pathlength with time is not easily achievable. Re-
cently, it has been demonstrated that the ability to control the release of highly soluble drugs such as diltiazem hydrochloride (>50% water soluble at 25°C) can be accomplished through the principle of electrolyte-induced compositional heterogeneity within hydrophilic monolithic polymeric matrices [1,2]. This principle essentially depends on the ability to induce differential swelling boundaries and a texturally variable matrix manifested as a ‘peripheral matrix stiffening’ phenomenon. Through the application of these principles, simple monolithic delivery systems with zero-order release kinetics were developed in our laboratories for a range of drugs with different solubility profiles, such as the hydrochloride salts of propranolol (5% water soluble at 25°C), verapamil (8% water soluble at 25°C) and diltiazem (>50% water soluble at 25°C). In this work further expansion of the above-described principles is applied to develop an extended release zero-order drug delivery system for the 100% water-soluble drug, metoprolol tartrate. The enhanced therapeutic efficacy of this drug through the provision of constant rate input and maintenance of steady-state blood levels is well-documented [3,4].

From a purely biopharmaceutical perspective, metoprolol, a β₁-selective adrenoceptor antagonist, is widely used, particularly in the long-term treatment of hypertension and coronary heart disease. Early pharmacokinetic studies have established that it has a relatively short plasma half-life of 3–4 h and its absorption is rapid as well as consistent throughout most of the gastrointestinal tract, including the distal region [5,6]. As a prerequisite, a combination of both these properties makes metoprolol a suitable candidate for development into a controlled release formulation. In addition, the relationship between plasma concentrations and β₁-blocking effect (i.e., reduction in exercise-induced tachycardia) is well defined for metoprolol [7,8]. However, the main disadvantage of β-blockers in general (including receptor-selective blockers) is that they may cause significant adverse effects in patients with heart failure, asthma and peripheral vascular disease. Typical effects mediated by the β₂-receptors include bradycardia, heart failure and hypotension, while the adverse consequences of blocking β₂-receptors may include bronchospasm, impairment of peripheral circulation and disturbed glucose homeostasis. In these patients β-blockers are best avoided. On the other hand, patients with cardiomyopathy may benefit from β₂-blockade [9]. It therefore seems appropriate that in order to reduce the above-described β-mediated adverse effects, maintenance of a minimum therapeutic constant plasma concentration should be a better alternative in dosing and may be achieved through development of an extended release system capable of providing zero-order drug delivery rates.

In terms of delivery system types, the merits of multiple-unit dosage forms over single-units are well-documented [10]. The therapeutic benefits achieved from a compressed multi-particulate delivery system capable of providing extended release zero order delivery of metoprolol succinate (20% water soluble at 25°C) over a 24-h period is provided in the literature [3,4,11]. Two significant characteristics of the above delivery system include the attainment of lower and constant plasma levels (with reduction in exercise-induced tachycardia) and maintenance of β₁-blockade up to the terminal 24-h time period in the release process (i.e., post dose) [12]. It is however, important to recognize that even with the demonstration of reliable therapeutic efficacy, from a technological viewpoint the design of multi-particulate or multiple-unit dosage forms involve numerous process variables (e.g., control of temperature, stirring rates, coating process, drug loading) and formulation variables (e.g., choice of plasticizers, crosslinking agents, coating agents) which ultimately limits manufacturing capability and increases cost. Subsequently, over the years industries and pharmaceutical research have placed more emphasis on the design and development of directly compressed monolithic controlled release drug delivery systems, within which the development of such formulations for highly soluble material, still remains a challenge.

In this work design of an extended release zero-order drug delivery system for metoprolol tartrate by employing a gel-forming swellable hydrophilic polymer namely, polyethylene oxide (PEO) 7 × 10⁶ MW, and various electrolyte species is proposed. The influence of the electrolyte-induced processes of peripheral matrix stiffening and subsequent swelling dynamics on release are evaluated and possible mechanisms for achieving steady-state release kinetics are discussed.
2. Materials and methods

Metoprolol tartrate, sodium carbonate and pentasodium tripolyphosphate (Sigma, St. Louis, MO, USA) were used as obtained. Polyethylene oxide (Union Carbide, CT) of $7 \times 10^6$ MW was chosen as the model hydrophilic polymer. Toprol-XL® (an extended release metoprolol succinate commercial product, Astra Pharmaceutical Products, MA) was obtained from Temple University Hospital (PA).

2.1. Formulation and preparation of tablets

In all formulations, 100 mg of metoprolol tartrate were employed. The formulation consisting only of polymer and drug (i.e., without electrolyte) was considered as the control in the experiment. Three test formulations were designed. Two were comprised of polymer, electrolyte (sodium carbonate or pentasodium tripolyphosphate) and drug in a 3:3:1 ratio. The other contained polymer, sodium carbonate, pentasodium tripolyphosphate and drug in a 3:1.5:1.5:1 ratio.

All ingredients in their specified ratios were simultaneously blended in a laboratory-scale V-blender for 15 min, after which tablets were prepared from the different blends by direct compression on a Carver Press (Fred S. Carver, IN) at 1000 lbs. For such preparation an 11.5-mm die with flat-faced punch was employed.

2.2. In vitro drug release studies

Dissolution studies were performed on each formulation in a calibrated six station dissolution test apparatus (VK 7000, Vankel Industries, NJ) using a modification of the USP 23 Apparatus 2 in USP-recommended buffers (pH 2.6, 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 222 nm. Based on the high density swellable sticking nature of PEO, a newly designed device (i.e., the ring/mesh assembly) was used to ensure full surface area exposure of the tablets to the release medium by placing the dosage form over such device. This ring/mesh assembly exactly fits into the lower portion of a standard dissolution vessel. Further details and application of this device can be found elsewhere [13,14].

2.3. Textural profiling on hydrated matrices

Textural transitions associated with the dynamics of differential matrix swelling were evaluated by profiling analysis (Texture Analyzer, TA XT2i, Stable Micro Systems, UK). One planar base as well as the entire lateral surface of each tablet was sealed off with an organic coating consisting of 20 g Eudragit RS PO® in a mixture of 50 ml acetone and 50 ml isopropanol. 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. Triplicate samples sealed on petri dishes were placed in dissolution vessels containing 900 ml buffer medium, pH 2.6, at 37°C during separate tests. The paddle speed was set at 50 rpm to simulate the actual tablet dissolution process. At pre-determined time intervals triplicate tablet sets were removed and subjected to textural analysis in a similar manner described in recently published work [15].

The Texture Analyzer instrument (TA XT2i) has an ability to capture stress–strain profiles with a high degree of accuracy. Data was captured at a rate of 200 points/s 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: pre-test speed, 1 mm/s; test speed and post-test speeds, 0.2 mm/s; maximum compression force, 40 N; and auto trigger force, 0.005 N.

2.4. Simultaneous electrolyte conductivity and textural measurements

A conductivity meter (ATI Orion, MA) with 100 ppm resolution, 0–19900 ppm measurement range, ±2% full scale accuracy and automatic temperature compensation from 5 to 50°C, was carefully attached
to the advancing probe fixture of the texture analyzer instrument such that a simultaneous evaluation of conductivity and force-displacement could be performed. Essentially, the conductivity electrode (dual probes each with diameter of 1.5 mm and separated by a distance of 3 mm) was employed as both a moving probe and conductivity detector. Tablets were prepared in a similar manner as described above for textural measurements. Instead of hydrochloric acid buffer, deionized water was used as the penetrant in order to exclude the interference of external buffer medium ions on electrical potential of matrix electrolytes. During a typical test, the conductivity electrode was advanced at a predetermined rate into the axial plane of the hydrating tablet compacts, held within the matrix for an optimized time period and thereafter detracted at constant rate. The following instrument settings were employed: pre-test speed, 1 mm/s; test speed and post-test speeds, 0.2 mm/s; hold time, 180 s; maximum compression force, 0.10 N; and auto trigger force, 0.010 N. A hold time was necessary for stabilization of the conductivity reading.

2.5. Analysis of drug release kinetics

In order to establish the kinetic mechanism associated with drug release, dissolution data obtained from formulations with and without sodium carbonate in buffer medium, pH 2.6, was modeled in terms of two exponential equations (i.e., see Eqs. (1) and (2) below). Release data were modeled on WinNonlin, Version 1.0 (SCI Software) using the Guassian–Newton (Levenberg–Hartley) approach for all least-squares analyses.

3. Results and discussion

3.1. Electrolyte-induced water competition within gelling matrices for control of drug release

In Fig. 1a it is apparent that electrolyte-inclusion plays a significant role in reducing the drug release rate (buffer medium, pH 2.6). Release from the control (i.e., without electrolytes) more closely resembles a square-root kinetic process as determined by model fitting and statistical analysis. In the case of the electrolyte-containing formulations, constant drug release over a 20-h period is achieved \((r^2 > 0.98)\). Sodium carbonate was chosen over its bicarbonate ion due to its less vigorous interaction with both acidic and basic buffer ionic species. In either pH environment minimal floatation was observed which may be attributed to limited carbon dioxide formation, based on the low reactivity of sodium carbonate.

In order to establish if drug release was pH sensitive or not, both the control and test formulations were subjected to a dissolution study in phosphate buffer, pH 6.8. In Fig. 1b it is observed that pH does not significantly influence the kinetics of drug release, i.e., zero-order drug delivery is still apparent from the electrolyte-containing formulations in keeping with the recent report [1]. Furthermore, in order to determine the influence of increasing polymer content on drug release, a control tablet was formulated to contain 600 mg PEO, which was equivalent to the total matrix weight of the test formulation, i.e., 300 mg each of polymer and electrolyte. In this case it was observed that an increase in polymer content does not play a significant role in suppressing drug release in comparison to the control that contained 300 mg PEO. This unusual behavior may be due to: (i) extensive matrix swelling; (ii) increase in PEO free volume [16]; and (iii) high drug solubility. On closer examination of drug release in pH 2.6 and 6.8 (Fig. 1c), minimal deviation from linearity is observed and hence the delivery system may be considered pH independent.

Employing pentasodium tripolyphosphate as the primary electrolyte in a formulation consisting of 300 mg PEO and 100 mg metoprolol tartrate, tends to considerably extend the duration of drug release over a 20-h period in a relatively pH-independent manner (Fig. 1d). However, the kinetics of release was no longer linear and this may be attributed to the lower matrix stiffening potential of pentasodium tripolyphosphate, as outlined in the following sections. Consequently, it is apparent that in this experimental formulation sodium carbonate is an essential component of the system for achieving constant rate drug delivery.
3.2. Examination of phase transitions within swollen gelled matrices by textural profiling and photomicroscopy

Textural profiling of swelling dynamics in hydrophilic gel-based polymeric systems is now a routinely performed technique, as it offers significant advantages over more tedious imaging and NMR analysis [1,14,15,17,18]. The combined use of textural profiling and photomicroscopy can provide a more meaningful interpretation of swelling dynamics. In this work, the texture analyzer instrument and photomicroscopy was employed to evaluate the phenomenon of ‘matrix stiffening’ and its role as a mechanism to provide zero-order drug delivery [1].

Textural measurements revealed that in formulations used in this work the overall degree of swelling was enhanced within the matrices (Fig. 2a–d).
uniform increase in force–distance ($F-D$) values for the control accompanied by insignificant change in its gradient (i.e., up-curving segments) reflects a sequential increase in peripheral gel growth (Fig. 2a). However, in the case of the electrolyte-containing formulations (Fig. 2c–d), in addition to an overall increase in matrix swelling observed from higher baseline displacements, an increase in the $F-D$ gradient values is noted (Fig. 2b). For example, from Fig. 2a,b it is evident that after 6 h of hydration the maximum displacement attained for the control matrix was 7.03 mm, while the corresponding value for the electrolyte-containing matrix was 9.63 mm.

Compositional heterogeneity as a result of in situ chemical interactions between electrolyte/s, drug and polymer are manifested as different zones or moving boundaries within the matrix environment as depicted in the photomicrograph (Fig. 3a). Based on boundary changes observed from actual $F-D$ textural profiles, a typical schematic is constructed and represented beside the photomicrograph (Fig. 3a) in order to depict the stipulated four distinct transition phases/regions that form fundamental components of the inwardly shifting boundaries shown in the micrograph. These phases are, namely: water-saturated diffusion front (I), peripheral gel boundary (II),

Fig. 2. Textural profiles for PEO compacts (a) without electrolytes; and with (b) 300 mg sodium carbonate, (c) 300 mg pentasodium tripolyphosphate, and (d) combination of 150 mg each of sodium carbonate and pentasodium tripolyphosphate after 2, 4, 6 and 8 h of exposure to buffer medium, pH 2.6.
Fig. 3. Photomicrograph (a) of hydrated matrix (pH 2.6) of PEO tablet containing 300 mg of sodium carbonate and 100 mg metoprolol tartrate, depicting compositional heterogeneity (magnification, ×8). The continuous influx of penetrant medium is balanced by the efflux of drug, electrolyte and associated ionic species. The associated schematic of a typical F–D profile represents different boundary layers corresponding to: (I) water-saturated diffusion front; (II) peripheral gel boundary; (III) swollen infiltrated region; and (IV) glassy swelling front. In addition, profiles are shown for total work performed (Joules) in penetration of PEO matrices (b) using the textural data on control and electrolyte-containing formulations, i.e., in the absence of electrolytes (●) and in the presence of 300 mg sodium carbonate (○), 150 mg each of sodium carbonate and pentasodium tripolyphosphate (▼) and 300 mg of pentasodium tripolyphosphate (▽) after exposure to buffer medium, pH 2.6, for pre-determined time periods (n = 3).

swollen infiltrated region (III), and glassy swelling front (IV). During influx of the dissolution medium, chemical species likely to exist within the gelled boundaries include both ionized and unionized species of sodium carbonate, pentasodium tripolyphosphate, sodium tartrate formed via the interaction between the former electrolyte and salt species of the drug, ionized metoprolol and possibly formation of free drug base. Precipitation of the drug base along the polymer backbone may result in hindrance of
both chain mobility and polymer relaxation. The electrolyte species within the matrix would consequently compete for water species at the outset and hence attract part of the water in order to dissociate. This initial competition for water of hydration possibly ‘dehydrates’ the polymer molecules (salting-out phenomenon), leading to suppression of initial swelling. However, once sufficient water has been attracted by electrolyte species into the polymer matrix, the solubilized species undergo an efflux process, creating significant porosity within the hydrating network for more water penetration, after which an enhancement in peripheral swelling in comparison to controls is observed.

It is stipulated that the cause of peripheral matrix densification (I and II) may be attributed to the rapid interaction between electrolyte and drug with subsequent entrapment of the complex at the peripheral zone, which is a composite of both proposed phases, namely I and II. In addition, the continuous up-cursing progression in force demonstrated by textural analysis (Fig. 2) and schematics (Fig. 3a) is indicative of multi-exponential changes associated with the dynamics of glassy swelling boundaries and rubbery matrix core.

Based on total work performed on the matrix by probe penetration (Fig. 3b), it is seen that the control (i.e., without electrolytes) demonstrates a relatively constant, unchanged level of matrix rigidity as opposed to the electrolyte-containing formulations. In each of these formulations, significantly higher levels of matrix stiffening are apparent, with respective work maxima at 8, 6 and 2 h for matrices containing sodium carbonate, tripolyphosphate and their combination. It may be assumed that through the above-described mechanisms associated with inwardly shifting stiffening regions, drug diffusion and release rate can be optimally modulated during formulation development.

3.3. Inter-relationship between electrolytic conductivity and textural properties during matrix hydration

In this study conductivity measurements within the microenvironment of the hydrating matrix were performed in conjunction with simultaneous textural profiling in order to assess the impact of medium penetration and possible ionic interactions.

Concurrent textural changes in association with ionic interaction within the matrix showed an increase in probe penetration distance reflecting an increase in peripheral gel thickness (Fig. 4a). The

![Fig. 4. Profiles generated at specific time intervals during simultaneous textural profiling and conductivity measurements on hydrating compacts. (a) Textural profiles established with conductivity electrode/probe showing the plateau phase during which conductivity measurements were made. (b) Conductivity profiles for pure PEO (●), control compacts containing only drug, i.e., no electrolytes (○), and sodium carbonate-containing compacts (▼) (n = 3).](image)
plateau regions of the textural profiles represent a 180-s hold time during which electrolytic conductivity and gel resistance restructuring at peak force were measured. The negative values below the abscissa are representative of probe retraction force from the highly viscous matrix which is the subject of further study.

To facilitate clearer understanding of the use of conductivity measurements as a tool for assessment of in situ ionic interactions within the gel matrix, only selected profiles are depicted in Fig. 4b, while a full explanation is provided for all electrolyte-containing systems below. Based on analysis of triplicate samples, pure PEO compacts did not demonstrate any conductivity potential simply due to the non-ionic nature of the polymer (Fig. 4b), while compacts loaded with only drug showed a small increase in conductivity followed by a relatively constant phase. However, in the case of compacts containing sodium carbonate, a highly reactive matrix was apparent within the first 3 h, followed by a constant phase. This initial increase in conductivity (up to 2.5 h) may be attributed to rapid formation of electrolyte ions within the matrix periphery. This is followed by a sharp reduction in conductivity values as 3 h exposure time is approached. The maintenance of a constant conductivity value after 3 h may be due to synchronization of ionic formation and diffusion during medium influx and ongoing hydration.

From conductivity measurements, it was observed that control and tripolyphosphate compacts provided a similar trend, except for the higher conductivity values in the presence of electrolyte. The larger molecular size and lower water solubility of tripolyphosphate (MW, 367.9 g/mol; solubility, 16.67 wt%) in comparison to sodium carbonate (MW, 106 g/mol; solubility, 23.5 wt%), may explain the absence of its rapid ionic efflux and presence of a plateau phase. On combination of sodium carbonate and pentasodium tripolyphosphate within the matrix, a decline in conductivity was seen after 3 h and this may be related to ionic association, and greater propensity for diffusion as free volume increases. Such complex interactions within the matrix may produce physical alteration in matrix rigidity as reflected by the matrix stiffening phenomenon.

3.4. Drug release kinetics

In view of more recent applications of the simple exponential expression [1,18–21] for simultaneous determination of release constant and profile shape, the following equation was used:

\[ \frac{M_t}{M_\infty} = k t^n \]

(1)

where \( M_t \) and \( M_\infty \) are the amounts of drug released at time \( t \) and the overall amount released, respectively, \( k \) is a release constant and \( n \) is a release exponent indicative of profile shape. Classically, \( n = 0.5, 0.5 < n < 1 \), or \( n = 1 \) for a slab, is indicative of Fickian release, anomalous transport, or steady state kinetics, respectively, up to 60% of the release profile.

Furthermore, in line with the current utility of the geometry-independent bi-exponential expression [1,18–21] for determination of contributions of Fickian diffusion and matrix relaxation/dissolution on drug release, the following equation was employed:

\[ \frac{M_t}{M_\infty} = k_1 t^n + k_2 t^{2n} \]

(2)

where \( k_1 \) is the Fickian kinetic constant and \( k_2 \) is the relaxational/dissolution rate constant.

Table 1 provides a summary of the important model fitting and statistical parameters for release kinetics in the absence and presence of electrolyte. From model fitting, it was observed that the simple exponential expression (Eq. (1)) provided an \( n \) value

<table>
<thead>
<tr>
<th>Model Formulation</th>
<th>( k ) or ( k_1 ) (h(^{-1}))</th>
<th>( k_2 ) (h(^{-2n}))</th>
<th>( k_2/k_1 )</th>
<th>( n )</th>
<th>AIC</th>
<th>SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k t^n ) Without electrolyte</td>
<td>0.157</td>
<td>–</td>
<td>–</td>
<td>0.771</td>
<td>–119.87</td>
<td>–121.31</td>
</tr>
<tr>
<td>With electrolyte</td>
<td>0.054</td>
<td>–</td>
<td>–</td>
<td>1.02</td>
<td>–152.01</td>
<td>–152.87</td>
</tr>
<tr>
<td>( k_1 t^n + k_2 t^{2n} ) Without electrolyte</td>
<td>0.002</td>
<td>0.156</td>
<td>78</td>
<td>0.386</td>
<td>–115.95</td>
<td>–118.10</td>
</tr>
<tr>
<td>With electrolyte</td>
<td>0.038</td>
<td>0.024</td>
<td>0.632</td>
<td>0.619</td>
<td>–159.72</td>
<td>–161.01</td>
</tr>
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of 0.771 for the control, indicating that drug release was regulated through both mechanisms of diffusion and polymer relaxation. On separation of these components, using Eq. (2), it was observed that relaxation was the dominant mechanism in the release process, i.e., $k_1 = 0.156 \text{ h}^{-2n}$ while $k_2 = 0.002 \text{ h}^{-2n}$. In the case of the electrolyte-containing formulation an $n$ value of 1.02 was obtained with Eq. (1), reflecting the attainment of ideal steady-state kinetics with release constant of 0.054 h $^{-n}$. Based on application of the geometry-independent bi-exponential expression (Eq. (2)), an $n$ value of 0.62 was obtained with $k_1 = 0.038 \text{ h}^{-2n}$ and $k_2 = 0.024 \text{ h}^{-2n}$. In view of the statistical fit factors, the lower Akaike information criteria (AIC) and Schwartz criteria (SC) values for Eq. (1) in the case of the control suggests better model suitability. Using the same criteria in the case of the electrolyte-containing formulation, Eq. (2) appears to provide a suitable model fit. The marginally smaller relaxational constant $k_2$ in comparison to Fickian constant $k_1$ in the presence of electrolyte further illustrates the important role of matrix swelling as a control mechanism in drug release. This statement is supported by experimental data generated from textural analysis studies (Figs. 2 and 3). It should be further noted that PEO $7 \times 10^6$ MW demonstrates minimal erosion (i.e., <20% in 8 h, data not shown), with predominant relaxational behavior; hence the contributions of surface erosion on drug release kinetics are considered to be less significant. In view of the $k_2/k_1$ ratios (Table 1), the lower ratio in the presence of electrolyte reflects a higher level of matrix stiffening.

3.5. Comparison of metoprolol tartrate release profile from the designed monolithic system to that of a multi-particulate commercial product

Toprol XL is a commercial metoprolol succinate (20% water soluble at 25°C) extended release product with pH-independent release properties (Fig. 5). The product is formulated as a tablet which immediately disintegrates upon exposure to dissolution medium into small spherical subunits. Therefore, this product mechanistically functions as a multi-particulate preparation. In the present study, through manipulation of polymeric and electrolyte composition [2], a simple monolithic formulation (PEO:drug:sodium carbonate, 200:100:200 mg) of metoprolol tartrate was developed (100% water-soluble at 25°C) to mimic the release pattern of Toprol-XL (Fig. 5). In addition, the directly compressed new system possesses pH-independent drug release characteristics as shown in Fig. 1c.

4. Conclusions

This work has demonstrated the effectiveness of modulating matrix swelling through inclusion of appropriate electrolytes for achieving steady-state drug release kinetics. One of the most desirable features of this approach is the ability to demonstrate zero-order release for a 100% water-soluble drug such as metoprolol tartrate over an extended period of time in a pH-independent manner. Through matrix textural profiling the process of matrix stiffening via electrolyte interaction was accomplished with pronounced stiffening and densification in the case of sodium carbonate–pentasodium tripolyphosphate combination. Simultaneous measurements in textural transitions and electrolyte conductivity reflect the
complexity of polymeric gelation and relaxation, as seen in conductivity transitions associated with electrolyte solubilization, interaction and penetrant diffusion. In general, electrolyte solubility and molecular weight seem to influence the diffusion process and the consequent overall matrix conductivity. Moreover, plateau phases observed in conductivity profiles seem to suggest development of synchronous processes of ionic generation, diffusion and medium infiltration. The driving principle behind such phenomenon has been identified as matrix scaffolding, stiffening and constantly changing peripheral densification. From kinetic modeling, the simple exponential relationship (Eq. (1)) adequately describes the release mechanism ($n = 1.02$). Through formulation modification, it was possible to design a pH-independent directly compressible monolithic system capable of mimicking the release pattern of Toprol-XL® (compressed multi-particulate system). The application of this technology for extended release systems may be of particular value to pharmaceutical scientists involved in the area of rate-controlled drug delivery design.

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References

