Heterogeneous Tube Model for the Study of Small Intestinal Transit Flow

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Purpose. A Monte-Carlo computer simulation technique was employed to study the details of the small intestinal transit flow in the gastrointestinal (GI) tract.

Methods. A heterogeneous tube model was constructed using a numerical computer simulation technique. The model was built from first principles and included several heterogeneous characteristics of the GI tract structure. We used a random, dendritic-type internal structure representing the villi of the GI tract. The small intestinal transit flow was simulated using two diffusion models, namely, the blind ant and the myopic ant models, which are different models to account the elapse of time, and which are both based on statistical properties of random walks. For each one of the models we utilize two types of biased random walk, placing different emphasis in the motion towards the output of the tube. We monitored the flow of the drug in terms of Monte-Carlo time steps (MCS) through the tube walls and dendritic villi present.

Results. The frequency of the transit times was dependent on the structure of the dendritic villi and on the type of biased random walk. The small intestinal flow profile of literature data for a large number of drugs was well characterized by the heterogeneous model using, as parameters, a certain number of villi per unit length of the tube and specific characteristics for both types of the biased random walk. A correspondence between the MCS and real time units was achieved.

Conclusions. The transit process of the oral dosage forms in the GI tract can be reproduced with the heterogeneous model developed. This model can be used to study GI absorption phenomena.

KEY WORDS: heterogeneous; tube; model; intestinal; transit; flow.

INTRODUCTION

The complexity of the gastrointestinal (GI) tract has led to the use of simple models for the study of oral drug absorption. Thus, compartmental models with one or more serial compartments have been developed to study a variety of GI absorption and relevant phenomena, such as dose-dependent absorption (1), dissolution controlled absorption (2,3), effect of bile sequestrants on bile salt excretion (4), double peak phenomenon (5), and small intestinal transit flow (6). In addition, the tube model in which physiological characteristics, such as the volume of intestinal fluids and the volumetric flow rate have been incorporated, has been used for estimating the extent of the drug absorption (7,8). In parallel, a dispersion model with constant input rate has been utilized to simulate oral drug absorption (9) and to analyze the small intestinal transit flow in humans (6).

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Undoubtedly, all these models accompanied with the assumptions of perfect mixing and/or homogeneous flow represent oversimplifications of the reality given the enormous complexity of the GI tract (10), both in terms of structure and function, e.g., villi, microvilli, motility, as well as the variety of dosing conditions, e.g., fed or fasted state, fluid volume administered, etc. Since the fundamental process for all GI absorption phenomena is the small intestinal transit flow, this study utilizes a heterogeneous model to characterize the intestinal transit process in humans. To this end, we use a tube model in which several heterogeneous features of the GI wall structure and of the drug flow in the intestine are introduced.

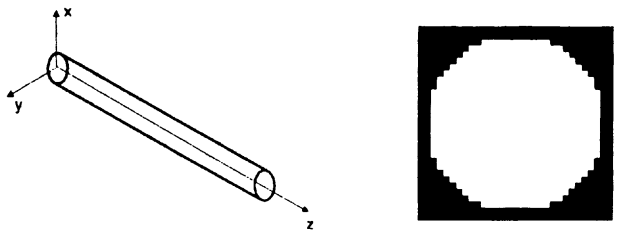
Since the structure of the GI tract is highly complicated it is practically impossible to write down and solve the equations of motion for the drug flow. We, therefore, resort to a numerical computer simulation technique that incorporates the desired features. We build a Monte-Carlo algorithm from first principles, in which we initially prepare the complicated system structure, and subsequently perform the drug flow. This technique, based on principles of statistical physics, generates a microscopic picture of the system, in our case of the GI tube. The desired features of the complexity are built-in in a random fashion. During the calculation all such features are kept frozen in the computer memory (in the form of arrays), and are utilized accordingly. The principal characteristic of the method is if a very large number of such units is built, then the average behavior of all these will approach the true system behavior. Thus, we typically utilize a structure of several million units in size. Such techniques have proven to be highly successful in problems of a similar nature to the present one. Nevertheless, we do not intend to give a universal solution to drug flow, dissolution, and absorption with this model. Rather, our purpose is to check if a proposed simple mechanism is in agreement with the current experimental evidence available. It is understood that this is the very first approximation, and further improvements are to follow. Any possible limitations that may appear on the way will have to be adjusted accordingly.

METHODS

Construction of the Heterogeneous Tube

Our model is constructed by use of a cylinder whose length is several orders of magnitude larger than the size of its radius. Thus, we can ignore any entanglements present, as they do not influence the dynamics taking place in it, while we consider the structure to be mostly 1-dimensional. Initially we start with a three dimensional parallelepiped with a square cross section, of size x:y:z equal to 31:31:3000, Figure 1a. Inside it we build a cylinder with a radius of 14 units, a cross-section of which appears in Figure 1b. Hence, the quotient of (radius/length) = 14/3000 in our tube model is quite similar to the ratio of physiological data 1.3 cm/3 m for the human small intestine.

All work can be performed in continuous space, but for convenience in the calculations we use an underlying lattice of discrete spacings, forming in effect a 3-dimensional grid. This grid covers the entire cylinder, while for all spatial considerations we utilize the grid sites. The interior of the cylinder has a finite concentration of villi attached to the cylinder wall, which possess the property to possibly absorb the dissolved



(a) (b)

Fig. 1. (a) The cylinder used for the tube construction, and (b) cross-section of the tube.

drug particles flowing through the cylinder. The villi have the usual random dendritic structure and are formed by the diffusion limited aggregation (DLA) method (see below). The absorption of the drug particles in the model takes place when a flowing particle happens to have a position right next to the villi coordinates, implying that when a particle comes in contact with a villi structure it can be absorbed. The probability for absorption by the villi or walls is k_a. Since, in the present work, we concentrate in the tube structure and on the characteristics of the flow, we take $k_a = 0$, while the case of $k_a \neq 0$ will be treated elsewhere.

The villi have a random dendritic-type structure and are formed initially by use of an algorithm based on the well known DLA (11) model from solid state physics. We place 2z seed particles (z the cylinder length) on the cylinder surface by positioning 2 particles on each z value at random positions. Following the DLA model, another particle, starting at a random point of each cross-section, makes a three dimensional random walk (diffusion) inside the cylinder. The walk stops when a moving particle visits any of the neighbor sites of the original seed particles. At this points it stops and gets attached to the neighboring seed particle. The particle is confined to move inside the cylinder. Then, a second particle starts a random walk until it meets either one of the seeds or, the already "frozen" particle. The process continues and, using a total of N particles per length unit, we build the internal structure of the tube, which can be of varying complexity. The size of each villi cluster is limited to the value $1.5N$. This is done in order to achieve a uniform distribution of villi cluster sizes. The higher the N value, the more ramified the ensuing structure. A few examples of various values of N are shown in Figure 2. This Figure shows typical 2-dimensional cross-sections of the cylinder for four different N values, N = 50, 100, 150, and 200, at random places. We clearly see how the villi complexity is built up with increasing N. We note here that there are some squares that appear not to be connected to any others in these pictures. In fact, these are indeed connected to adjacent (first neighbor) squares in the next or previous cross-section of the tube (i.e., with $z' = z + 1$ or $z' = z - 1$), which are not shown in this figure.

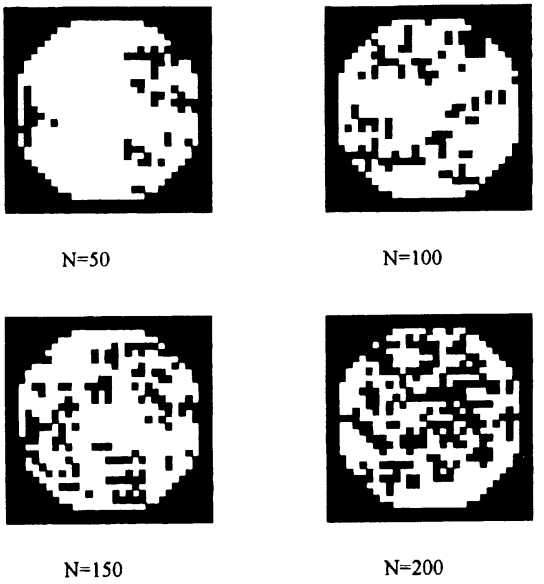


Fig. 2. Cross-sections of the tube for various concentrations of villi. N = *50, 100, 150, 200* particles per length unit of the cylinder. The positions where the cross-sections were taken are random. See text for the explanation of how the villi structure was prepared using the N parameter. In all cases the higher the N value the more ramified is the ensuing structure.

Dynamics

The dynamics of the system is also followed by utilizing the Monte-Carlo technique, as in the formation of the heterogeneous tube structure. This includes motion of the particles through the tube, dissolution in the solvent flow, and absorption by the villi or the tube walls. Time is incremented by arbitrary time units, called Monte-Carlo steps (MCS), during which a variety of events takes place. One MCS is the smallest time unit in which an event can take place. This is typically defined as the time it takes for a particle to move to one of its neighbor positions. A pill can be inserted in one end of the tube (input end) at predefined time increments expressed in MCS. A pill is modeled as an aggregate of drug particles of mass M = 100. This means that one pill can later be broken down successively to 100 units which represent the solid drug particles. These can be further dissolved in the encompassing solution. But as long as the pill has a mass larger than one (1) it cannot be dissolved in the solution. All pills and dissolved particles flow through the cylinder from the input end towards the direction of the other end (output end). This is done by using a diffusion model of a biased random walk that simulates the fluid flow. A simple random walk is the prototype model of the regular Brownian motion. Such a model is modified here by including a bias factor, which makes the motion ballistic rather than simply stochastic. This bias factor, ϵ, increases the probability for motion in the z-direction, i.e., towards the output end, as compared to the probabilities in all other directions. This makes the flow of the particles and the dissolved drug molecules possible. If $\epsilon = 0$, then there is a motion but it is rather stationery and in all possible directions. If $\epsilon > 0$, then this makes the flow possible. The rate of flow is also directly affected by the numerical value of ϵ, with increasing ϵ values resulting in increasing flow rates. With this statistical model the diffusing species can momentarily go against the flow or sideways. This is a realistic feature but, it occurs with reduced probability. We are interested only in the motion of the drug species in the medium and thus, we do not follow the motion of the solvent.

We use two different models of the biased random walk. In model I the three directions of space, x, y, and z are all

equally probable but in the z direction, the probability towards the output end (z+) is now $1/z + \epsilon$, while the corresponding probability towards the input end (z−) is $1/z - \epsilon$ (where z is the coordination number of the underlying space, e.g., $z = 6$ in a three dimensional space). This model has the characteristic of diffusion being equally probable in all possible directions, the species spending equal times in all of them but, due to the ϵ factor, when the z direction is chosen a positive flow drives the solution to the output end. In a second model, model II, we give more emphasis to the motion towards the output and less to the other directions. The probabilities for motion in the different directions are now defined differently. While in the simple random walk the probability for motion in a specific direction is $1/z$, here the probability for motion in the output direction is $1/z + \epsilon$, while the probability in any of the other five directions is:

$$\frac{1 - \left(\frac{1}{z} + \epsilon\right)}{z - 1} \tag{1}$$

Thus, the values that ϵ can take is in the range

$$0 < \epsilon < 1 - \frac{1}{z}, \tag{2}$$

while the overall forward probability (fp), i.e., the probability towards the output end, is in the range:

$$\frac{1}{z} < fp < 1 \tag{3}$$

At each time step there is a probability (k_d) for the pill to dissolve, *i.e.* $0 < k_d < 1$. In the Monte-Carlo method every pill is tested at every step to find out if a fragment (one new particle) is to be released. When this happens a fragment of the pill with mass $m = 1$ breaks off and gets separated from the larger mass. It is understood that this $m = 1$ particle is immediately dissolved, and it is never reattached to the original mass. This dissolved particle now performs a random walk of its own, with the same characteristics (bias) as the main pill. The mass (M) of the pill is then reduced by m. When a pill (or a fragment), reaches the end of the tube then it is discarded.

At the end of the simulation time we compute the mass that has exited from the end of the tube. We also keep track of the time it took for the particles to reach the end of the tube, so we can compute the mean transit time.

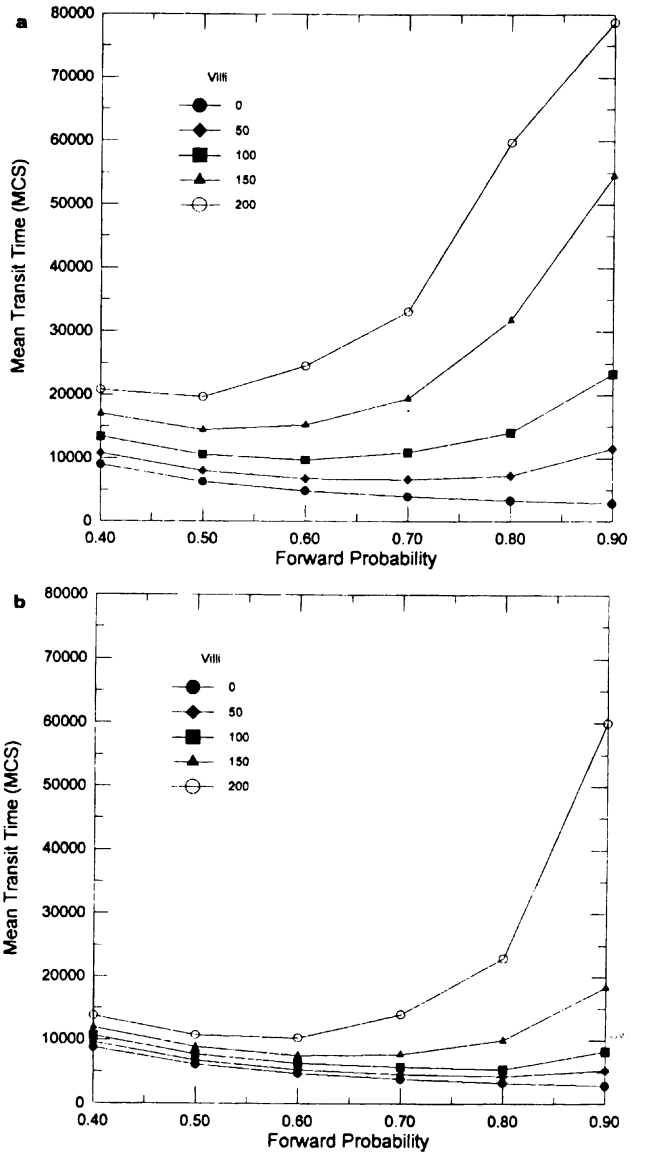


Fig. 3. Mean transit time (MCS) vs. the forward probability for various concentrations of villi. One MCS is defined as the time it takes for a particle to move to one of its neighbor positions. From top to bottom $N(villi) = 200, 150, 100, 50, 0$. (a) Blind ant model. (b) Myopic ant model. See text for the explanation of how the villi structure was prepared using the N parameter. In all cases the higher the N value the more ramified is the ensuing structure.

RESULTS AND DISCUSSION

In order to study the kinetic properties of the model we use a large number of drug particles (10000) with mass $m = 1$ inserted simultaneously at time $t = 0$ in the tube and which are allowed to diffuse. To concentrate on the transit process we used $k_d = 1$, so dissolution is instantaneous. The absorption constant was set to zero ($k_a = 0$), so as not to allow any particles to be absorbed. The simulation continues until all the drug fragments exit the tube.

While diffusion of particles in regular homogeneous space is a tractable problem, even in certain cases of biased diffusion, this is not so for diffusion in the presence of obstacles, traps, fractal objects, etc. Some of these cases constitute well known problems with no analytical solution, due to the complexity present and thus, only approximations and limiting cases can be described. Although there is difficulty, these problems have a continued interest because many technological aspects are based on such a picture. The problem we have here is in this class of situations. When the diffusing species come in contact with a closed site (such as the villi sites in our case) there are two options we can take. In the first option, the particle does not "feel" the presence of the closed site, and it may attempt, unsuccessfully, to go to it. This model is called the "blind ant" model. In the second model, the particle feels the presence of the closed site and thus, it never attempts to land on it. This is called the "myopic ant" model. The difference between these two models is the blind ant consumes a long amount of time

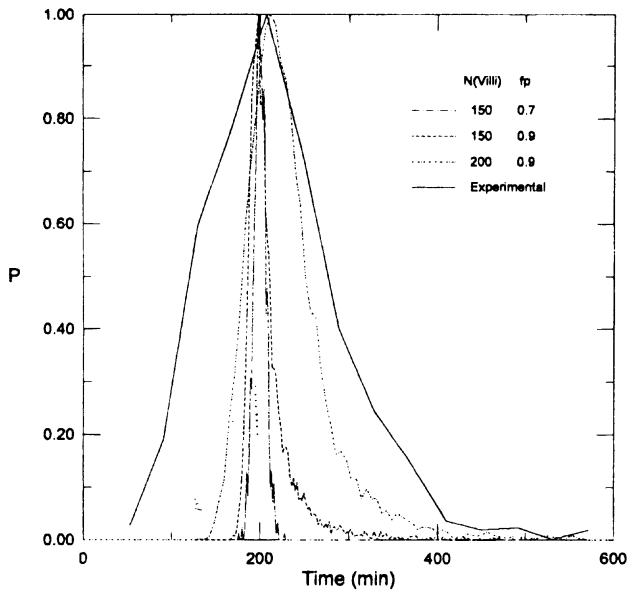


Fig. 4. Frequency of mean transit times versus time (min) for various different $N(villi)$ and forward probability (fp) values, using diffusion model I, for the blind ant model. The values are shown in the figure. The experimental data were taken from Fig. 3 of Ref. 6.

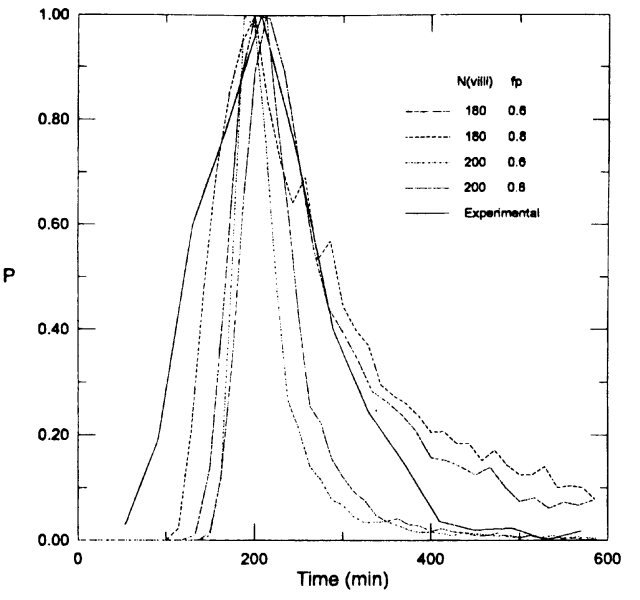


Fig. 6. Frequency of mean transit times versus time (min), using diffusion model II for the myopic ant model, for various different $N(villi)$ and forward probability (fp) values. The values are shown in the figure. The experimental data were taken from Fig. 3 of Ref. 6.

in unsuccessful attempts and thus, its motion is slower than the myopic ant case.

The details of the flow of particles in the heterogeneous tube were studied using model II biased random walk. In Figure 3 we plot the mean transit time of the drug particles versus the forward probability (i.e., the probability towards the output along the z-axis), for various villi concentrations, for the two cases of blind ant (part a), and the myopic ant (part b). For no villi structures ($N(villi) = 0$) and for $N(villi) = 50$ we observe

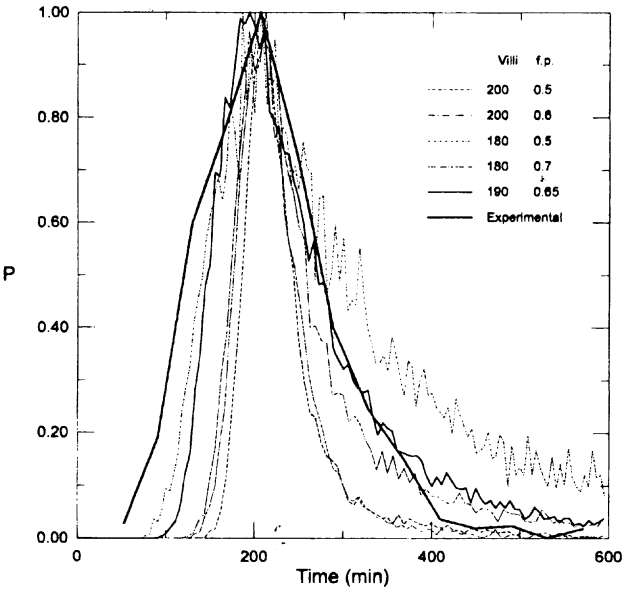


Fig. 5. Frequency of mean transit times versus time (min), using diffusion model II for the blind ant model, for various different $N(villi)$ and forward probability (fp) values. The values are shown in the figure. The experimental data were taken from Fig. 3 of Ref. 6.

that for larger forward probability values the transit time of the particles were shorter, as one would expect. For larger villi concentrations the transit time became longer as we increased the forward probability. This behavior may seem inconsistent, but can be easily explained if we consider that when a drug fragment meets an obstacle (villi) then its forward motion is hampered, and it must move in the x or y directions (sideways) in order to circumvent it and continue moving towards the end of the tube. It happens that when the forward probability values are large then the probability for movement in the x or y axis is reduced. This does not give the particle the freedom to easily surpass the obstacle, so it wastes time trying to move in the z direction. This explains the rise in the transit times which is larger for larger villi concentrations. This qualitative picture is valid for both models in parts (a) and (b) of Fig. 3. When we compare the two figures we observe the transit times are always longer in the blind ant case for any villi concentration. This is so, because as expected and described above, the blind ant wastes considerably more time in unsuccessful attempts, while the myopic ant finds more easily and faster its way out of the villi labyrinths resulting in a smaller mean transit time.

The system behavior as shown in Figure 3 implies the interplay of these two factors, namely the villi structure and the bias probability (flow rate) is important in determining the dynamics of the flow. At this point, it is important to use existing experimental data in order to determine a realistic set of parameters to characterize the intestinal transit process in humans. Additionally, this comparison will provide a direct correspondence of time units, i.e., will give the length of 1 MCS in real time units. We compared the frequency of transit times resulting from our simulations for various values of villi and forward probability with experimental data (6), and some of these results are shown in Figures 4–6. In Figure 4, we give the results for model I of the biased diffusion together with the experimental data. We varied the two parameters, i.e. the bias

factor ϵ, and the villi concentration N in a wide range. It is then seen we do not achieve a good agreement for any combination of parameters. In Figure 5 we use model II of biased diffusion, again for a wide range of parameters, and observe that we achieve a much better agreement. Actually the difference between these two figures lies mainly in the width of the curves. Model I consistently produces narrower frequencies than model II and the experiments. This is because in model I motion in the preferred z direction occurs with the same frequency as motion in the other directions. The effect of the flow along the tube length is downplayed, as opposed to the other model (II), in which it is emphasized. By occurring more often, motion along the tube length covers a wider frequency of transit times (i.e., both slower and faster) resulting in a wider overall frequency curve. The best resemblance between simulation and experimental data was achieved for the values of $N(villi) = 190$ and forward probability = 0.65. We clearly see the entire frequency function is necessary in order to make a meaningful comparison, while only the average value is not adequate. The x-axis here is in units of minutes. This is done by establishing a correspondence of 1 sec = 1.5 MCS, since this is the value that produces the best possible fit. For these plots we again used only the kinetic properties of the model, i.e., $k_a = 0$.

Finally, in Figure 6 we give the results for the myopic ant model, which are seen to be quite similar to the blind ant model of the previous figure, and also, in good agreement with the experimental data. This is expected because the transit times in the two models of the blind and myopic ant are not very different. As it was seen in Fig. 3, the difference between the two models is typically a few percent points, and in the worst case, it is a factor of 2, depending on the forward probability chosen. This results in frequency curves which are shaped quite similar, and which are in close agreement to the experimental data.

CONCLUSIONS

The heterogeneous tube model developed provides a new tool for the study of the intestinal transit flow. It was shown, that the biased random walk which places more emphasis in the motion towards the output end and less to the other directions, mimics more closely the transit profile of the experimental data. Both diffusion models, i.e., the blind and the myopic ant models, can reproduce the basic features of the real small intestinal transit profile.

It should be noted here, that the parameter values for the villi structure and the diffusion rate that best fit the experimental data should not be interpreted as the only and exact solution for this problem. Our purpose has not been to accurately determine these values using a rather crude simulation model but rather, to give a qualitative picture and explanation of how one can assign a model with realistic features to current experimental data. Currently, the heterogeneous model is being utilized to study dissolution and absorption phenomena in the GI tract.

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