Rate Control in Drug Therapy

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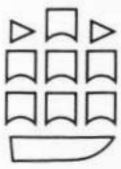

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15. Physiological limitations: gastric emptying and transit of dosage forms

J. W. Fara

Within recent years, a variety of oral dosage forms has been introduced to deliver their drug content over a specified period of time after administration. Because drug absorption from these forms may depend on where the delivery system resides in the gastrointestinal tract, gastrointestinal motility, gastric emptying, and intestinal transit became important considerations in the rational design of oral dosage forms.

The general events that govern the emptying of food from the stomach have been known for some time. Indeed, over 150 years ago it was recognized that the stomach is a digestive vat, which not only contributes digestive secretions, but also performs the important function of reducing food to small particles by a vigorous grinding and mixing action.

In addition, physiological studies have elucidated many of the mechanisms which control gastric emptying, and have given insight into gastric activity following a meal. At least three factors are recognized as influencing gastric emptying:

1. Distension of the stomach, and various physiological influences such as emotional state.
2. Physical characteristics of food: e.g. liquids empty faster than solids.
3. Chemical composition of food: a light carbohydrate meal empties faster than a protein-rich meal, which empties faster than a fatty meal. Duodenal feedback mechanisms, involving hormone release and nerve reflexes, are triggered by components of the meal and by such factors as osmolality and pH. Also, a metering of calories delivered to the duodenum may be involved.

These statements are at best incomplete descriptions of the multiple aspects of motility that govern and differentiate the emptying of solids and liquids from the stomach and their transit of the intestinal tract.

MOTILITY MODES

Over the past five to eight years the disciplines of physiology and gastroenterology have contributed to a clearer understanding of how food components and solid objects pass through the gastrointestinal tract. The

stomach handles objects greater than 2 mm in diameter quite differently from the way it handles smaller particles and liquids. In fact, the gastric residence time of larger objects is quite predictable compared to that of small particles. This difference arises from the prevailing gastrointestinal motility pattern.

Two distinct gastrointestinal motility patterns are fairly well characterized in animals and man (Code & Schlegel, 1974; Code & Marlett, 1975): a so-called 'fasting mode', and ' 'fed mode', which begins after ingestion of food and continues until after food components are digested and emptied from the stomach (Table 15.1)

Table 15.1 The gastrointestinal motility modes characterised in dogs

Fed mode	9–12 h	Clamped in same pattern
Fasting mode	2-h cycle	Cycles regularly through three recognizable patterns:
		quiescent: 56 ± 4 min
		build up: 40 ± 28 min (fed-like)
		housekeeper: 20 ± 6 min

The fasting mode prevails during night-time rest and into the early morning hours. It consists of three phases of motility that recur every one to two hours. These interdigestive motor cycles are: a quiescent period (phase I), a period of gradual increase in motor activity (phase II), and a period of intense bursts of contractions (phase III). Phase III is known as the migrating motor complex or the 'housekeeper' motility pattern. This pattern begins about mid-way down the stomach and continues uninterrupted down the intestinal tract to the distal ileum. After most of the meal has been emptied, these housekeeper waves clear the stomach of any remaining digested contents, and also of relatively large, indigestible solids.

Ingestion of a meal replaces the fasting cyclic motor activity with a pattern of continuous activity, known as the fed mode. In the stomach, this fed mode consists of regular contractions at a frequency of 3–5 per minute. In the intestine, a somewhat more irregular pattern of contractions occurs. During this time, food is digested and ground into smaller and smaller particles such that an orderly flow of partially digested food leaves the stomach over the next several hours. Because of the heterogenity of the usual human diet, both within and between individuals, the duration of the fed mode is variable, but probably continues as long as nutrients remain in the stomach. In dogs, the fed mode lasts 9–12 hours. after ingestion of a large-protein fat meal (Table 15.1). When the stomach is completely empty, it enters the fasting mode.

MOTILITY MODES AND GASTRIC EMPTYING

Code and coworkers laid the groundwork for understanding how the stomach empties food and solid objects. These investigators used fluoroscopic observation of the intragastric transit of 1-cm-diameter radiopaque plastic spheres (Carlson et al. 1960). Subsequent experiments then defined the relationship between each

motility mode and the handling of food and solid objects (Code & Schlegel, 1974; Code & Marlett, 1975; Hinder & Kelly, 1977; Meyer et al, 1979). The stomach selectively empties solids according to particle size (Fig. 15.1). The studies were first done in dogs and were subsequently confirmed in humans (Hinder & Kelly, 1977; Meyer et al, 1979; Meyer et al, 1981; Malagelada et al, 1976).

Radiolabelled liver was fed as cubes of different sizes and as homogenate, together with 7 mm radiopaque plastic spheres, and a quantity of non-absorbable fluid labelled with another radionuclide. Transit of the respective radionuclide through the gastrointestinal tract was then followed. By sampling the duodenal contents, a profile of gastric emptying was constructed (Fig. 15.1).

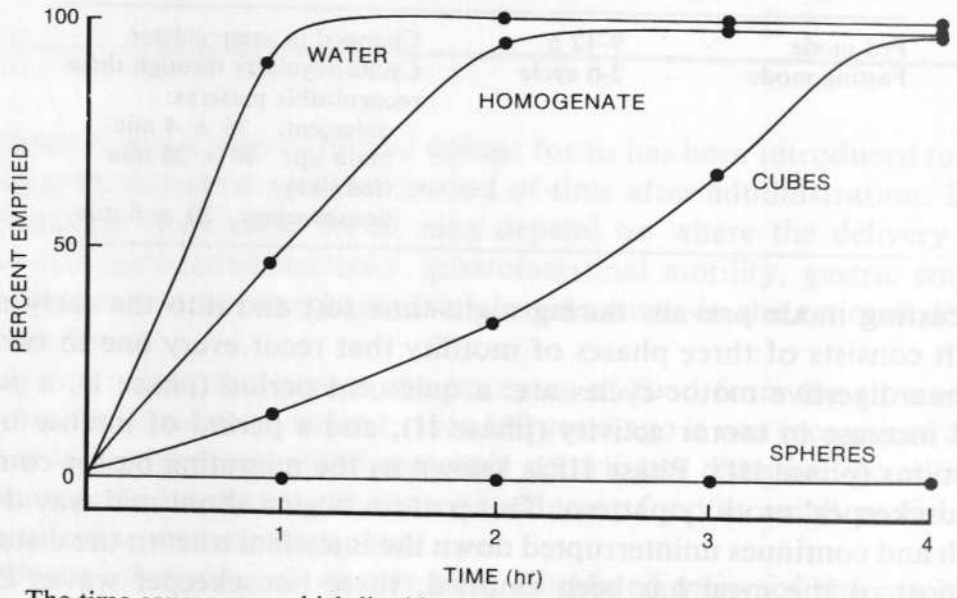

Fig. 15.1 The time course over which liquids, particles, and larger spheres empty from the stomach

Liquids emptied quite rapidly, followed by liver homogenate and then the liver cubes emptied substantially more slowly. Solid plastic spheres of 7 mm diameter, fed with the liver, remained in the stomach for over four hours; during that time the rest of the meal emptied completely. Significantly, examination of the duodenal contents showed that all the food particles present were less than 2 mm in diameter. Thus, digestible substances are ground into smaller and smaller particles until they approach 2 mm in diameter, when the are emptied from the stomach.

After ingestion of a meal, gastric motility switches rapidly into the fed mode pattern. There is mixing, propulsion, and retropulsion of the food as particles are reduced in size, and the stomach gradually empties. Large, non-digested particles are selectively retained, however, as the semi-liquid, partially digested particles flow irregularly into the duodenum. Some time after the meal has emptied completely, the stomach enters the fasting mode. With the subsequent appearance of the housekeeper motility pattern, strong propulsive contractions clean out all that remains (including the 7 mm spheres).

GASTROINTESTINAL TRANSIT OF DOSAGE FORMS

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