Enteric-Coated Pellets: Theoretical Analysis of Effect of Dispersion in the Stomach on Blood Level Profiles

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Abstract □ The advantages of encapsulated enteric-coated pellets as dosage forms are discussed theoretically and compared to enteric-coated tablets. An enteric-coated tablet may take from approximately 0.5 to more than 8 hr to pass from the stomach to the duodenum. On the other hand, enteric-coated pellets are subjected to dispersion in the stomach, but they pass through the pyloric sphincter after a mean residence time in the stomach that would not be different from that exhibited by a suspension dosage form. The dispersion effect causes a theoretical reduction in peak blood level over that of an enteric-coated tablet of equivalent potency while maintaining bioavailability. It is hypothesized that enteric-coated pellets will reduce intestinal side effects that may occur with enteric-coated tablet preparations.

Keyphrases □ Pellets, enteric coated—theoretical analysis of effect of dispersion in stomach on blood level profiles □ Enteric-coated pellets—theoretical analysis of effect of dispersion in stomach on blood level profiles □ Dosage forms—enteric-coated pellets, theoretical analysis of effect of dispersion in stomach on blood level profiles

Various drugs, when administered orally, either cause GI problems (*e.g.*, aspirin, indomethacin, and tetracyclines) or are degraded by gastric acid into metabolites leading to poor bioavailability (*e.g.*, erythromycin and penicillin G) or GI side effects (*e.g.*, levodopa). In some cases, these problems have been overcome by the use of enteric-coated tablets. They remain intact during passage through the stomach, the enteric coat not being shed until the tablets pass into the duodenum.

Two outstanding problems are inherent in the administration of enteric-coated tablets:

1. There is a "hit-or-miss" effect; *i.e.*, the tablet may take from about 0.5 to more than 8 hr before it passes into the duodenum, leading to the possibility of two tablets, each from different dosage times, passing through the pyloric sphincter at effectively the same time.
2. Intestinal side effects may result due to a sudden, highly localized dose of drug at one site in the small intestine.

The latter point could account for the significant blood loss reported with enteric-coated aspirin tablets, even though no salicylic acid was detected at any time in the stomach (1). This study illustrates, from a theoretical approach, the advantages of administering drugs, requiring enteric protection, in the form of encapsulated enteric-coated pellets. The model used is based on a simple physical picture of what is envisaged to occur. However, *in vivo* experimental studies to quantify this theoretical analysis probably will show that a more sophisticated analysis is not warranted in view of the large variability of *in vivo* data.

THEORETICAL

Solutions, suspensions, tablets, and capsules, which disintegrate and/or dissolve in the stomach, and enteric-coated pellets all spread (or disperse) throughout the stomach before passing through the pyloric sphincter into the duodenum. The drug particles or molecules do not pass through the pyloric sphincter as a bolus but assume a random distribution. Some drug particles or molecules tend to pass through before the mean passage time, and others pass through at random times greater than the mean passage time. Once the particles or molecules pass through the pyloric sphincter, they are assumed to be no longer subject to dispersion. However, the particles or molecules still in the stomach are subject to dispersion; *i.e.*, the longer they stay in the stomach, the greater the effect of dispersion. The distribution will be skewed.

To illustrate the effect that dispersion has on absorption and, subsequently, on blood levels, it is necessary to assume a simple model for the dispersion effect. The simplest case is provided by considering the stomach as a straight length of pipe of uniform cross-section through which a fluid is passing. The fluid is subjected to a longitudinal mixing or axial dispersion effect, which is superimposed on the mean flow.

The drug is assumed to be chemically inert on passage through the stomach, a property inherent in enteric-coated pellets. The dosage is $n_a{}^0$ mg, and the mean passage is $\bar{t}$ hr from the time of release from a capsule (or from the time of disintegration of a tablet or from the time of administration of a suspension or solution) to the time of passing through the pyloric sphincter.

If the drug can be envisaged to be instantaneously and evenly distributed throughout the stomach at time zero, then the drug passes through the pyloric sphincter at a rate of $n_a{}^0/\bar{t}$ mg/hr if no further dispersion occurs. If the drug dose is administered normally and dispersion does occur, then the amount of drug passing through the pyloric sphincter in time interval Δt is designated $\Delta n_a{}^0$. Thus, from the work of Levenspiel and Smith (2):

$$\frac{\Delta n_a/\Delta t}{n_a{}^0/\bar{t}} = \frac{1}{2\sqrt{\pi\frac{t}{\bar{t}}N_D}} \exp\left[-\frac{\left(1-\frac{t}{\bar{t}}\right)^2}{4\frac{t}{\bar{t}}N_D}\right] \qquad \text{(Eq. 1)}$$

where $\Delta n_a/\Delta t$ is the rate of drug passage through the pyloric sphincter at time t, and N_D, the dispersion number, is equal to D/uL, where D is the longitudinal or axial dispersion coefficient (equivalent to a macroscopic diffusion coefficient), u is the average linear velocity, and L is the length of the "pipe" from the point of drug administration to the pyloric sphincter. In physiological terms, D and u each depend on motility, viscosity of the fluid, and the total volume of fluid in the stomach.

The fraction of the drug dose, $\Delta X_a(t)$, that passes through the pyloric sphincter in time Δt and is available for absorption in the small intestine,

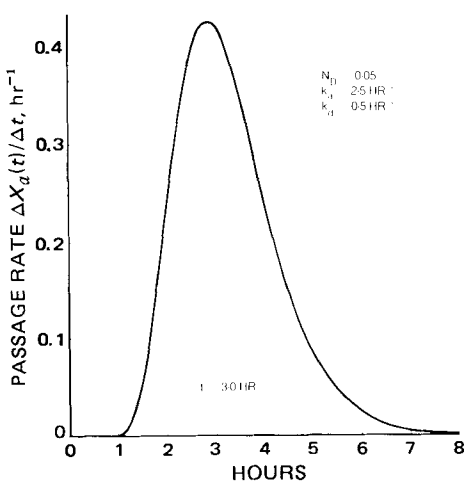

Figure 1—*Rate of passage of drug through pyloric sphincter as a function of time.*

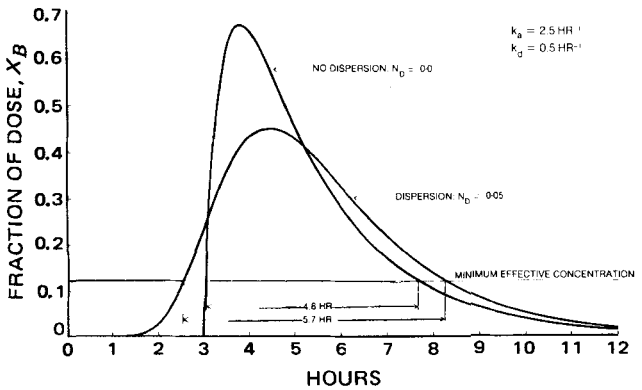

Figure 2—*Fraction of dose in single body compartment as a function of time for the cases of dispersion and no dispersion.*

assuming a rapid dissolution time such that there is negligible deviation in the blood level curve from that for instantaneous dissolution, is given by:

$$\Delta X_a(t) = \frac{\Delta n_a}{n_a{}^0} = \frac{\Delta t}{2\sqrt{\pi t \bar{t} N_D}} \exp\left[-\frac{\left(1-\frac{t}{\bar{t}}\right)^2}{\frac{t}{\bar{t}}N_D}\right] \quad \text{(Eq. 2)}$$

The fraction of the drug in the single body compartment at any time can be calculated for the one-compartment open model with the following working equations:

$$X_A(t) = X_A(t-\Delta t) + \Delta X_A(t) - \frac{k_a}{2}[X_A(t-\Delta t) + X_A(t)]\Delta t \quad \text{(Eq. 3a)}$$

or:

$$X_A(t) = X_A(t-\Delta t)\left[\frac{1-0.5k_a\,\Delta t}{1+0.5k_a\,\Delta t}\right] + \frac{\Delta X_a(t)}{1+0.5k_a\,\Delta t} \quad \text{(Eq. 3b)}$$

and:

$$X_B(t) = X_B(t-\Delta t) + \frac{k_a}{2}[X_a(t-\Delta t) + X_A(t)]\,\Delta t - \frac{k_d}{2}[X_B(t-\Delta t) + X_B(t)]\,\Delta t \quad \text{(Eq. 4a)}$$

or:

$$X_B(t) = X_B(t-\Delta t)\left[\frac{1-0.5k_d\,\Delta t}{1+0.5k_d\,\Delta t}\right] + \frac{k_a[X_A(t-\Delta t) + X_A(t)]\Delta t}{2(1+0.5k_d\,\Delta t)} \quad \text{(Eq. 4b)}$$

where $X_A(t)$ and $X_A(t-\Delta t)$ are the fractions of drug in solution in the small intestine at times t and $t-\Delta t$, respectively; $X_B(t)$ and $X_B(t-\Delta t)$ are the fractions of drug in the single body compartment at times t and $t-\Delta t$, respectively; $\Delta X_a(t)$ is the amount of drug that enters the small intestine and is dissolved between times $t-\Delta t$ and t (see Eq. 2); k_a is the first-order absorption constant; and k_d is the first-order elimination constant, accounting for total metabolism and excretion from the single body compartment.

RESULTS

To demonstrate the effect of dispersion on blood level curves, the following parameters were selected: $\bar{t}$ = 3.0 hr, N_D = 0.05, k_a = 2.5 hr^{-1}, k_d = 0.5 hr^{-1}, and Δt = 0.001 hr.

Figure 1 shows a plot of the rate of passage of the drug through the pyloric sphincter as a function of time, determined from Eq. 2 as $\Delta X_a/\Delta t$. The skewed effect of continued dispersion on the particles remaining in the stomach is observed as time increases beyond the mean time. Figure 2 shows a plot of the fraction of the drug in the single body compartment as a function of time for the case of dispersion in the stomach and zero dispersion. The zero-dispersion case represents, for example, an enteric-coated tablet that takes 3 hr before it releases its coat in the duodenum and is available for absorption in the small intestine.

DISCUSSION

Figure 2 shows that dispersion of the particles or molecules in the stomach leads to a depression of the peak blood level but not at the expense of bioavailability. The value of the use of a large number of enteric-coated pellets in place of a single enteric-coated tablet is indicated by the fact that the blood level exceeds the minimum effective concentration for 5.7 hr in the dispersion case compared to only 4.6 hr in the zero-dispersion example. The use of enteric-coated pellets, therefore, introduces an effective mild sustained-release effect without the reduced bioavailability inherent in the standard sustained-release preparation. Such an effect was noted by Green (3) in studies with enteric-coated aspirin microspheres.

The depression of peak blood level with unimpaired bioavailability may be a distinct advantage with some drugs, because the peak blood level for zero dispersion may be in the toxic region. Aspirin is being marketed as enteric-coated tablets; but despite the fact that no salicylic acid has been detected in the stomach, confirming the effectiveness of the enteric coating, the blood loss is still significantly above that for administration of placebo tablets (1). It is suggested that the blood loss is due to the sudden appearance of a large concentration of aspirin at one location, the total dose moving along the small intestine as a bolus until it is absorbed.

Enteric-coated aspirin pellets would release the drug in the small intestine as small "minidoses"; the drug would be distributed along the small intestine without large concentrations at a particular location at any time. Therefore it is predicted that, for drugs exhibiting GI side effects, the enteric-coated pellet form will obviate intestinal side effects as well as gastric side effects.

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