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Simulation of gastrointestinal drug absorption I. Longitudinal transport in the small intestine

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Summary

A computer simulation model of transport of material along the small intestine is proposed. The model is developed by considering a succession of boluses, created by stomach emptying, which proceed by discontinuous jumps along the small intestine. During a jump material can be exchanged between adjacent boluses to simulate longitudinal mixing. The model is tested by comparison of simulated distribution profiles of test markers with reported distribution of non-absorbable radioactive test markers in the small intestine of the rat and with colonic arrival times in man, resulting in good agreement between simulations and experimental data.

Introduction

Although many of the individual aspects of drug absorption from the gastrointestinal tract (GIT) are well-understood, there have been few attempts to develop models which reflect the degree to which the various factors involved interact. The present work is part of a project to develop a comprehensive simulation model of drug absorption from the GIT. The aim of this article is to develop a simulation model of transport along the small intestine which is generally accepted as the major site for drug absorption.

Mathematical models have been used for many years to study various aspects of drug absorption, but these models have generally ignored intestinal transport. In pharmacokinetics, it is common to represent the gut as a single compartment. This assumes uniform distribution throughout the region where absorption occurs, and implicitly assumes that transport along the intestine plays no significant role in determining the absorption rate. A simple extension of the one-compartment model is to represent the gut by more than one compartment; for example, as in the MacDope model (Bloch et al., 1980). This model proposes separate compartments for the stomach and the small intestine. Modelling the stomach as a single compartment in this approach seems reasonable; but

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representation of the small intestine as a single compartment has many problems because it still implicitly assumes that the small intestine is well-mixed throughout its entire length. In addition, there are pH and mucosal surface area variations along the length of the intestine which are difficult to model by a single compartment; absorption windows also exist for some substances. The importance of these factors in the absorption process would be significantly influenced by differing transport rates along the intestine.

A different approach is to represent movement along the intestine as flow in a pipe (Amidon et al., 1981). In this approach the intestine is represented as a tube, well-mixed in the radial direction and experiencing constant flow; mathematical expressions are introduced to describe various possible forms of absorption from the intestine under quasi-steady-state conditions. This model was found to be useful for studying the interplay of various factors in in situ perfused rat intestinal absorption experiments, and in the estimation of reserve length for a drug. Ni et al. (1980) proposed an improvement to the model of Amidon and co-workers by including terms to describe simultaneous turbulent diffusion under non-steady-state conditions, in addition to the flow and absorption terms originally described. Both of these models assume that flow is continuous. While this may be a reasonable assumption for a continuous flow in situ intestinal loop, there is ample evidence that flow is non-continuous in vivo (Kelly, 1981).

A major feature of the present model is that it attempts to provide a realistic picture of the discontinuous movement of the gut contents. The model is developed on the basis of a succession of individual boluses travelling along the small intestine. Individual boluses are created by emptying of stomach contents. The model is built up by considering the processes which each individual bolus undergoes in its transit along the intestine. The net sum of events associated with each of the individual boluses represents the total behaviour of the intestinal contents during the course of absorption.

All these processes are incorporated into a computer program and the model is solved numerically (see Appendix 1). The cycle of events described by the complete model are:

(1) the stomach continuously empties new boluses into the small intestine;

(2a) boluses are propelled by gut movements as a series of discrete jumps;

(2b) some mixing of the contents of a bolus with the following bolus occurs during movement;

(3) a period of quiescence occurs between jumps, when absorption, secretion, dissolution, etc., can occur; and

(4) when a bolus reaches the end of the ileum it empties into the colon.

The operation of the model involves the simultaneous monitoring of all the boluses currently present in the small intestine.

In the model, drug absorption (and other processes of interest) occurs during step 3. Although drug absorption is a major process of interest, it is the purpose of this article to consider just the transport terms (all steps except 3). In the following article of this series the model will be extended to incorporate water and electrolyte absorption, and subsequent articles will report simulations with drugs.

There is a major difficulty in simulation models of complex events when attempts are made to compare the performance of the model with experimental observations. This is because a complex simulation involves many parameters which are not readily assigned. It is usually necessary to some extent to adjust parameter values to obtain agreement with the data. There is always a danger that agreement with experimental data obtained in this way is entirely spurious, because with sufficient manipulation of parameter values quite arbitrary behavior can often be reproduced. For this reason it is important in such studies to attempt to evaluate the performance of each component of the model independently of the other components. Quantitative data on intestinal transport are scarce, but in recent years there have been some reports on the intestinal transport of non-absorbable markers in humans. This provides the opportunity to investigate the performance of those features of the model which deal just with the longitudinal transport properties. The aim of this approach is to provide a foundation in experimental observations of the basic features of the model

before attempting our major objective, which is simulation of drug absorption.

Theoretical

Stomach emptying

Stomach emptying is a non-continuous process which is generally thought to occur as a series of spurts with a period of approximately 3/min (Kelly, 1981). We have assumed in the model that the output from these spurts is such that there is no significant difference between spurts over a 1 min interval. A single bolus is therefore defined in the model as the accumulation of the total amount of material emptied over a 1 min interval. One minute is an arbitrary interval which we found convenient to use and can be varied easily. Computer time is the major consideration in this choice, since it is significantly increased with every increase in the number of boluses formed.

In the literature, stomach emptying is often represented by an exponential function (e.g. Hunt and Stubbs, 1975), although there are other possibilities, such as the square-root law (Hopkins, 1966) and a number of reports show other forms of nonexponential emptying (e.g. Clements et al., 1978; Hunter et al., 1982; Christensen et al., 1986). Stomach emptying is implemented in the model as either a simple exponential or, for non-exponential stomach emptying, by means of linear interpolation of the observed or assumed emptying rate.

Bolus movement and mixing

We assume in the model that bolus movement is non-continuous; that is, movement is made up of a series of finite jumps with intermediate periods of quiescence. Luminal pressure traces show sharp peaks of pressure, corresponding to contractions, interspersed with periods of basal pressure where there are no contractions (Davenport, 1982). The relatively long duration of a period of quiescence compared to a period of contraction allows us to make the simplifying assumption that jumps are effectively instantaneous. Statistical study of contractions in the intestine in man shows that contractions are spaced in time at intervals which cluster around integer multiples of 5 s (Christensen et al., 1971). We assume in the model that these contraction cycles can be adequately represented by an averaged regular contraction cycle which we arbitrarily set at a 1 min interval. Computer time is again the major consideration in this assumption, since it depends on the number of boluses which need to be followed concurrently by the computer program; it also adjusts the period of intestinal movement so that it is in phase with that of stomach emptying.

During the movement of a bolus, represented in the model as a discrete jump, two factors need to be considered:

(1) the mixing between adjacent boluses that occurs during a jump; and

(2) the distance that a bolus moves during a jump.

Mixing. As pure peristalsis is rarely seen in man, any movement that a bolus undergoes is not entirely propulsive, and some mixing with adjacent boluses will occur. We assume that boluses follow the normal physiological pattern and stay in chronological order during a jump (Lew et al., 1970); i.e. the contents of any bolus will not be propelled more than one step forward in any particular jump. In the process of propulsion, some portion of the bolus will be left behind; this could either be due to frictional drag, to leakage of material back through the nodal constriction of the intestine, or to retropulsion of chyme. To describe this process we define the parameter F_{left} as the fraction of a bolus which is not propelled along with the rest of the bolus and which mixes with the bolus immediately behind it. Boluses are numbered so that bolus 1 is closest to the ileocaecal valve and the latest bolus formed (closest to the stomach) has the largest index (with a time interval of 1 min, bolus number T is formed at time T). When bolus J executes a jump, the fraction F_{left} of its contents mixes with the trailing bolus (i.e. bolus $J+1$); we also assume that the individual boluses are internally well-mixed at all times.

A mathematical description of the process is:

$$A(J, T+1) = (1 - F_{\text{left}})A(J, T) + F_{\text{left}}A(J-1, T) \quad (1)$$

$A(J, T)$ is the amount of substance in bolus J

during interval T. Eqn. 1 states that the amount in bolus J during time interval $T+1$ arises from the fraction retained in that bolus from the previous interval (the first term on the right) and the fraction left behind by the leading bolus (the second term on the right). A jump is assumed to be effectively instantaneous. Thus, the jump referred to in Eqn. 1 can be regarded as occurring either at the end of interval T or the beginning of interval $T+1$.

Distance jumped. In order to model the distance that a bolus moves during each jump, an equation was chosen to describe the velocity of a bolus at any position in the intestine. Results from studies in the rat suggest that the velocity of material moving along the intestine varies substantially with its position in the intestine (Sikov et al., 1969). There is also limited evidence that velocity is a function of position in humans (Kaus et al., 1984; Soergel, 1971). As discussed later, it was also found to be necessary to incorporate time-dependence in the velocity profile.

Sikov et al. (1969) proposed a logarithmic relationship to describe the position-dependence of velocity but this is not a suitable function for our purposes (it approaches infinity as distance travelled approaches zero). A number of equations with similar profiles were investigated as possible alternatives. The results are presented in the following section.

The velocity needed to describe the movement of an individual bolus is not in general the same as the mean velocity of the intestinal contents since the latter is also influenced by mixing between adjacent boluses (in our notation, by the parameter F_{left}). In the model, an individual bolus with velocity V (as judged by position and time) travels a distance V during a jump (which occurs once every minute in our implementation of the model; if a time ΔT is used instead of a 1 min cycle the bolus jumps the distance $V\Delta T$). At the same time the "mixing equation", Eqn. 1, describes the exchange of material between adjacent boluses. Thus, the bolus progresses along the intestine in discrete jumps, leaving a certain amount of material behind at each jump and gaining material left behind by the bolus in front of it. The passage of a bolus along the intestine, and the mixing of the intestinal contents, is simulated by repeated application of these two procedures.

Results

All simulations were carried out using the University of Sydney Cyber 825/830 computers with programs written in FORTRAN, making use where needed of the NAG library routines.

Simulation of transport in rats

In view of the limited amount of data available in humans, preliminary investigations were conducted using data from studies in rats. In particular, data on the amount of marker as a function of position along the length of the intestine do not appear to be available in humans, but are available in rats (Sikov et al., 1969; Poulakos and Kent, 1973). In spite of the possibility of substantial differences between rats and humans (in addition to the obvious differences due to size) it was thought useful to examine the general performance of the simulation in an animal model.

As a first approximation, data on the position of the leading edge of a test meal at various times (such as that of Sikov et al., 1969) would seem to present the possibility of modelling the velocity profile without interference from mixing; whether this happens in practice depends on the method of detecting the leading edge, and the extent of bolus mixing. The difficulties involved with this approach are discussed later with the aid of simulated data. Our conclusion is that the use of "leading edge" data is unreliable for the purpose of establishing a suitable velocity function. Instead, preliminary analysis was carried out by means of simulations of the amount of material as a function of position along the length of the intestine, for comparison with reported rat intestinal profiles (Poulakos and Kent, 1973). The model used here also included Eqn. 1 and stomach emptying. In all cases linear interpolation was carried out to match the simulated stomach emptying profiles to the experimentally reported stomach emptying profiles that did not display simple exponential behaviour. Simulations were carried out with various parameter values selected to give

reasonable values for the transit time, and the resulting profiles were compared with those reported. As a final step, non-linear regression was carried out to calculate best estimates of the parameters for these equations.

Preliminary investigations were carried out with the following trial functions to describe the position-dependence of velocity, V:

$$V = ab/(b + x) + c - dx \quad (2a)$$

$$V = a\ e^{-bx} + c - dx \quad (2b)$$

$$V = a\ e^{-bx^2} + c - dx \quad (2c)$$

$$V = a - bx \quad \text{for } x \leqslant c \quad (2d)$$

$$= a - bc - d(x - c) \text{ for } x > c$$

$$V = a - bx \text{ for } x \leqslant c \quad (2e)$$

$$= a - bc \text{ for } x > c$$

where a, b, c and d are parameters and x is the position along the small intestine (in percent). In each case the function was chosen to allow for a more rapid transport in the duodenum (small x), as shown by the data of Sikov et al. (1969) in the rat. Eqn. 2e was chosen as the best representation of the velocity profile; the performance of Eqn. 2e was essentially the same as the more flexible function given in Eqn. 2d, but Eqn. 2e involves one less parameter. For the other functions, adjustment of parameter values to give adequate agree-

TABLE 1

Parameter values used to obtain simulated intestinal profiles in the rat.

Parameter	Value	
	Fed rats	Fasted rats
a (% h^{-1}) [a]	914	214
b (h^{-1})	36.9	12
c (%) [a]	18.4	9.1
F_{left}	0.75	0.172

[a] % of intestinal length.

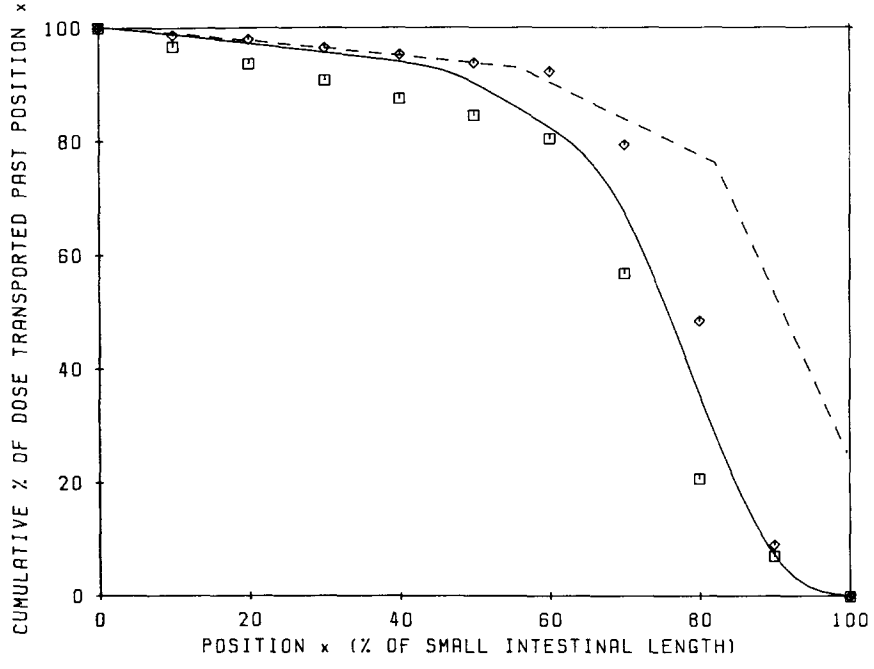

Fig. 1. Distribution of radioactive test markers. □, $Na_2^{51}CrO_4$; and ◇, ^{125}I-polyvinylpyrrolidine (PVP) in the small intestine of fasted rats (Poulakos and Kent, 1973) compared with model simulated distribution. Solid line, simulation with mixing, $F_{left} = 0.17$; dashed line, simulation with plug flow, $F_{left} = 0$.

ment with intestinal profiles (such as those shown in Figs. 1 and 2) resulted in unreasonable velocity values, or unrealistic transit times. It is important to note that Eqn. 2e is not directly comparable with observed velocity data, such as those of Sikov et al. (1969). Observed velocity data are also a function of mixing; i.e. the combined effect of Eqns. 1 and 2e.

Figs. 1 and 2 show a comparison of the simulated intestinal profiles with data from fasted and fed rats at time 60 min after gavage of a test marker (Poulakos and Kent, 1973). Figs. 1 and 2 show that the simulations fit the experimental data well. Table 1 shows the values used for the parameters in these simulations. It can be seen that the values for the parameters are different for the fed and the fasted case. This is to be expected, due to the major differences in the pattern of gut activity associated with the presence of food (Davenport, 1982). This is especially evident in the values for the parameter F_{left}. In the fed state, where much more mixing is expected, the value for F_{left} is higher. Conversely, in the fasted state, very little spreading of contents is observed experimentally, which is consistent with the low value found for the parameter F_{left} in simulations of fasted profiles. The dashed lines in Figs. 1 and 2 represent the simulated distribution of marker if no mixing occurs (i.e. plug flow; in our notation, $F_{left} = 0$). In the case of fasted rats little difference between the simulation with and without mixing is noted, whereas for fed rats the two profiles are significantly different. Simulated distribution profiles for plug flow (i.e. $F_{left} = 0$) are not smooth curves because linear interpolation is used to simulate stomach emptying. In simulations where mixing is present (i.e. $F_{left} > 0$) this effect is smoothed out.

Simulations of the data of Poulakos and Kent (1973) at earlier times showed similar agreement with observations to that presented in Figs. 1 and 2, but different parameter values were needed. Simulation based on a fixed set of parameter values did not show good agreement with the

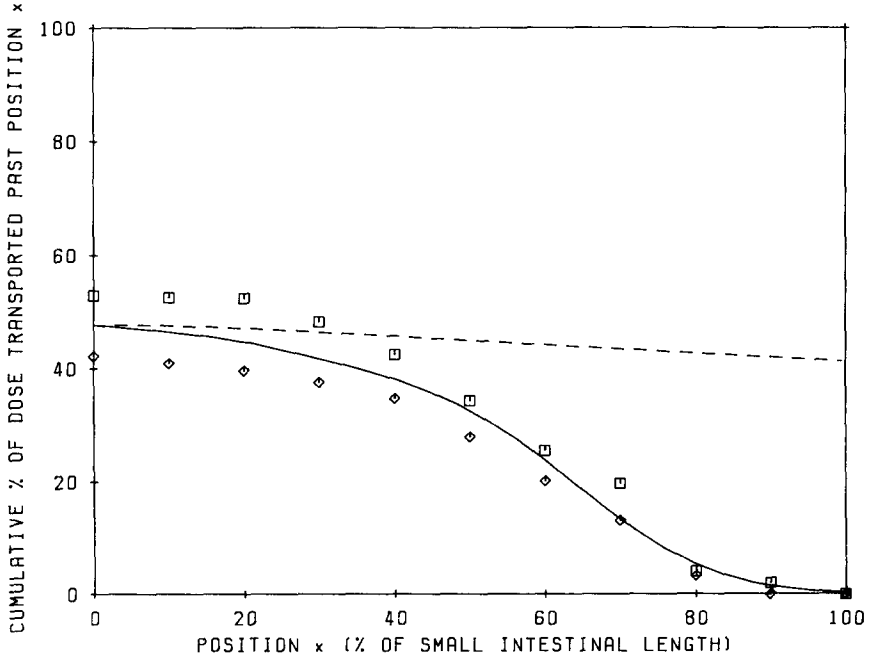

Fig. 2. Distribution of radioactive test markers. □, $Na_2^{51}CrO_4$ and ◇, ^{125}I-PVP in the small intestine of fed rats (Poulakos and Kent, 1973) compared with model simulated distributions. Solid line, simulation with mixing, $F_{left} = 0.8$; dashed line, simulation with plug flow, $F_{left} = 0$.

experimental profiles at all times. This suggests that a time-dependent velocity profile may be necessary. The need for a time-dependent velocity was not investigated intensively in the rat. The experimental data for rats were obtained by sacrifice of the animals, so there is the possibility of experimental artefacts due to post-mortem manipulations; also, test marker was administered by gavage, which may have prematurely forced material from the stomach into the intestine. These problems would have a greater effect on the early-time data than on the 60 min data. The possibility of time-dependent velocity was noted and investigated more thoroughly in the human simulations.

Parameter estimation for human simulations

As there are insufficient experimental data in man to enable characterization of each of the parameters independently, parameter estimation was carried out by indirect means. Preliminary assignments were made to provide reasonable values for transit times and velocities, then further adjustments were made to simulate the colonic arrival-time data discussed below.

Estimates of transit time vary widely; in a recent literature survey, Ho et al. (1983) found reports of transit time ranging between 73 min and 6 h. Davis et al. (1986) suggest that average transit time has a relatively constant value of 3–4 h and is independent of meal conditions and dosage form. However, the range of transit times measured in this study also varied widely, from about 1.3 to 9 h. The possibility that this variability is to some extent an artefact of the means of measurement is discussed later. As there is such a wide range of transit times reported in the literature, in simulations of the available experimental data we have adjusted the parameters to suit the transit time found for each of the individual experimental studies discussed below.

Table 2 shows the parameter values used for each of the human simulations.

TABLE 2

Parameter values used to obtain simulated profiles in man

Parameter	Value		
	Fig. 3	Figs. 4, 6	Fig. 5
a (%h^{-1}) [a]	700	610	610
b (h^{-1})	29	29	29
c (%) [a]	15	15	15
F_{left}	0.8	0.8	0.8
ϵ (min^{-1})	0.0025	0.001	0.0005

[a] % of intestinal length.

Simulation of transport in humans

Christensen et al. (1985) studied the transit of a 100 ml suspension of radiolabelled pellets along the intestine given with a 300 ml liquid nutrient meal. In this study, accumulation of the radioactive marker in the colon was used as the measure of transit time. Preliminary simulations were carried out using the stomach-emptying profile observed experimentally, and intestinal mixing according to Eqn. 1 with a time-independent velocity profile. This yielded simulated colonic profiles where the effective leading edge of the model marker arrives in the colon at approximately the correct time, but the rest of the marker arrives in the colon too quickly. The extent of mixing influences the effective velocity of the chyme; therefore an increase in the value of F_{left} is expected to slow down the rate of arrival of chyme in the colon. Even when this parameter is increased to almost 1, with a fixed transit time for the leading edge, model-predicted colonic arrival is still too fast; at $F_{left} = 1$ the chyme does not progress in the model, as theoretically all of the bolus is left behind during a jump.

Two possible explanations for the slow transit of the latter parts of the meal are that small intestinal transit time is a function of stomach-emptying rate, or that the velocity of chyme in the small intestine exhibits some dependence on the time that a particular meal remains in the GIT. Previous workers could not find any correlation between stomach-emptying rate and small intestinal transit time (Read et al., 1982). Therefore, simulations using a time-dependent velocity profile were carried out.

To incorporate time-dependence in the velocity profile the following equation was used for the time-dependent velocity V^*.

$$V^* = V e^{-\epsilon t} \tag{3}$$

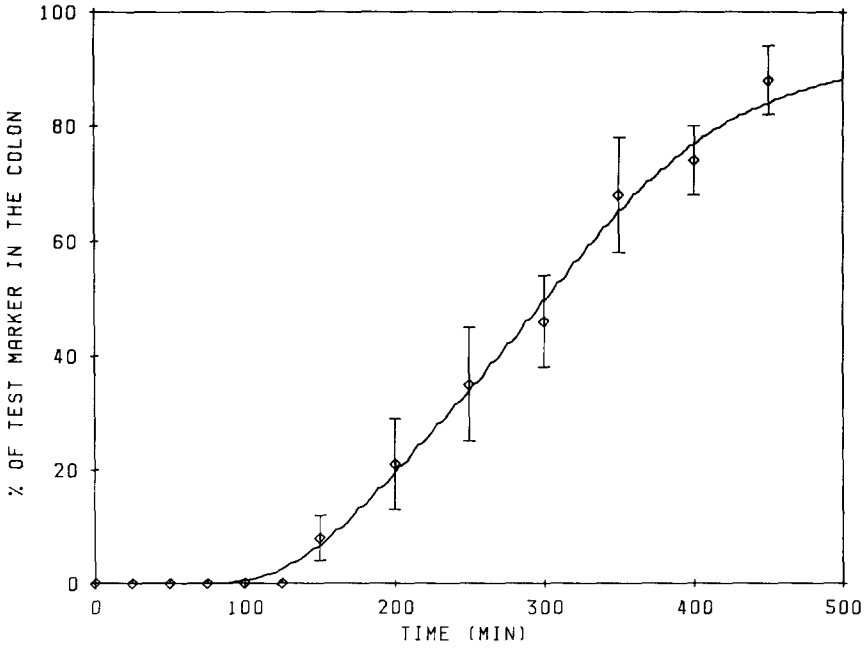

Fig. 3. Experimentally observed colonic arrival of test marker (mean ± S.E.M.) (Christensen et al., 1985) compared with model simulated colonic arrival.

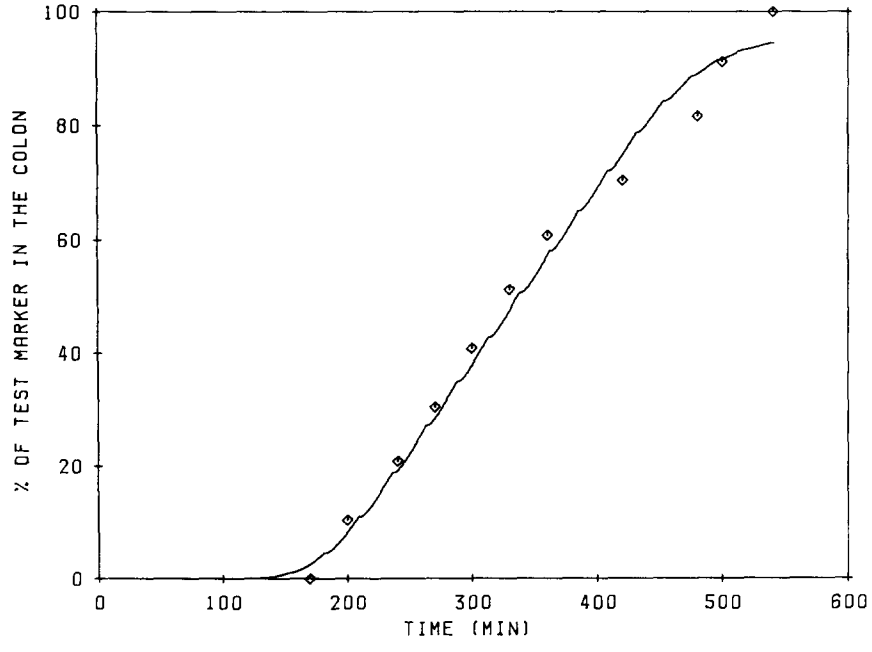

Fig. 4. Experimentally observed colonic arrival of test marker (Read et al., 1986) compared with model simulated colonic arrival.

where ϵ is a parameter, t is the time after administration of the meal that the bolus enters the duodenum and V is the time-independent profile described previously. For positive ϵ (found to be appropriate in the simulations) the velocity decreases exponentially with time. Simulations based on Eqn. 3 fit the experimental data significantly better than when transit time is held constant.

Fig. 3 shows a comparison of the fit obtained using a time-dependent velocity profile with the data of Christensen et al. (1985). The fit shown in Fig. 3 was subjected to non-linear regression to see if any improvement could be obtained. However, there was little improvement over the fit obtained by eye, due mainly to the large uncertainty in the data. However, in no case was there any tendency for the non-linear regression to set the parameter ϵ to zero, which would correspond to the case of a time-independent profile. Due to the model assumption of non-continuous movement, the simulation curves representing arrival of material in the colon are not smooth. There is a possibility that no bolus reaches the colon in any particular time interval; hence the curve is scalloped where there is a significant time interval in which no boluses arrive in the colon.

Simulations were also carried out for comparison with a study using radioactive test meals (Read et al., 1986). In this study mashed potato was labelled with ^{99m}Tc and the marker followed via γ-scintigraphy. Again, simulations with constant transit time did not fit the data well. Much improved fits were obtained when variable transit time was used as discussed above. Fig. 4 shows a comparison of the percentage of test marker in the colon versus time observed experimentally with that for the simulation. Parameter values for this simulation are similar to those used for the simulation of the data of Christensen et al. (1985), but slight adjustments were needed to obtain the best fit due to the differences in transit time observed experimentally in each study. This difference in observed transit time may be due to differences in the size and nature of the test meals used.

In order to investigate the effect of meal size further, simulations were obtained for comparison with the data of Davis et al. (1987). This study used pellets containing tiaprofenic acid and a re-

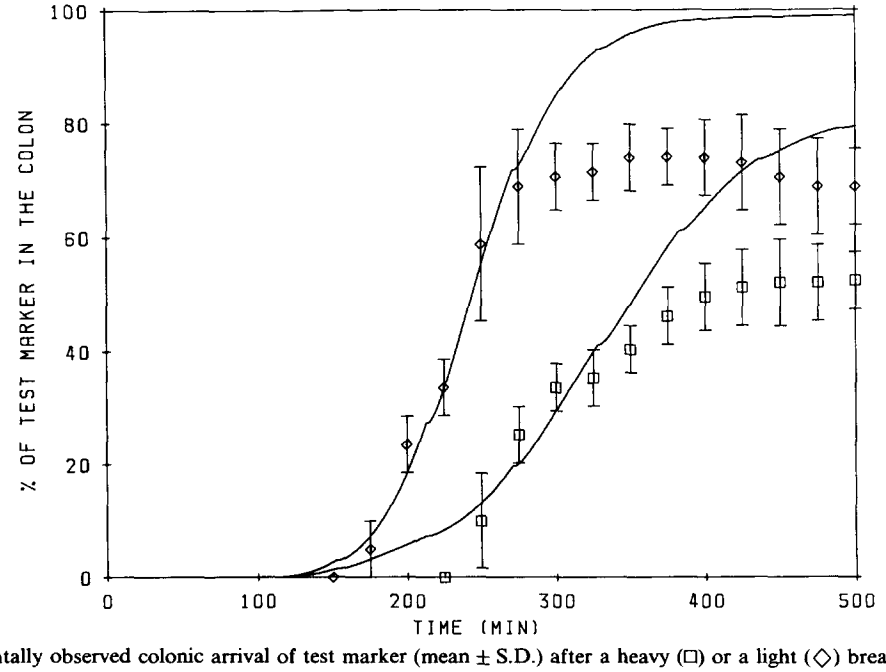

Fig. 5. Experimentally observed colonic arrival of test marker (mean ± S.D.) after a heavy (□) or a light (◇) breakfast (Davis et al., 1987) compared with model simulated colonic arrival for each meal.

sin onto which was adsorbed the γ-emitting label, [^{99m}Tc]sodium pertechnetate, as a non-absorbable marker. A γ-camera was used to follow the progress of these pellets along the small intestine after experimental subjects had eaten either a heavy or a light breakfast. Comparisons of the experimental profiles and the simulation profiles for the two breakfasts are shown in Fig. 5. Agreement at earlier times is good (especially for the light breakfast), but at later times there is considerable discrepancy. The most probable explanation for this disagreement is instability of the non-absorbable marker, as evidenced by the plateau at 70–80% of the dose in the experimental data. Stability studies discussed by Davis et al. (1987) show that 10% of the ^{99m}Tc-label was lost from the base resin in a study period of 5 h. Our model shows excellent qualitative agreement at earlier times, but deviated from the experimental data when the effect of this loss of label is likely to be most significant. The most significant aspect of these simulations is that the parameter values used to fit the early times in this simulation are almost exactly the same as for those for Read et al. (1986). Both studies followed the radioactive marker after solid food; the meal used in the Read study is closer in composition to the light breakfast used in the Davis study.

Measures of colonic arrival times are relatively insensitive to the velocity or transit time in the early part of the small intestine. This is because the transit time for the early segment, where material moves more rapidly, is a small proportion of the total transit time. It would be possible to have relatively large errors in the velocity function for the initial segment and at the same time reasonable agreement with observed colonic arrival times. This is potentially significant in view of the importance of the initial segment in drug absorption. To further investigate this possibility, simulations were carried out for a study conducted by Lagerlöf et al. (1974). In this study, markers (vitamin B_{12} modifications) were infused into the first 15 cm of the small intestine and sampled by an intraluminal tube at 75 cm. These observations are therefore sensitive to velocities in the initial

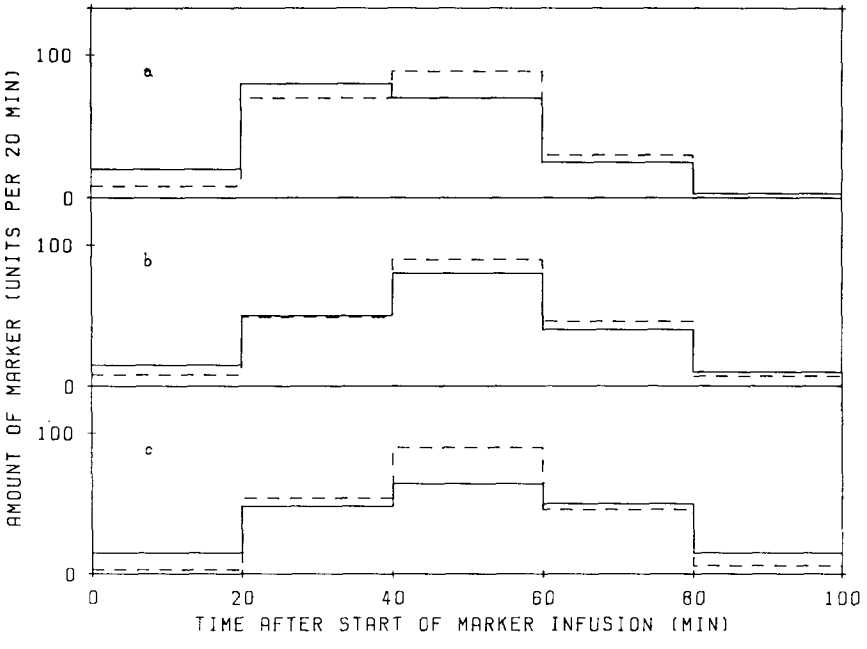

Fig. 6. Amount of marker at 75 cm following infusion into the small intestine at 15 cm at various times after a meal. Solid lines, experimental data (Lagerlöf et al., 1974); dashed lines, simulation. a: marker 1, infused from time 0–40 min after the meal. b: marker 3, infused from time 80–120 min after the meal. c: marker 5, infused from time 160–200 min after the meal.

segment (which in our model occupies the first 45 cm). The simulation used the same parameter values as for the Read study, reported in Table 2. The good agreement between simulated and observed data for 3 of the markers is illustrated in Fig. 6 (similar results were obtained for 3 other markers). The observations also indicate clearly the need for a mixing term (such as our F_{left}) in an intestinal transport model. The profiles differ substantially from those predicted by a compartment model (uniform with position) or by a plug flow model (a sharp leading edge, then uniform).

Another test of the performance of the model is to compare the velocities predicted by the model with the limited information available from direct measurements. In experiments using a dye dilution technique, Soergel (1971) measured intestinal flows over a period of 180 min after a test meal. Mean values of 2.2 cm · min^{-1} were reported for the jejunum and 1.5 cm · min^{-1} for the ileum. At this time terminal bolus velocity predicted by the model is 7.3–8.4 cm · min^{-1}. However, as a result of intestinal mixing, material in solution will not travel at the same velocity as the bolus but somewhat slower. The model predicts that the mean velocity $\overline{V}$ of intestinal contents is related to the bolus velocity V^* by the equation

$$\overline{V} = (1 - F_{left})V^* \quad (4)$$

With a value of F_{left} of about 0.8, found to be suitable in the simulations of colonic arrival times after food, we expect the value of $\overline{V}$ to be about 20% of the value of V^*. Thus, we expect dye in solution to travel at about 20% of the velocity of a bolus (1.5–1.7 cm · min^{-1}), in good agreement with observation.

Eqn. 4 may also help to explain some observations on the intestinal movement of large non-disintegrating objects. In an investigation into the behaviour of a non-disintegrating capsule in fasted subjects given 200 ml of orange juice and 100 ml of water with the capsule, Kaus et al. (1984) reported capsule speeds of 4.2–5.6 cm · min^{-1} in the jejunum and ileum during the study period. These values are very close to the model predictions of the bolus velocity, but substantially higher than the mean velocity for the simulations in Figs. 3–5, or the velocity measured by the dye dilution technique. Under the conditions of the study (small fluid volume, large non-disintegrating object) it is likely that intestinal movement is controlled by the interdigestive migrating motility complex (IMMC). Since the IMMC clears the GIT of solid residues, it is expected that the value of F_{left} in this case would be low (less mixing), and the solid object would be propelled at close to the bolus velocity. In the same study velocities > 25 cm · min^{-1} were reported in the duodenum. This result is consistent with the model predictions if we again suppose that the capsule travels at speeds near the bolus velocity (model predicted value 30–35 cm · min^{-1}).

Another study which looks at the transit of non-disintegrating devices is that of Davis et al. (1984). In this study 6 devices were given with a light breakfast. Some of the devices emptied early, with the meal, and these devices showed a transit time of about 180–240 min. The device which emptied later (~ 8 h after the meal) showed a shorter transit time of about 70–80 min. The latter value suggests that the device is being carried along with the IMMC (less mixing, faster transit). Transit times for those devices emptied with the meal were consistent with a value of F_{left} of about 0.8. In this case we cannot interpret F_{left} as the fraction left behind in a single jump, since the devices are non-disintegrating. Instead, we can take this to indicate that the device is propelled along the intestine with a bolus in 20% of jumps, and left behind in 80% of jumps. This interpretation is consistent with the interpretation for a dispersed material if the non-disintegrating object is randomly distributed within a bolus.

Discussion

The simulations presented here show an agreement with experimental observations of colonic arrival times, and data on transport over the first 75 cm of the small intestine, which is well within experimental error. Good agreement is also found between the model predictions and independent measures of velocity of intestinal contents. In addition, the model predictions agree with observed amount–position profiles in rats.

A number of different velocity profiles were examined as possible alternatives to the simple profile chosen for the simulations reported here. However, we cannot exclude the possibility of superior performance of some untried function. Similarly, the time-dependence we found necessary in our simulations could be implemented in other ways. For example, it might be possible to show similar behaviour with selected parameters varying with time or position (e.g. F_{left}). However, the available experimental data are probably insufficient to distinguish between these possibilities. We adopted the simplest option at the present stage of development of the model. It is likely that further refinement of simulation of longitudinal transport will be possible with further development of the model, for example by simulation of absorption of compounds with an absorption window to provide information on transport characteristics in the absorption region.

Eqn. 1, which expresses the basic assumptions about discontinuous movement, can be written in the form of a finite difference equation which can be solved analytically (see Appendix 2). However, all the simulations presented above were carried out numerically (see Appendix 1) using the finite difference form. This approach has a number of benefits. The present work is part of a larger program to develop a comprehensive model of drug absorption, incorporating transport of drug across the gastrointestinal membrane, water absorption and secretion, drug dissolution and a number of other features. All these processes are readily described within the framework of the model as presented here. These can all be treated as events which occur *between* jumps (since there is a relatively long period of quiescence between contractions (Davenport, 1982)), and the extension of the model to cover these events involves additional descriptions of the added features without any change to the transport model described here. By contrast, the use of analytical solutions will generally require a new integrated model to be solved with each new development. The present approach is also very flexible with respect to variation in the parameters of the trans-

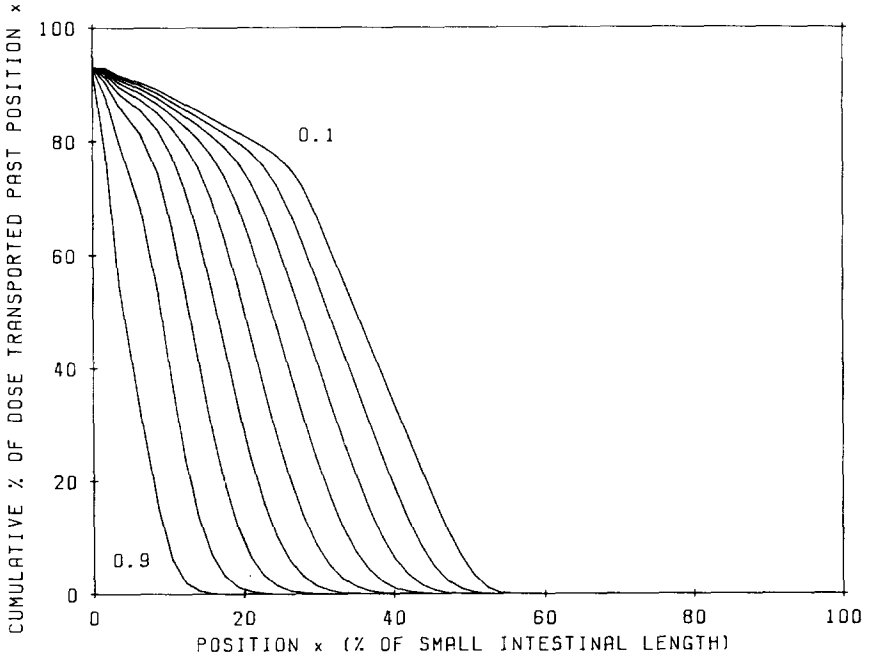

Fig. 7. The effect of F_{left} on the model simulated small intestinal distribution and the effective leading edge of test marker (velocity profile is the same for each curve, range of F_{left} is 0.1–0.9 in increments of 0.1).

port model. For example, if the influence on drug absorption of the pharmacological action of a second drug is of interest, it would be a simple matter to regard parameter values as a function of, say, the plasma concentration of the second drug as a function of time (but not so simple to specify the exact functional dependence). An analytical solution, on the other hand, would be much more difficult to obtain in this case.

A possible criticism of the present approach is that the numerical method used is actually a rather inefficient method for evaluating a partial differential equation, which our Eqn. 1 expresses in finite difference form. We take the contrary view that the processes involved in intestinal transport are intrinsically discontinuous, and that it is more appropriate to work directly with the finite difference forms, and to avoid the dubious assumption, which must be made to derive the partial differential forms, that the various functions involved are continuous.

One of the applications of the transport model is to simulate the distribution of material along the intestine at any time. This is an important feature when drug absorption is dependent on position within the intestine. The results presented here, as well as illustrating the significant effect that mixing has on the distribution of material within the small intestine, are of some interest in the interpretation of measurements of transit time. Fig. 7 shows typical profiles generated by various values of F_{left}. All of the curves were simulated using identical velocity profiles; the true leading edge for all of the simulations is at ~ 60% of the length of the small intestine. However, in an experimental study the detection of the leading edge depends on a measurement of limited sensitivity and the "effective" leading edge will be identified when the measurement exceeds some threshold value. It is apparent from Fig. 7 that, except for the very lowest values of F_{left}, the shape of the profile is such that the true and observed leading edges may be very different, and that the position of the observed leading edge of the test marker may be highly sensitive to the lower limit of detection. This observation may in part explain some of the extremely wide variation in intestinal transit times obtained using different techniques.

Appendix 1

This appendix describes some details of the implementation of the equations in the text.

As given in the text in Eqn. 1 we have

$$A(J, T+1) = (1 - F_{left})A(J, T) + F_{left}A(J-1, T) \qquad \text{(A1.1)}$$

where $A(J, T)$ is the amount in bolus J at the start of interval T and F_{left} is the fraction left behind during a jump. The first bolus formed is given the index $J = 1$ and J is incremented by 1 as each new bolus is formed. With a time increment of 1 min, bolus T is formed at the beginning of time interval T. Given the amounts in each bolus at time T, this equation is used to calculate the new distribution of material at time $T+1$, after a jump. The amounts in each bolus are stored as an array, updated for each new time interval.

Stomach emptying causes the formation of new boluses. While stomach emptying continues a new bolus is formed at the pylorus at the beginning of every interval. $S(I)$ denotes the amount of material emptied from the stomach at the beginning of time interval I. This can be calculated in various ways; e.g. using an exponential function for first-order emptying, using some other empirical function for stomach emptying, or by interpolation from numerical data. The IMMC can be simulated by taking $S(I) = 0$ for values of I corresponding to periods of quiescence, then $S(I)$ equal to the amount dumped into the duodenum per minute during active periods of the IMMC, followed by $S(I) = 0$ for a subsequent period of quiescence. The same formulation can be used to simulate experiments in which a drug or marker is infused into the upper duodenum.

The connection between stomach emptying and intestinal distribution and transport arises from the relation

$$A(T, T) = F_{left}A(T-1, T-1) + S(T) \qquad \text{(A1.2)}$$

That is, the amount in the bolus just formed at time T is the sum of the amount emptied from the

stomach and the amount left from the bolus formed in the previous interval.

The first few steps in the calculation of amounts are as follows. The amount in bolus 0 is taken as 0 in the calculations for bolus 1.

$$A(1, 1) = S(1)$$

$$A(1, 2) = (1 - F_{\text{left}})A(1, 1)$$

$$A(2, 2) = F_{\text{left}}A(1,1) + S(2)$$

$$A(1, 3) = (1 - F_{\text{left}})A(1, 2)$$

$$A(2, 3) = (1 - F_{\text{left}})A(2, 2) + F_{\text{left}}A(1, 2)$$

$$A(3, 3) = F_{\text{left}}A(2, 2) + S(3)$$

$$\vdots$$

This calculation provides values for the amount in each bolus, but it is also necessary to track the position of each bolus. The current position of bolus J is stored in the array *Pos(J, T)*. If $V^*(J, T, X)$ is the velocity of bolus J at time T at position X, the position of each bolus is calculated using the relation

$$Pos(J, T+1) = Pos(J, T) + V^*(J, T, Pos(J, T)) \tag{A1.3}$$

If a time interval other than 1 min is used, the second term on the right should be multiplied by the time interval.

A bolus is emptied into the colon once it has travelled the length of the simulated small intestine. When *Pos(J, T)* exceeds this length, the contents of the bolus are accumulated with the amount in the colon and further calculations are continued only with later boluses.

The evaluation of these equations over the simulation time produces data which can provide various forms of output. For example:

(1) An amount versus position profile at a particular time can be obtained by referencing $A(J, T)$ for the amount and *Pos(J, T)* for the corresponding position.

(2) The cumulative % marker past a position can be estimated by first calculating the largest value of J (call it $J_{\max}$) for which *Pos(J, T)* exceeds the required position value, then summing the $A(J, T)$ values for all $J \leqslant J_{\max}$, including any marker emptied into the colon (Figs. 1 and 2 of the text). Alternatively (and this must be done if absorption occurs) the required amount can be estimated by accumulating the contents of each bolus as it jumps past the required position.

(3) The cumulative amount of drug or marker in the colon as a function of time can be obtained, as indicated above, by accumulation of the amount array, A, for those boluses J for which $Pos(J, T)$ exceeds the length of the small intestine.

Appendix 2

This appendix presents an analytical solution to Eqn. 1 of the text. This solution may be of use for theoretical considerations of the influence of the factors involved on intestinal profiles, but for numerical evaluation the finite difference forms discussed in Appendix 1 are more convenient.

Eqn. 1 of the text is

$$A(J, T+1) = (1 - F_{\text{left}})A(J, T) + F_{\text{left}}A(J-1, T) \tag{A2.1}$$

As a result of mixing, bolus J at time T contains material originating from amounts emptied from the stomach at all earlier times; i.e. from amounts $S(I)$, $I = 1, 2, \ldots, J$ where $S(I)$ is the amount emptied into the intestine at the beginning of interval I. Therefore we can write

$$A(J, T) = \sum_{I=1}^{J} \Phi(I, J, T)S(I) \tag{A2.2}$$

where $\Phi(I, J, T)$ is the fraction of $S(I)$ which ends up in bolus J at time T. To simplify discussion we say that a jump occurs when material is carried along with an advancing bolus and that a lag occurs when material is left behind to merge with the trailing bolus. This means that a contribution from $S(I)$, formed at time I, has executed

a total of $T-I$ lags and jumps at time T. A contribution to bolus J must experience $J-I$ lags and $T-J$ jumps. Therefore the fraction of material from $S(I)$ which reaches bolus J by a particular sequence of lags and jumps is $F_{\text{left}}^{J-I}(1-F_{\text{left}})^{T-J}$, the same for any sequence. However, there is more than one sequence starting from I and ending at J: the total number is the number of ways of selecting $J-I$ entities from $T-I$ entities, namely the binomial coefficient

$$\begin{bmatrix} T-I \\ J-I \end{bmatrix} = \frac{(T-I)!}{(T-J)!(J-I)!} \qquad \text{(A2.3)}$$

Adding the separate contributions from each sequence we get

$$\Phi(I, J, T) = \begin{bmatrix} T-I \\ J-I \end{bmatrix} F_{\text{left}}^{J-I}(1-F_{\text{left}})^{T-J} \qquad \text{(A2.4)}$$

Combining Eqns. A2.4 and A2.2 and rearranging we obtain the solution to Eqn. A2.1 as

$$A(J, T) = \frac{F_{\text{left}}^{J}(1-F_{\text{left}})^{T-J}}{(T-J)!} \times \sum_{I=1}^{J} \frac{(T-I)!}{(J-I)!} F_{\text{left}}^{-I} S(I) \qquad \text{(A2.5)}$$

The solution can be verified by direct substitution into Eqn. A2.1.

References

Amidon, G.E., Ho, N.F.H., French, A.B. and Higuchi, W.I. Predicted absorption rates with simultaneous bulk fluid flow in the intestinal tract. *J. Theor. Biol.*, 89 (1981) 195–210.

Bloch, R., Ingram, D., Sweeney, G.D., Ahmed, K. and Dickinson, C.J., MacDope: a simulation of drug disposition in the human body. Mathematical considerations. *J. Theor. Biol.*, 87 (1980) 211–236.

Christensen, F.N., Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R. and Wilson, C.G., The use of gamma scintigraphy to follow the gastrointestinal transit of pharmaceutical formulations. *J. Pharm. Pharmacol.*, 37 (1985) 91–95.

Christensen, J., Glover, J.R., Macagno, E.O., Singerman, R.B. and Weisbrodt, N.W., Statistics of contractions at a point in the human duodenum. *Am. J. Physiol.*, 221 (1971) 1818–1823.

Clements, J.A., Heading, R.C., Nimmo, W.S. and Prescott, L.F., Kinetics of acetaminophen and gastric emptying in man *Clin. Pharmacol. Ther.*, 24 (1978) 420–431.

Davenport, H.W., *Physiology of the Gastrointestinal Tract,* Year Book Medical Publishers, Chicago, 1982.

Davis, S.S. Hardy, J.G. and Fara, J.W., Transit of pharmaceutical dosage forms through the small intestine. *Gut*, 27 (1986) 886–892.

Davis, S.S., Hardy, J.G, Taylor, M.J., Whalley, D.R. and Wilson, C.G., The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet). *Int. J. Pharm.*, 21 (1984) 331–340.

Davis, S.S., Khosla, R., Wilson C.G. and Washington, N., Gastrointestinal transit of a controlled-release pellet formulation of tiaprofenic acid and the effect of food. *Int. J. Pharm.*, 35 (1987) 253–258.

Ho, N.F.H., Merkle, H.P. and Higuchi, W.I., Quantitative, mechanistic and physiologically realistic approach to the biopharmaceutical design of oral drug delivery systems. *Drug Dev. Ind. Pharm.*, 9 (1983) 1111–1184.

Hopkins, A., The pattern of gastric emptying: a new view of old results. *J. Physiol. (Lond.)*, 182 (1966) 144–149.

Hunt, J.N. and Stubbs, D.F., The volume and energy content of meals as determinants of gastric emptying. *J. Physiol. (Lond.)*, 245 (1975) 209–225.

Hunter, E., Fell J.T. and Sharma, H., The gastric emptying of pellets contained in hard gelatin capsules. *Drug Dev. Ind. Pharm.*, 8 (1982) 751–757.

Kaus, L.C., Fell, J.T., Sharma H. and Taylor, D.C., On the intestinal transit of a single nondisintegrating object. *Int. J. Pharm.*, 20 (1984) 315–323.

Kelly, K.A., Motility of the stomach and the gastroduodenal junction. In L.R. Johnson (Ed.), *Physiology of the Gastrointestinal Tract, Vol. 1,* Raven, New York, 1981, pp. 393–410.

Lagerlöf, H.O., Johansson, C. and Ekelund, K., Studies of gastrointestinal interactions. VI. Intestinal flow, mean transit time, and mixing after composite meals in man. *Scand. J. Gastroent.*, 9 (1974) 261–270.

Lew, H.S., Fung, Y.C. and Lowenstein, C.B., Peristaltic carrying and mixing of chyme in the small intestine (an analysis of a mathematical model of peristalsis of the small intestine). *J. Biomechanics*, 4 (1971) 297–315.

Ni, P.F., Ho, N.F.H., Fox, J.L., Leuenberger H. and Higuchi, W.I., Theoretical model studies of intestinal drug absorption V. Non-steady-state fluid and absorption. *Int. J. Pharm.*, 5 (1980) 33–47.

Poulakos, L. and Kent, T.H., Gastric emptying and small intestinal propulsion in fed and fasted rats. *Gastroenterology,* 64 (1973) 962–967.

Read, N.W., Al-Janabi, M.N., Holgate, A.M., Barber, D.C. and Edwards, C.A., Simultaneous measurement of gastric emptying, small bowel residence and colonic filling of a solid meal by the use of the gamma camera. *Gut*, 27 (1986) 300–308.

Read, N.W., Cammack, J, Edwards, C., Holgate, A.M., Cann P.A. and Brown, C., Is the transit time of a meal through the small intestine related to the rate at which it leaves the stomach. *Gut*, 23 (1982) 824–828.

Sikov, M.R., Thomas J.M. and Mahlum, D.D., Comparison of passage of a tracer through the gastrointestinal tract of neonatal and adult rats. *Growth*, 33 (1969) 57–68.

Soergel, K.H., Flow measurements of test meals and fasting contents in the human small intestine. In L. Demling and R. Ottenjann (Eds.), *Gastrointestinal Motility: International Symposium on Motility of the GIT, 1969,* Academic, New York, 1971.