DRUG DELIVERY TO THE GASTROINTESTINAL TRACT

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Enteric Coatings and Delayed Release

J N C Healey

Enteric coatings have traditionally been reserved for drug substances that cause gastric irritation, produce nausea if released in the stomach, or are destroyed by acid or gastric enzymes. More recently this type of coating has also found application in achieving delayed release effects, by which disintegration and drug release in the upper gastrointestinal tract are prevented in favour of delivery to more distal segments. This might be with the objective, for example, of achieving a slower rate of absorption than would occur following conventional release in the upper small intestine, or of achieving a sufficiently high concentration of drug at distal sites of action in the colon. The term 'delayed-release' is sometimes used to include all enteric coated products, even those with a conventional enteric coating, as for example in recent supplements to the United States Pharmacopoeia.

The principle by which enteric coating polymers act is that their solubility is highly pH dependent, the polymers being insoluble in gastric acid but dissolving at intestinal pH. Whilst pH is of major importance in determining the point of drug release from these systems, a number of other factors has been found critical.

The first part of this chapter is concerned with the various parameters that determine the point of release, and examines instances of ineffective performance that have contributed to current understanding of enteric coatings. The remaining sections deal with coating polymers in current use, the ways in which coated products should be assessed, and some recent applications of these coatings in achieving colonic delivery.

GASTROINTESTINAL pH

Views as to the precise pH at which enteric coating polymers should dissolve have had to change in recent years as more accurate assessments of the gastrointestinal tract have been made using miniature pH electrodes and radiotelemetry.

The pH of the gastric fluid in the fasting stomach lies predominantly within the range 0.8 to 2.0, although a small percentage of healthy individuals are sufficiently achlorhydric to show occasional high fasting pH values up to about 5. The buffering and dilution of acid that is caused by ingestion of food results in a transient rise to pH 4 - 5 or higher, but this provokes further gastric secretion and restores a strongly acid pH within 30 to 45 minutes (Fimmel *et al.*, 1985). Gastric acid is subsequently neutralised by bicarbonate in the duodenum, where the pH rises rapidly to about 5.5 at the jejunal junction, in both the fasted and post-prandial states.

Whereas gastric pH has been relatively well defined, fewer studies have been carried out into intestinal conditions and data are consequently more limited. The proximal jejunum usually lies within the pH range 5.0 to 6.5 (Ovesen *et al.*, 1986). The pH rises slowly along the length of the small intestine to reach only pH 6 to 7 in most subjects, although high values in the range 7 to 9 have occasionally been found (Hardy *et al.*, 1987a). The caecum and ascending colon are usually more acid than the small intestine, by a half to one pH unit, but a higher pH of 6.0 - 7.0 or above is restored more distally. The contents of the gut are not homogeneous and the pH recorded by a radiotelemetry capsule is of the local pH in the immediate environment of the device, rather than reflecting either the average pH of the lumen or the pH at the gut wall. Nevertheless, such results accurately reflect the range of conditions to which an enteric coated dosage form might be exposed in its transit through the intestines.

A summary of the pH range for healthy subjects is given in Table 1, but intra- and inter-subject variability as well as the effects of disease states will result in a small but significant proportion of readings lying outside these values. pH is of course also affected by the administration of some drugs particularly antacids and H_2- antagonists.

Various polymers are available for use in enteric coatings. All are insoluble and impermeable in acid but begin to dissolve at pH values in the range 4.5 to 7.0. Products coated using polymers that dissolve at the lower end of the pH range may be prone to release in the stomach in a proportion of instances, whether owing to a high fasting pH or to the buffering effects of ingested food. To ensure full gastric resistance, a coating impermeable to at least pH 5.0 is therefore essential. With polymers that dissolve at relatively high pH values, concern arises as to whether the coating will

Table 1 - Ranges of Gastrointestinal pH typically Found in Healthy Subjects.

Location	pH
Stomach	0.8-5.0
Jejunum	5.0-6.5
Ileum	6.0-7.5
Colon	6.0-8.0

dissolve sufficiently promptly in the small intestine to provide adequate opportunity for drug absorption in all instances.

ENTERIC POLYMERS

Polymers that are used in enteric coating depend on the presence of ionisable carboxyl groups in their molecular structure for their pH sensitivity. A sufficient proportion of these acid groups, about 10%, must be ionised for water solubility to be achieved. This degree of ionisation is reached, as defined by the Henderson-Hasselbach equation, when pH rises to within one pH unit of the pK_a value:

$$pH\text{-}pK_a = \log \frac{\text{concentration ionised}}{\text{concentration unionised}}$$

There is not in fact a precise pH threshold above which a material is soluble, rather a range of about one pH unit over which a polymer coating varies from being virtually impermeable to being quite readily soluble and fast to rupture. An awareness that the intestinal tract is not as alkaline as once believed, and consideration of the *in vivo* performances of enteric coatings, have led to the introduction of polymers that release at increasingly acid pH values. A list of commonly used enteric coating materials is given in Table 2, together with the pH values at and above which the polymers will dissolve moderately readily in buffer solutions *in vitro*. Although Shellac is now considered to be soluble at too high a pH and has become largely superseded, it is included in Table 2 for comparison.

The threshold values range from below pH 5, particularly for some newer materials, to about pH 6 for cellulose acetate phthalate and Eudragit L, and to pH 6.6 - 6.8 for Eudragit S. Mixed films may be formulated from compatible polymers to achieve intermediate effects, for example between CAP and CAT and between Eudragit L and S. The threshold values are

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