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Chapter 3

POLYMERS FOR ENTERIC COATING APPLICATIONS

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I. DEFINITION AND HISTORY

An enteric coating is one that resists disintegration or dissolution in gastric media, but disintegrates or dissolves in intestinal fluids.

The notion that some coatings could delay the release of substances until they had emptied from the stomach was first noted in 1867, when it was reported that collodion-protected pills did not dissolve in the stomach.[1] Unna is credited as being the first to use gastric insolubility as a basis for medication when he introduced keratin coated pills in 1884.[2-4] Ceppi is reported to have introduced salol as an enteric coating a few years later.[4,5]

The realization that certain medicaments needed to be protected against the gastric environment occurred after elucidation of the chemistry and mechanics of the process of digestion by Prout, Beaumont, and Pavlov.[6,7] In 1889 Bourquelot listed four groups of medicaments that required gastric protection.[6-8] The groups included drugs attacked by gastric contents, drugs influencing gastric performance, and drugs that irritate the stomach.

As soon as it became clear that some types of drugs needed gastric protection, efforts were directed at finding substances that would do the job. Shroeter has listed a number of materials that have been tried or used as enteric coatings together with references to their investigations.[9] Among the older materials used were formalized gelatin, keratin, salol, steric acid, and sandarac. Most of the earlier materials are no longer used because they did not perform satisfactorily as enteric coatings, for one reason or another. Keratin, for example, did not withstand gastric digestion.[3] Formalized gelatin proved unreliable because polymerization of the gelatin on storage often resulted in failure of the coatings to release the drug contained in the coated product.[3,7,10] Salol-coated tablets were also found to go through the intestine without dissolving.[3] There were also instances when salol-coated tablets broke in the stomach.[3]

The search for better performing materials has continued through the years. We now have a variety of materials, including several new materials, available as enteric and delayed-release coatings, which are discussed in later sections of this chapter. The search still continues for new enteric polymers and polymer forms.

II. PURPOSE OF ENTERIC COATINGS

The function of enteric coatings is primarily protective. This may be either to protect the stomach from the effect of the drug, or to protect the drug from the effect of the gastric contents. There are a number of drugs which, if directly exposed to gastric mucosa, will result in gastric irritation, and in some cases, actual corrosion of the gastric wall. Such drugs are enteric coated to protect the individuals taking them from their harmful side effects. Aspirin is an important example of such a drug. Several reports of gastric bleeding following aspirin medication can be found in the literature.[11-14] Other drugs that fall in this category are strong electrolytes such as ammonium chloride and potassium chloride.

Enteric coatings also protect drugs from degradation. For example, erythromycin and digoxin are unstable in gastric media. Other reasons for enteric coatings are

1. to better deliver drugs that are absorbed from a region of the intestine, or that act in the intestine and require a high concentration of drug to be released there to be effective a (some anthelmintics);
2. to provide a delayed component for repeat action dosage forms; and
3. to prevent interaction of certain drugs with pepsin and peptones that would lead to a hindrance of gastric digestion.

III. GASTROINTESTINAL PHYSIOLOGY RELATIVE TO ENTERIC COATING FUNCTIONING AND DESIGN RATIONALE

Enteric coatings rely on the differences in environment between the stomach and intestine for their performance. Understanding the requirements of enteric coatings demands consideration of gastrointestinal (GI) physiology and function.

The most important GI physiological factors affecting the functioning of enteric coatings are

1. The pH of the stomach and intestinal contents
2. Gastric emptying
3. Enzyme activity of the gastrointestinal tract

Based on these regional differences in environment between the stomach and the intestines, there are two mechanisms by which an enteric coating may be made to be resistant to dissolution or hydration in the stomach, yet release rapidly in the upper intestinal tract. These two mechanisms involve the pH change and the enzyme environment change between the stomach and the intestines.

A. pH

The pH of the stomach varies from about 1.0 to 3.5 depending on the presence or absence of food and reflux of intestinal contents into the stomach.[15-19] The pH of the intestine may range from about 3.8—6.6[20] in the small intestine to about 7.5—8.0 in the large intestine.[21] This range results from progressive dilution of acid chyme from the stomach by bicarbonate ions in the pancreatic secretion, which is delivered by the bile duct to the duodenum as well as from intestinal secretions.[16,17]

Based on the pH of the stomach and small intestine, enteric coatings must be designed to resist dissolution at pH values below 4 to avoid disintegration in the stomach, but to begin dissolving at pH 5 and above, and be readily soluble at pH 7. A number of earlier enteric formulations failed to release their contents appropriately because their design was based on the mistaken assumption that the pH of the small intestinal contents was alkaline.

B. GASTRIC EMPTYING

Gastric emptying of coated tablets have been reported to be highly variable, and may take anywhere from 30 min or less to 7 h or more depending on the presence and type of food in the stomach, in addition to other factors.[16,18-20]

Bukey and Brew[18] reported an *average* gastric emptying time of about 6 h. There is general agreement, however, that because of the wide variability in emptying time, an arbitrary gastric emptying time of 1 or 2 h is not a reliable factor on which to base enteric performance. It might be reasonable to assume that any enteric polymer which can resist gastric contents for 6 h is likely to give satisfactory performance in terms of gastric protection in most patients under most circumstances. Although some coatings may be able to resist gastric acid for 1 h, as specified by the compendia, these tablets may not be able to remain intact if held in the stomach for substantially longer periods.

The fact that an enteric tablet has adequate protection against gastric acid does not guarantee that the tablet will be an effective dosage form/drug delivery system, *unless* the enteric coating quickly dissolves/disintegrates on leaving the stomach, when it contacts a new environment.

A general description of gastric motility and activity may be helpful in understanding the manner in which materials are handled by the stomach. The presence of food in the stomach, especially of fatty foods, reduces both the rate of emptying from the stomach and

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