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Measurement of pH near dissolving enteric coatings

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Abstract

Previous authors have predicted the pH at the surface of enteric coatings using mathematical models. The purpose of our work is to experimentally determine the pH. A modified laser spectrometer was constructed to excite fluorescein in the medium above a dissolving enteric coating—hydroxypropylmethylcellulose phthalate (HP) in buffer (pH 6.5 and 7.0) in the absence and presence of forced convection. As predicted by mathematical models, the pH near dissolving enteric coatings is reduced relative to bulk pH. The reduction in pH is 0.2 to 0.4 depending upon the pH of the buffer relative to the pK_a of the polymer. The pH near (i.e. about 250 μm from the surface) HP-50 is lower than that near HP-55 under the same conditions. The experimental data agree to a first approximation with data from mathematical models.

Keywords: Fluorescein; pH; Microenvironment; Hydroxypropylmethylcellulose phthalate (HP); Enteric coating

1. Introduction

Enteric coatings are designed to remain intact in the stomach and release the contents of the underlying core in the intestines. With pK_a values reported to be between 4 and 5 (Davis et al., 1986), these acidic polymers are intended to have low permeabilities in their unionized state in the low pH environments expected in the stomach. When they reach more neutral to alkaline environments characteristic of the intestinal milieu, enteric polymers ionize and erode to release drug from the underlying core. At the surface of dissolving enteric coatings, the ionization of the polymers is expected to reduce local pH. The role of the reduction in local pH on the release of drugs from enteric coated dosage forms has been the subject of some investigation. A detailed mathematical model of the pH profile in the dissolving coating region and the aqueous boundary layer surrounding an enteric coating was described (Ozturk et al., 1988). Using an ideal 150 μm enteric polymer film with a pK_a of 4.5 and intrinsic solubility of 5×10^{-6} M on an aspirin core dissolving into a phosphate buffer of pH 6.8, their simulation suggested that the pH at the interface

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between the polymer and solution fell to 6.2–6.6 from a bulk pH of 6.8 in 0.05 M phosphate buffer. The lower value of 6.2 assumes a higher diffusivity of aspirin through the film while the higher value of 6.6 assumes a lower diffusivity of aspirin through the film. Among other necessary simplifications, this model assumed steady state conditions and that the diffusivity of the protons be that of the bulk. The effect of aspirin is expected to have a large influence on the simulated pH profile shown by Ozturk et al. in their figure 3 (Ozturk et al., 1988). Evidence for this influence is shown in their figure 8 where both simulated and experimental data for disintegration show a dependence on the acidity/basicity of the core. Dangel et al. also showed that that acidity/alkalinity of the drug in the underlying core influences the performance of the enteric coating (Dangel et al., 2000). In addition, upon dissolution of enteric polymers there may be a region of fairly high viscosity that impedes the transport of protons released as the enteric coating dissolves. The development of such a viscous layer has been described for dissolving polyethylene glycol (Bogner et al., 1997). Thus, the actual pH near the surface of a dissolving enteric coating could be somewhat different than that reported by Ozturk et al. In the present study, we used fluorescein to experimentally determine the pH near the surface of dissolving enteric films using a modified laser spectrometer described earlier (Bogner et al., 1997).

2. Materials and methods

2.1. Materials

Fluorescein was used as received (Molecular Probes, Eugene, OR). Stock solutions of the probes were prepared in ethanol to assure complete solution. These solutions were stored at 4 °C in amber volumetric flasks to prevent photodegradation. Spectral grade solvents were used as received. Hydroxypropyl methylcellulose phthalates (HP-50 and HP-55) were obtained as gift samples from Eastman Chemical Company (Kingsport, TN).

2.2. Polymer films

HP films were cast on glass slides from a 2% solution in 1:1 (v/v) methylene chloride:ethanol. Good quality films were obtained by slowing the evaporation of the solvents by placing a glass funnel over the cast films. The films (150–250 μm thickness) were stored in a dessicator to prevent hydrolysis of the polymer. Squares (1 × 1 cm) of the films were cut using a razor to fit inside a 1 cm cuvette.

2.3. Dissolution cell and medium

The film samples were mounted on a 1 × 1 cm black delrin block using double-sided tape. The delrin block was, in turn, held down to a glass slide by a second piece of double-sided tape. This assembly was inverted and pushed down atop a 1 cm path length disposable cuvette containing 3.5 ml of dissolution medium. This entire assembly was inverted again (such that the film was now at the bottom of the dissolution medium) at time = 0 min, from which all temporal data was referenced. The inverted cuvette assembly was then placed on

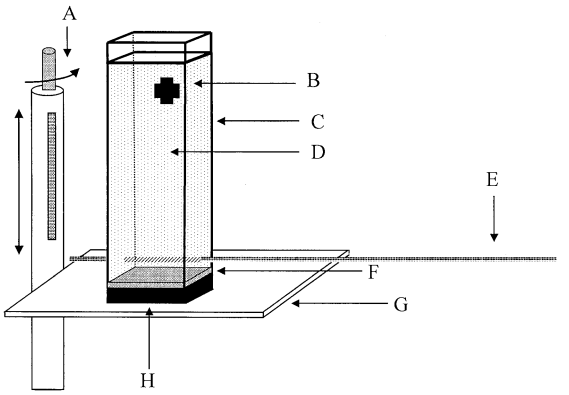

Fig. 1. The modified laser spectrometer used for studying the pH of polymer above dissolving HP films. A = Micrometer attached to the sample stage to allow fine and reproducible positioning of the sample stage relative to the incoming laser beam. B = Magnetic stirrer inside the cuvette coupled to a rotation system outside the cuvette. C = Standard fluorescence cuvette with 1 cm path length. D = Dissolution medium consisting of buffer. E = Laser beam. F = Polymer film. G = Sample stage. H = Black plastic block which raised the polymer film above the sample stage.

a translation platform which permitted precise vertical positioning of the cuvette as shown in Fig. 1.

The dissolution medium consisted of 0.05 M phosphate buffer at 6.50 or 7.00 and fluorescein (1.70×10^{-7} M). The pH value of 6.5 represented fasted (Russell et al., 1993) conditions within the human duodenum. The pH value of 7.0 represented the pH of the ileum (Horter and Dressman, 1997).

In some cases, the medium was stirred by placing a star magnet in the cuvette coupled to a stirring motor adjacent to (but not touching) the cuvette (Fig. 1). The stir bar was rotated at 120 rpm. At this rotation rate, the dissolution rate of a benzoic acid slab in the cuvette was determined to be 23% of that observed for a 235 mg 9 mm biconcave benzoic acid tablet in the USP Type II apparatus at 50 rpm. These relatively mild stirring conditions may be more consistent with in vivo conditions. For example, it was reported that the first phase of the absorption profile of a controlled release acetaminophen tablet was close to the in vitro profile at a paddle speed of 10 rpm (Katori et al., 1995).

Fluorescein was excited by a laser at specific distances from the initial film surface using an argon ion laser (488 nm) operating at 50 mW. The optimum exposure time of the laser beam to fluorescein dissolved homogeneously in the dissolution medium was 0.05 s. The short exposure time eliminated photobleaching of the probe. Fluorescence emissions from 500 to 725 nm were collected on a charge coupled device at a right angle to the laser.

The laser beam was focused to a narrow waist by a long focal length lens. Even so, thermal lensing limited the horizontal resolution to 0.5 mm. Fluorescence emission was collected at the film surface (0–0.5 mm, accounting for the laser diameter) as well as 0.5–1.0, 1.0–1.5, 1.5–2.0, and 3.5–4.0 mm from the film surface at intervals of 15 min for 2 h. The spatial intervals are denoted in the results as 0.25, 0.75, 1.25, 1.75 and 3.75 mm, respectively, which represent the center points of the laser beam at each position. The first four distances were very close to the film surface to monitor profiles of solution properties; the fifth distance was set further away from the film surface to monitor the bulk solution.

Prior to each dissolution experiment, signals from two standard solutions were determined. The fluorescence intensity of fluorescein (1.70×10^{-7} M) in 0.05 M phosphate buffers at pH 3.5 and pH 9.0 were determined. At pH 3.5, fluorescein was fully protonated and at pH 9.0 it was fully deprotonated with respect to its second ionization at the pK_a' of 6.4. A standard curve based on the fraction of fluorescein ionized at each pH was constructed. Preliminary data showed that the shift in pK_a' was negligible (Harianawala, 1998); no corrections for a shift in pK_a' were made.

If the readings of the standards before and after the experiment differed by more than 10%, then that particular data set was not retained. This procedure reduced the effect of day-to-day variation in the light source and detector, as well as any instability over the 2 h study period.

3. Results and discussion

The pH near dissolving surfaces of small molecules has been theoretically determined using a number of modelling approaches (Higuchi et al., 1958; Mooney et al., 1981; McNamara and Amidon, 1986). The surface pH was found to be

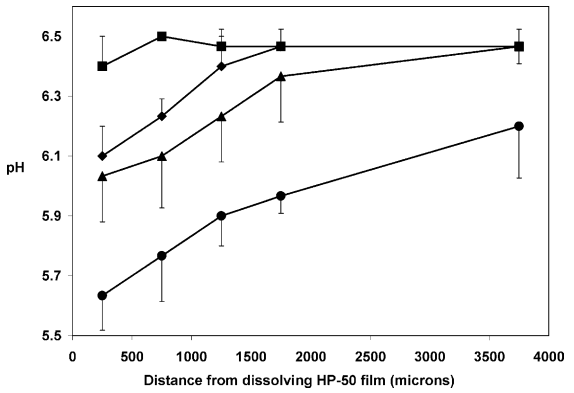

Fig. 2. pH profile above HP-50 dissolving into 0.05 M phosphate buffer at pH 6.5 in the *absence* of forced convection. Data are shown for 3 min (squares); 30 min (diamonds); 60 min (triangles); 120 min (circles). $N = 3$; bars represent one standard deviation.

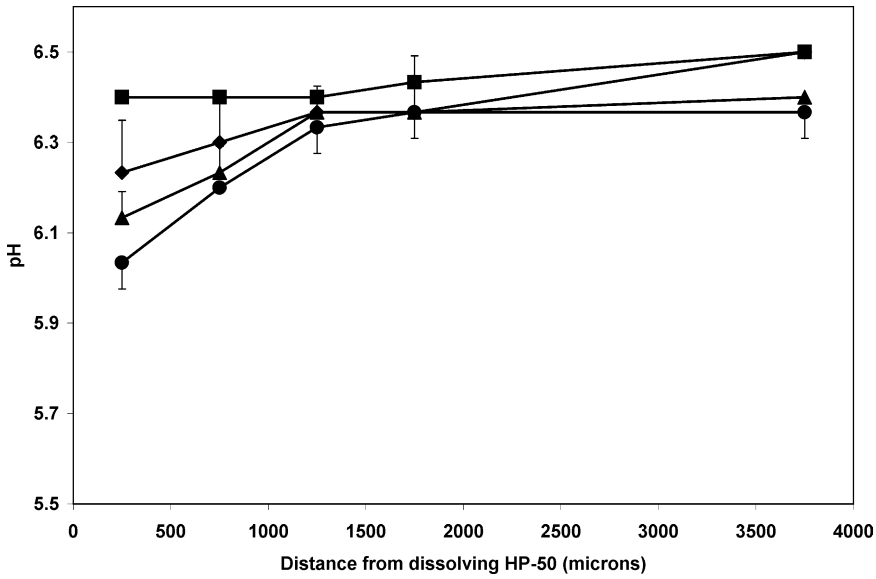

Fig. 3. pH profile above HP-50 dissolving into 0.05 M phosphate buffer at pH 6.5 in the *presence* of forced convection. Data are shown for 3 min (squares); 30 min (diamonds); 60 min (triangles); 120 min (circles). $N = 3$; bars represent one standard deviation.

highly dependent upon the pK_a and solubility of the dissolving molecule as well as the concentration and pK_a of the buffer into which it dissolved. In the area of enteric coatings, Ozturk et al. determined from a mathematical model a reduction of pH to be 0.2 to 0.6 units at the surface of an enteric coating having a pK_a of 4.5 dissolving into 0.05 M phosphate buffer at pH 6.8. However, that simulation was based upon a 150 μm coating over aspirin which itself has the ability to lower the pH significantly. The remaining question is: In the absence of an underlying aspirin core, does the enteric coating itself contribute to a drop in pH at its surface and how significant is that drop?

In the present work, we experimentally determined the reduction in pH using a modified laser spectrometer. Fig. 2 shows the pH profile above a HP-50 film dissolving into pH 6.5 buffer in the absence of forced convection. As predicted by mathematical models and now shown experimentally, the pH declines near the surface. As time proceeds the decline becomes greater and the decrease is seen further out into the solution. At 120 min into the dissolution process, the pH value 3.5 mm from the film surface has decreased 0.25 pH units from the initial pH of the buffer.

During the dissolution process, protons are essentially generated at the surface of the acidic polymer coating. They diffuse away from the surface as well as react with the buffer in the region. The local pH is governed by the rate of generation of protons, the rate of diffusion of protons away from the surface, and the extent of reaction with the buffer (Gupta et al., 2000). Note that it is the extent of reaction rather than the rate that contributes to the pH since the rate of reaction is much faster than the rate of diffusion. In this case the rate of diffusion is limiting and only the extent of reaction should be taken into consideration.

The pH determinations performed in the presence of forced convection are more relevant to dissolution in vitro and, presumably, in vivo. The pH above HP-50 dissolving into stirred buffer at pH 6.5 is shown in Fig. 3. In the dissolution cell used here, the convection achieved by rotating a star magnet near the top of the dissolution medium was equivalent to 23% of the convection responsible for dissolution of a tablet at 50 rpm in a USP Type II dissolution apparatus. Thus, the polymer is dissolving in the presence of only moderate convection. Fig. 3 shows no significant

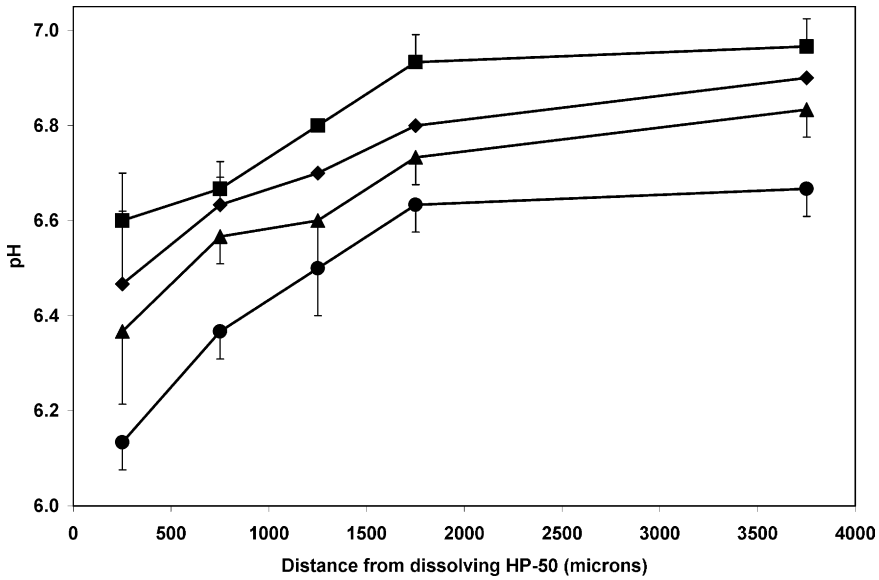

Fig. 4. pH profile above HP-50 dissolving into 0.05 M phosphate buffer at pH 7.0 in the presence of forced convection. Data are shown for 3 min (squares); 30 min (diamonds); 60 min (triangles); 120 min (circles). $N = 3$; bars represent one standard deviation.

drop in pH at the furthest distance monitored (3750 μm from the surface). In a stirred system such as this, the distance of 3750 μm can be considered to represent bulk solution. A trend in the reduction of pH from that of the buffer value is not seen until 750 μm from the surface. This is a large distance over which to observe a gradient that might be consistent with a diffusion layer. The mild stirring conditions used in this experiment would be expected to result in a diffusion layer larger than that expected in a USP Type II dissolution apparatus at 50 rpm.

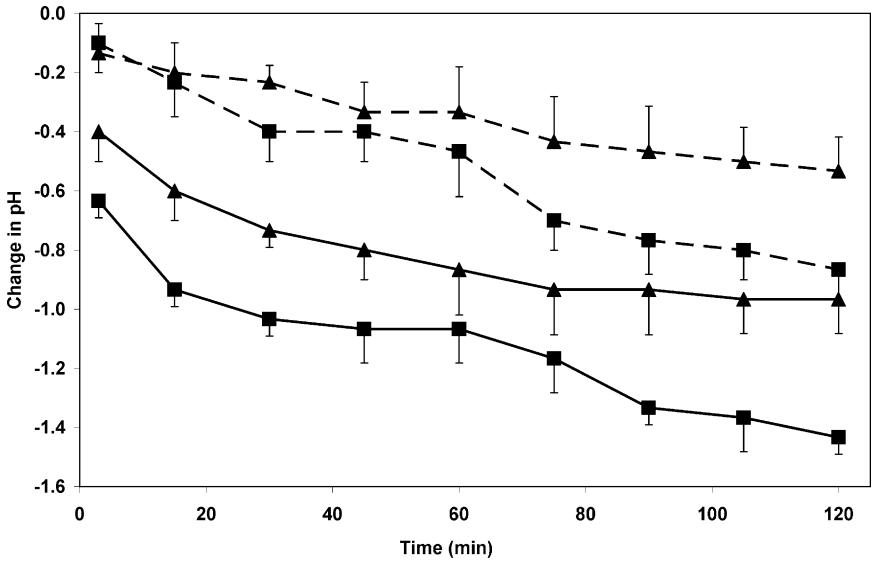

Fig. 5. Difference in pH at the surface (250 μm) from that of the buffer pH into which it is dissolving. The buffer was *unstirred* 0.05 M phosphate buffer at pH 6.5 (dashed lines) or pH 7.0 (solid lines). The polymers dissolving were HP-50 (squares) or HP-55 (triangles). $N = 3$; bars represent one standard deviation.

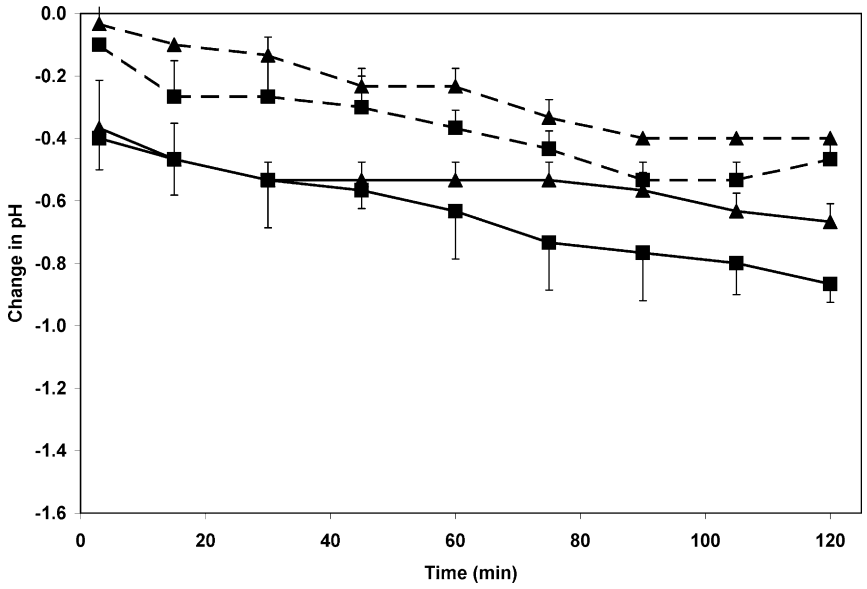

Fig. 6. Difference in pH at the surface (250 μm) from that of the buffer pH into which it is dissolving. The buffer was *stirred* 0.05 M phosphate buffer at pH 6.5 (dashed lines) or pH 7.0 (solid lines). The polymers dissolving were HP-50 (squares) or HP-55 (triangles). $N = 3$; bars represent one standard deviation.

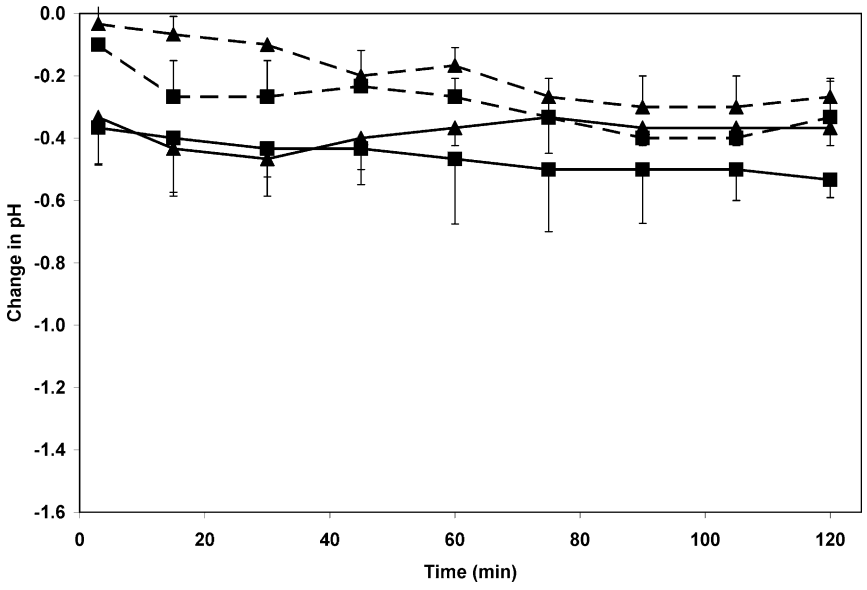

Fig. 7. Difference in pH at the surface (250 μm) from "bulk pH" (3750 μm) measured at the same time point. The buffer was *stirred* 0.05 M phosphate buffer at pH 6.5 (dashed lines) or pH 7.0 (solid lines). The polymers dissolving were HP-50 (squares) or HP-55 (triangles). $N = 3$; bars represent one standard deviation.

When the HP-50 polymer dissolves into a buffer just 0.5 units higher than the 6.5 buffer used to generate the profile in Fig. 3, a very different profile is seen (Fig. 4). The decrease in pH near the surface is large and immediate as shown by a decrease of 0.4 pH units at 250 μm and 3 min. This represents a much steeper drop in pH than that seen in the pH 6.5 buffer. In addition, the "bulk pH" indicated at 3750 μm declines with time indicating a high dissolution rate and effective transport of protons to the bulk even at this moderate stirring rate. As shown in Fig. 3, there is also a point in Fig. 4 where the pH begins to significantly decline from its "bulk pH" value. In Fig. 3, that distance was about 1250 μm whereas in Fig. 4 the distance is 1750 μm. This is consistent with a larger diffusion layer due to poorer stirring in the presence of a more concentrated, presumably more viscous, polymer solution.

Focusing on the decrease in pH close to the surface (i.e. at 250 μm) we can compare two grades of enteric coating polymer—HP-50 and HP-55. The HP-55 has greater phthalyl substitution and a higher pK_a. In the absence of stirring, Fig. 5 shows that, at 250 μm from the surface of HP-50, there is a greater decrease in pH (relative to the buffer pH) than at the same distance from HP-55. The higher pK_a of the HP-55 is apparent from the lower decline in pH near its surface.

Recall that in the case of a moderately stirred system, the bulk pH declined with time presumably due to the low volume of dissolution medium. This effect could complicate the ability to draw conclusions from Fig. 6. To clarify the issue, Fig. 7 shows the change in pH relative to the bulk pH. The trends are similar, but the magnitude of the drop in pH is much less and in the range of that predicted by Ozturk and coworkers (1988).

4. Conclusions

A method for directly measuring the pH near dissolving enteric coatings has been developed. The experimental data presented here agree to a first approximation with the 0.2–0.6 pH unit drop at the surface of dissolving enteric coatings suggested by Ozturk et al. (1988). Differences in conditions between the two studies do not allow for direct comparison with Ozturk's theory. However, general agreement of our results with their similar system has been demonstrated supporting their theoretical model. However, the pH measurements "near the surface" reported here are limited to about 250 μm (more specifically, the average of 0–500 μm) from the surface by our experimental apparatus. Future studies will focus on increasing the resolution of such measurements.

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