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Dynamic friction of some film coatings on rat stomach mucosa in vitro – effect of pH

T. Itoh [1,*], T. Higuchi [1] and L.J. Caldwell [2]

[1] *Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, KS 66045 (U.S.A.)* and [2] *MSDRL-INTER$_x$ Research Corporation, Lawrence, KS 66046 (U.S.A.)*

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The concept of using bioadhesive materials for controlled, site-specific drug delivery on mucosal surfaces has been a subject of interest for several years, and has been successfully utilized in the development of some commercial products (Ikura et al., 1981). More recently, other researchers have addressed the question of safety for certain materials used in the formulation of oral dosage forms which might cause "unwanted adhesion" in certain areas of the GI tract such as the esophagus or intestine (Marvola et al., 1983; Becket, 1983; Florence et al., 1984; Swisher et al., 1984). These recent concerns have generally dealt with the problem of "stickiness" or static adhesion of dosage forms at a particular site, due to surface properties of film coatings used in the manufacture of such forms.

The present work has sought to address yet a different aspect of oral dosage form properties, again associated with film coatings, but not with adhesive properties per se. The underlying notion for this work was to anticipate differences in surface frictional properties which might be reflected as a difference in intra-gastric mobility of tablets or small particles during the process of gastric emptying. That is, would it be reasonable to delay or accelerate gastric emptying of particles by selectively creating surfaces that are either "rough" or "slippery" after deployment in the stomach?

Therefore, we examined four different polymers used in conventional film coating procedures, for frictional properties in the dynamic sense, against the gastric mucosa of the rat in vitro. One of these polymers was not soluble; one was acid-soluble; one was soluble only at neutral or basic pH; and one was soluble independent of pH.

The dynamic friction of these four different polymers was measured at pH 3.0 and pH 6.1. No appreciable stickiness between the polymer membranes and the stomach mucosa was observed, except with hydroxypropylmethylcellulose. The polymer membranes tended to display less friction during dissolution, probably because of their ability to act as lubricants, The results of our work are summarized in this report.

Non-fasted Sprague–Dawley rats weighing 220–280 g were used for these experiments. The rats were killed by cervical dislocation and the

* *Present address:* Yamanouchi Pharmaceutical Co., Ltd., No. 180, Ozumi Yaizu-shi, Shizuoka 425, Japan.
Correspondence: T. Higuchi, Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, KS 66045, U.S.A.

stomach removed. The excised stomach was opened along the greater curvature and fastened inside out on a styrofoam block with pins. This styrofoam block was fixed onto the table of an infusion pump so that the horizontal mucosal surface could be moved at a constant speed for the measurent of sliding friction. Stomachs so prepared were used only for one or two measurements and discarded within 30 min of preparation. The polymer membranes were in contact with the stomach mucosa for a couple of minutes before the friction measurement. Four different kinds of polymers were used in this experiment: cellulose acetrate (CA) (Eastman, Type CA-398-10), Eudragit E (Rohm Pharma, Type E100), hydroxypropylmethylcellulose-phthalate (HPMCP) (Shin-etsu Chemical, Type HP-50), hydroxypropylmethylcellulose (HPMC) (Dow Chemical, Type E-15).

The coating solution was sprayed on the flat upper surface of a bakelite bottle cap (1.5 cm in diameter, 1 g in weight) until a polymer coating of considerable thickness (0.5–1.0 mm) was obtained. A thread was secured to this bakelite bottle cap by tying around the cylindrical portion, and was subsequently connected to a strain gauge myograph. The bottle cap was then placed upside down on the exposed mucosal surface of the excised rat stomach. The friction between the polymer membrane and the mucosa was measured by moving the styrofoam block away from the strain gauge at a constant speed of 0.15 cm/min; that is, we measured the dynamic friction when the polymer membrane was sliding on the inside surface of the stomach. Also several different weights (1–50 g) were added to the center of the bakelite bottle cap to examine the correlation of pressure and friction. The pH was controlled by adding dropwise, either an isotonic acetate buffer (pH 3.0) or an isotonic phosphate buffer (pH 6.1) to the stomach mucosal surface directly in the path of the sliding bottle cap during the friction measurement.

The results of the friction measurements are shown in Figs. 1–4. Even though CA does not dissolve in water at either pH 3.0 or pH 6.1, the friction between CA and the rat stomach mucosa is greater at pH 3.0 than at pH 6.1 (Fig. 1). There

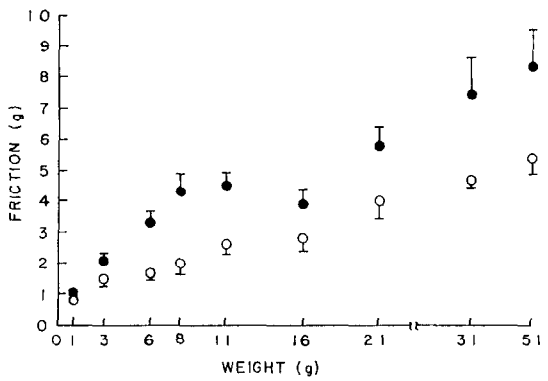

Fig. 1. The sliding friction of CA on the rat stomach mucosa at pH 3.0 (●) and pH 6.1 (○). Each point represents mean ± S.E. (n = 3–6).

is a general lowering of the viscosity of gastric mucous as pH increases, and this viscosity difference may have been reflected as a difference in sliding friction of CA at the experimental pH's. Eudragit E dissolves at pH 3.0 but does not dissolve at pH 6.1 while HPMCP dissolves at pH 6.1 but does not dissolve at pH 3.0. As shown in Fig. 2, Eudragit E displays less friction at pH 3.0 than at pH 6.1, while Fig. 3 shows that HPMCP has less friction at pH 6.1 than at pH 3.0. Finally, HPMC which dissolves at both pH 3.0 and pH 6.1, displays little dynamic friction at either pH 3.0 or pH 6.1, similar to Eudragit E at pH 3.0 and to HPMCP at pH 6.1. According to these observa-

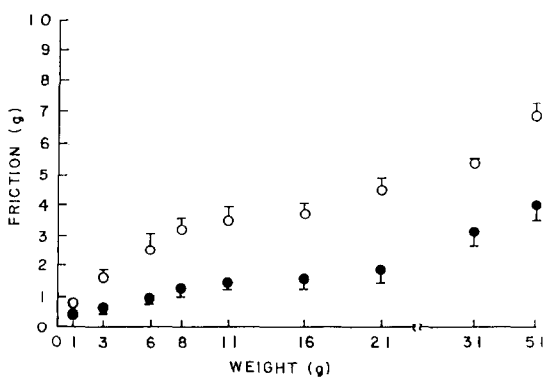

Fig. 2. The sliding friction of Eudragit E on the rat stomach mucosa at pH 3.0 (●) and pH 6.1 (○). Each point represents mean ± S.E. (n = 3–6).

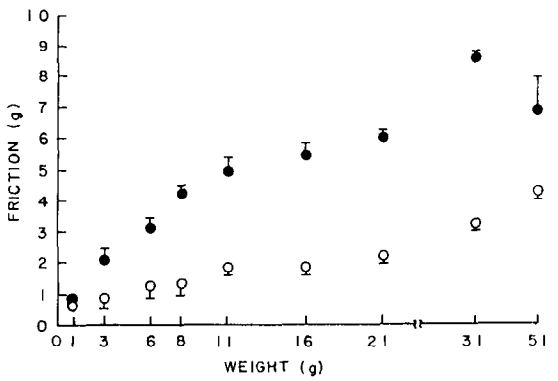

Fig. 3. The sliding friction of HPMCP on the rat stomach mucosa at pH 3.0 (●) and pH 6.1 (○). Each point represents mean ± S.E. (n = 3–6).

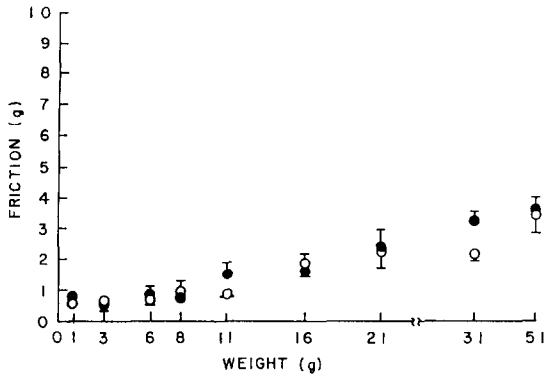

Fig. 4. The sliding friction of HPMC on the rat stomach mucosa at pH 3.0 (●) and pH 6.1 (○). Each point represents mean ± S.E. (n = 3–6).

tions the polymer films show less friction during dissolution. It is thought that the polymer solution at the interface is acting as a lubricant. When the polymer is not dissolving, such a lubricant action would not be expected, and the polymer membrane indeed displays a greater friction. For all these four polymers, at both pH 3.0 and pH 6.1, the sliding friction increased with an increase in added weight.

We did not observe any appreciable stickiness of these polymers to the rat stomach mucosa, with the single exception of HMPC. With HPMC, about 7 g of force was required to overcome static friction, or initial adhesion of this material, without any added weight at both pH 3.0 and pH 6.1. This force was in some instances great enough to detach the mucosal cell layer from the basement membrane. Once it began to slide on the stomach mucosa, however, we observed the lesser value for steady-state sliding friction shown in Fig. 4. The value for this sliding friction was much smaller than the value for the adherence of sugar-coated tablets to the esophagus (Marvola et al., 1983). Therefore it is unlikely that the film coating of HPMC delays the gastric transit of the dosage form.

Also it should be noted that the polymer coatings used in these measurements were much thicker than film coatings employed in tablet manufacture. Consequently, the time required for dissolution of the thick HPMC coat was much greater than would be required for dissolution of conventional thin film coatings. The thick films used in this work allowed such measurements during the dissolving process to have been made. Use of HPMC as a film coat for tablets is unlikely to display any substantial adhesion in the stomach for more than a few minutes.

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