

Note

Multipulse drug permeation across a membrane driven by a chemical pH-oscillator

Gauri P. Misra^a, Ronald A. Siegel^{a,b,*}

^aDepartment of Pharmaceutics, University of Minnesota, 308 Harvard St. SE, 9-177 Weaver-Densford Hall, Minneapolis, MN 55419, USA

^bDepartment of Biomedical Engineering, University of Minnesota, Minneapolis, MN 55419, USA

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Abstract

Chemical pH-oscillators provide a potential means for modulating the delivery of acidic or basic drugs across lipophilic membranes. Previous attempts to exploit this notion were not completely successful due to quenching of the pH oscillator in the presence of the drug, most likely by a buffering mechanism. Here we show that multiple, periodic pulses of drug flux across a membrane can be achieved when the concentration of drug is sufficiently low. Advantage is taken of a pH oscillator system whose periodicity is slower than that of previously considered oscillators. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

When considering the temporal dimension in drug delivery, two modalities have traditionally received the most attention. Zero order release is the preferred modality for most drugs, as it enables the maintenance of drug levels within the therapeutic range below which drug loses its efficacy, and above which toxic side effects become manifest. A second modality, in which release is modulated in response to changes in concentration of a physiological substrate, e.g. glucose-responsive insulin delivery, has also been pursued [1].

Recently, interest has turned towards delivery systems which automatically release drugs in periodic pulses. Among the classes of drugs that are best delivered in this manner are certain hormones that exhibit rhythmic, ultradian endogenous secretion patterns [2,3], cell-cycle specific chemotherapeutic agents for cancer treatment [4,5], and drugs that exhibit tolerance [6] or circadian variation in efficacy or toxicity [7]. Both passive and active approaches have been applied to rhythmic drug delivery [8]. Passive systems are constructed to release drug at different times due to layering [9–11], programmed disruption at a set of distinct times [12,13], or by utilizing nonlinear feedback instabilities within a device [14]. Active systems are triggered by the input of external energy at the desired times of release. Energy sources that have been considered

*Corresponding author. Tel.: +1-612-624-6164; fax: +1-612-626-2125.

E-mail address: siege017@tc.umn.edu (R.A. Siegel).

include pressure [15], electricity [16,17], magnetism [18], electromagnetic fields [19], and ultrasound [20].

Chemical oscillators [21,22] present a means for driving the periodic delivery of drugs. For example, an oscillator which features pH swings [23] can cause the solubility or the membrane permeability of an acid or base drug to fluctuate, with concomitant variations in drug flux. To demonstrate this notion, Giannos et al. [24] utilized a bromate–sulfite–thiosulfate (Landolt) pH-oscillator in semibatch mode to produce up- and downswings in flux of benzoic acid and nicotine across an ethylene–vinyl acetate copolymer (EVAc) membrane. Oscillations were limited to at most two such excursions, even though the pH-oscillator normally undergoes numerous cycles when drug is absent. This limitation appears to have arisen from two factors: (a) the high-frequency nature of the Landolt pH oscillations whose effects on flux are low-pass filtered by the membrane, and (b) damping and ultimate quenching of the pH-oscillator by the drugs which serve as pH-buffers.

After the publication of Giannos et al., Rábai and Hanazaki (RH) [25] demonstrated a pH oscillator, based on a bromate–sulfite–marble reaction, whose period is easy to control and can be made substantially longer than that of the Landolt oscillator. Giannos and Dinh [26] subsequently demonstrated that this reaction, in a semibatch configuration, undergoes a few pH swings, but they did not demonstrate modulated transport across a membrane.

In this note, we demonstrate that multiple alternating phases of high and low flux of the model drug benzoic acid (BzA) can be achieved across an EVAc membrane, provided the drug is at sufficiently low concentration. We utilize the RH oscillator to produce pH oscillations of lengthened periodicity.

2. Experimental methods

2.1. Materials

Sodium sulfite (Na_2SO_3 ; Fisher Scientific), sodium bromate (NaBrO_3 ; Acros), sulfuric acid (H_2SO_4 ; Acros), and benzoic acid (BzA; Matheson Coleman & Bell) were used as received. Granular

marble was crushed and sieved to particle size range 2–3 mm. A 2-mm-thick ethylene–vinyl acetate copolymer (EVAc) membrane (Cotran™ 3717 Film, 3M Corporation: 28% vinyl acetate) was used as a model lipophilic membrane.

2.2. Chemical (pH) oscillations

The oscillating chemical reaction occurred in a 100-ml water-jacketed beaker into which 3 g granular marble was introduced. Reactants were pumped in at 0.3 ml/min through two separate lines, one containing 50 mM NaBrO_3 and the other containing a mixture of 96 mM Na_2SO_3 , 6 mM H_2SO_4 , and 0.5 mM BzA. Solution was removed from the beaker by aspiration to maintain a constant volume of 80 ml, thus establishing continuous stirred tank reactor (CSTR) conditions. A schematic of the CSTR set-up is illustrated in Fig. 1.

2.3. Drug transport

The reacting solution in the CSTR (beaker) was circulated into the donor side of a specially constructed side-by-side diffusion cell and returned to the CSTR (see Fig. 1). The volumes of both the donor and receptor sides of the diffusion cell were 3.5 ml, and the diffusion aperture was 6.5 cm². Circulation rate was ~3.5 ml/min, leading to a mixing time of ~1 min in the donor side. Contents of the receptor side, which was initially filled with deionized water, were circulated through a UV detector (226 nm), with circulation time ~35 s. By this means BzA accumulation in the receptor cell was monitored continuously.

3. Results

Fig. 2a illustrates the behavior of the CSTR and the flux of BzA through the membrane when the concentration of BzA in the CSTR (and hence of the donor side of the diffusion cell) is 0.5 mM. Under these conditions the CSTR (and donor) pH oscillates. Oscillations are characterized by 1-h-long periods in which pH is in the range 6.5–7.0, followed by rapid descents to ~pH 3.2, and a slightly slower phase in which pH returns to the neutral range. An initial

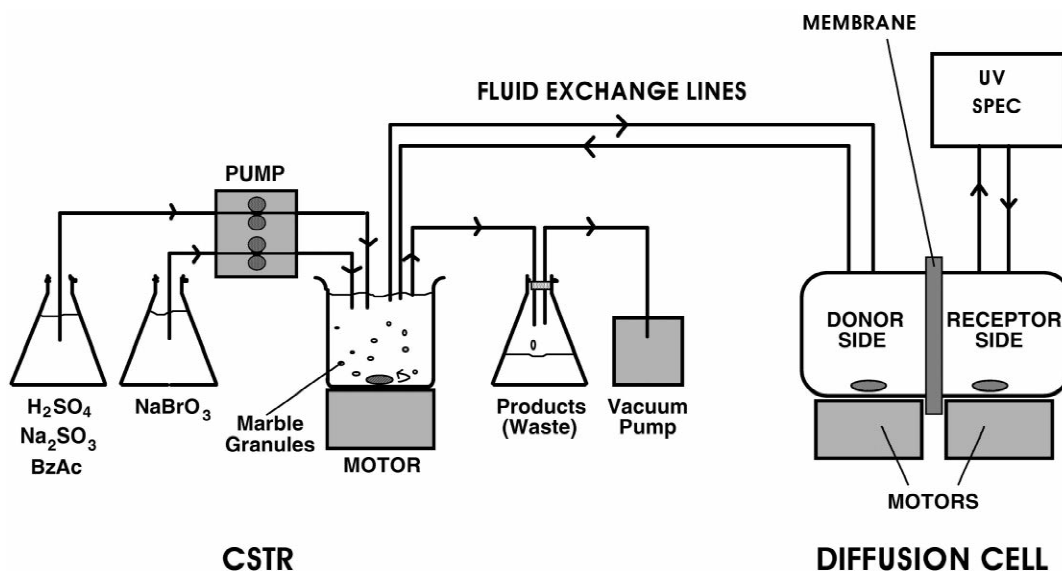


Fig. 1. Illustration of the CSTR/diffusion cell set-up, with rapid fluid exchange between the CSTR and the donor side of the diffusion cell.

induction period is seen before the system settles into its oscillatory pattern. Such pH profiles are expected since the RH reaction, like many chemical oscillators, includes autocatalytic and ‘recovery’ steps [22].

Flux of BzA across the membrane is determined from the slope of the curve representing BzA accumulation in the receptor side. During the near-neutral phase, there is virtually no flux of BzA across the membrane, since donor pH is well above BzA’s pK_a (4.2), and the compound is completely charged. Accelerated drops in donor pH are accompanied by rapid bursts of BzA flux across the membrane, which commence when pH approaches the drug’s pK_a . (A slight ‘slippage’ of BzA back across the membrane occurs during the near-neutral phase. The receptor side is unbuffered, so some of the drug is expected to remain in its nonionic state there, and can back diffuse to the donor side. However, pH in the receptor side was never observed to fall below 6.0.)

Fig. 2b illustrates the corresponding behaviors when BzA concentration is increased to 7.5 mM. After about 1.5 h, pH in the CSTR descends to just below 3.0, and then slowly recovers to a final steady state value of 4.7. Flux of drug across the membrane does not commence until donor pH reaches its minimum value. Following a temporary period dur-

ing which flux reaches a maximum, it settles to a stationary value, as is expected since the final pH is in the neighborhood of the pK_a of BzA, and a sizeable fraction of the drug is available for transport.

4. Discussion and conclusions

By suitable choice of pH-oscillator and consideration of the effects of drug concentration on the performance of that oscillator, we have succeeded in producing a prototype system which provides multiple pulses of drug delivery across a membrane.

Three circumstances favor our system over previously studied systems, in terms of producing multipulse permeation across the membrane. Firstly, we selected an oscillator whose periodicity is sufficiently long that pH surges in the donor side can be converted to distinctive pulses in drug flux, with little ‘low-pass filtering’ effects from the membrane [24]. Secondly, we used a low concentration of drug, which reduces the drug’s buffering effect on oscillator performance. Indeed, when drug concentration is increased in our system, the pH and flux oscillations are quenched. Thirdly, we used a CSTR system in which the concentrations of reactants and prod-

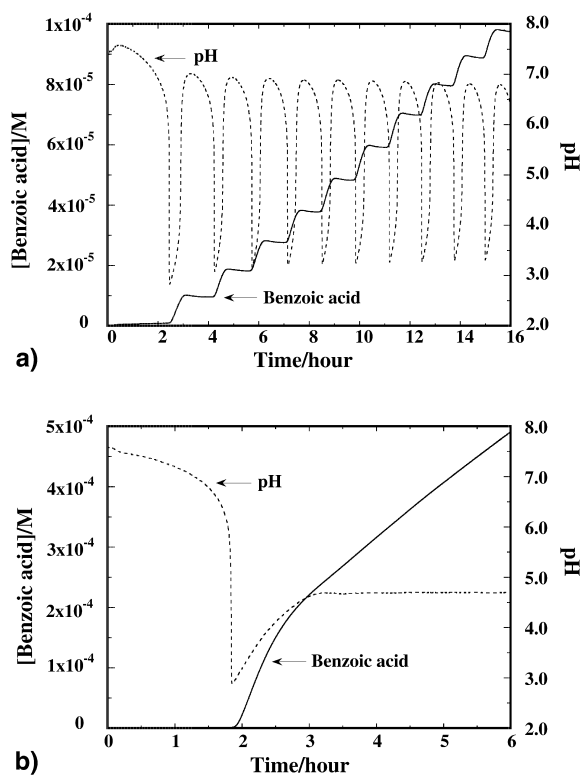


Fig. 2. Time course of pH in CSTR (dashes) and accumulation of benzoic acid in the receptor side of the diffusion cell (solid lines). pH in the donor side closely follows the pH in the CSTR due to rapid fluid exchange.

ucts, as well as system volume, are well defined and do not drift with time, as in the semibatch configuration.

Despite the experimental advantage of the CSTR, it should be remarked that the semibatch configuration is probably more realistic with respect to design of a working drug delivery system [24]. While constant inflow and mixing of reactants in a reaction space may be an achievable design goal, product removal is expected to be more problematic.

During the course of our experiments, marble in the CSTR is partially fragmented and depleted. As a result, the reaction conditions are not strictly stationary. Close scrutiny of our data reveals that the pH-oscillations seen in Fig. 2a drift slowly in period and amplitude, which would not be expected in a 'pure' CSTR in which all reactants are introduced and removed continuously. As drug concentration is

increased to intermediate values between those considered in Fig. 2, the oscillating system's stability becomes more vulnerable to the fragmentation and depletion of marble, and oscillatory behavior persists for only a finite duration (data not shown).

The quenching of oscillations seen at the higher concentration of BzA is believed to be due to buffering of pH changes by the drug. If so, then drug concentration and pK_a should jointly affect the dynamics of pH in the RH reaction. An extensive investigation of this latter point will be presented elsewhere [27].

Acknowledgements

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