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Commentary

Gastrointestinal Drug Absorption: Is It Time to Consider Heterogeneity as Well as Homogeneity?

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The current analysis of gastrointestinal absorption phenomena relies on the concept of homogeneity. However, drug dissolution, transit and uptake in the gastrointestinal tract are heterogeneous processes since they take place at interfaces of different phases under variable stirring conditions. Recent advances in physics and chemistry demonstrate that the geometry of the environment is of major importance for the treatment of heterogeneous processes. In this context, the heterogeneous character of *in vivo* drug dissolution, transit and uptake is discussed in terms of fractal concepts. Based on this analysis, drugs are classified in accordance with their gastrointestinal absorption characteristics into two broad categories i.e. homogeneous and heterogeneous. The former category includes drugs with satisfactory solubility and permeability which ensure the validity of the homogeneous hypothesis. Drugs with low solubility and permeability are termed heterogeneous since they traverse the entire gastrointestinal tract and therefore are more likely to exhibit heterogeneous dissolution, transit and uptake. The high variability of whole bowel transit and the unpredictability of conventional dissolution tests for heterogeneous drugs are interpreted on the basis of the fractal nature of these processes under *in vivo* conditions. The implications associated with the use of strict statistical criteria in bioequivalence studies for heterogeneous drugs are also pointed out.

KEY WORDS: gastrointestinal absorption; fractal; fractal kinetics; heterogeneity; bioequivalence.

Most research in gastrointestinal (GI) absorption is based on the concept of homogeneity, that is, the description of average behavior. Some of the most often used paradigms are those borrowed from chemical engineering literature to model hydrodynamics, permeability, and absorption. For example, in the field of dissolution testing, a well stirred (homogeneous) dissolution medium is used to mimic the *in vivo* conditions (1). Calculations associated with the effective intestinal permeability or the unstirred water layer thickness in permeability studies assume that the hydrodynamics of the solution in the intestinal segment obeys the well-stirred model (2). The tank and tube models, often used for the analysis of drug dissolution and uptake in the GI tract (3–5), are accompanied with the assumptions of perfect mixing and homogeneous flow, respectively.

One can argue, however, that the assumptions of homogeneity and well stirred media are not only not obvious, but that they are in fact contrary to the evidence given the anatomical and physiological complexity of the GI tract. Both *in vivo* drug dissolution and uptake are heterogeneous processes since they take place at interfaces of different phases i.e liquid-solid and liquid-membrane boundaries, respectively. In addition, both processes occur in heterogeneous environments i.e. variable stirring conditions in the lumen. The mathematical currently-used analysis of all models (1–5) relies furthermore on the assumption that an isotropic three dimensional space exists in order to facilitate the application of Fick's laws of diffusion (6). However, recent advances in physics and chemistry have shown that the geometry of the environment in which the processes take place is of major importance for the treatment of heterogeneous processes (7). In media with topological constraints, well-stirred conditions cannot be postulated while Fick's laws of diffusion are not valid in these spaces (7,8). Most of the arguments questioning the validity of the diffusion theory in a biological context seem to be equally applicable in the complex media of the GI tract (8,9). However, advances in heterogeneous kinetics have led to the development of "fractal-like kinetics" which is suitable for processes taking place in heterogeneous media and/or involving complicated mechanisms (10). Several reports in the literature (11) provide indications that many biological phenomena such as intraorgan flow heterogeneity (12), ion channel kinetics (13), drug distribution (14), and drug-receptor interaction (15) can follow the principles of fractal kinetics.

In the light of the above-mentioned GI heterogeneity, a rethinking of the GI processes is called for in terms of fractal concepts. Accordingly, the purposes of this commentary are i) to draw the attention of the pharmaceutical scientists to some recent findings which give an insight into the heterogeneous character of transit, dissolution and uptake in the GI tract, ii)

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to discuss the importance of these findings and concepts in terms of the relevant theoretical and practical aspects of biopharmaceutics drug classification (16) and the bioequivalence issue, and iii) to offer some alternative hypotheses which deviate radically from long-held views about order and variability in drug GI absorption.

The Heterogeneous Character of GI Transit. Since GI transit has a profound effect on drug absorption, numerous studies have focused on the gastric emptying and the intestinal transit of different pharmaceutical dosage forms. Gastric emptying is totally controlled by the two patterns of upper GI motility i.e the interdigestive and the digestive motility pattern (17). The interdigestive pattern dominates in the fasted state and is organised into alternating phases of activity and quiescence. Studies utilizing gamma scintigraphy have shown that gastric emptying is slower and more consistent in the presence of food (18,19). The transit through the small intestine, by contrast, is largely independent of the feeding conditions and physical properties of the system (18,19) with an average transit time of ~3h (20). Thus, normal transport seems to operate in the various segments of the small intestine and therefore a linear evolution in time of the propagating packet of drug molecules or particles' mean position can be conceived.

Several studies with multiparticulate forms have indicated that the movement of pellets across the ileo-caecal junction involves an initial regrouping of pellets prior to their entrance and spreading in the colon (21–23). According to Spiller *et al.* (24) the ileocolonic transit of 1 mL solution of a ^{99m}Tc-diethyltriamino-pentaacetic acid (DTPA) in humans is rapid postprandially and slow and erratic during fasting. Under fasting conditions the ileum is acting as a reservoir in several cases and the colonic filling curves of DTPA exhibit long plateaus and low slopes which are indicative of episodic colonic inflow and wide spreading of the marker in the colon (24). Similarly, Krevsky *et al.* (25) have shown that an 8 mL bolus containing ^{111}In-DTPA installed into the cecum was fairly evenly distributed throughout all segments of the colon by 3h. Finally, the colonic transit of different sized tablets have also shown to follow the same spreading pattern (26). This type of the markers movement is most likely due to the elecrtical activity of the proximal and distal parts of the colon (17). The electrical waves in these regions are not phase locked and therefore random contractions of mixing and not propulsion of contents is observed. From a kinetic point of view, the wide spreading of the marker in the colon is reminiscent of what is known in physics as "dispersive transport" (27). This conclusion can be derived if one compares time distribution analysis data of colonic transit (see for example the data of the first 3h in Fig. 3 of Ref. 25) with the general pattern of dispersive transport (Fig. 4 in Ref.27). These observations substantiate the view that dispersive tranport (27) operates in the large intestine and therefore the mean position of the propagating packet of drug particles is a sublinear function of time. However, dispersive transport is a scale-invariant process with no intrinsic transport coefficients; in other words, a mean transit time does not exist since transport coefficients become subject-time dependent (27). These observations provide an explanation for the extremely variable whole bowel transit i.e. 0.5–5 days (26) since the greater part of the transit is attributable to residence time in large intestine.

Is in vivo drug dissolution a fractal process? In the pharmaceutical literature there are several reports which demonstrate that flow conditions in the GI tract do not conform to standard hydrodynamic models. Two recent investigations (28,29) assessed the GI hydrodynamic flow and the mechanical destructive forces around a dosage form by comparing the characteristics of *in vitro* and *in vivo* release of two different types of controlled release paracetamol tablets. The results (28) indicate that the hydrodynamic flow around the dosage forms in the human GI tract are very low corresponding to a paddle speed of 10 rpm in the paddle method or a velocity of about 1 cm/min (1–2 mL/min flow rate) in the flow-through cell method. In parallel, low and high *in vitro* destructive forces were found to be physiologically meaningful and essential for establishing a useful *in vitro* dissolution testing system (28,29).

Besides, data from GI physiology have long time ago shown the heterogeneous picture of the GI contents as well as the importance of the mechanical factors in the GI processes (17,30). It is very well established that, the gastric contents are viscous while shearing forces in the chyme break up friable masses of food. As chyme moves slowly down the intestine by segmentation and short, weak propulsive movements the flow is governed by resistance as well as by pressure generated by contraction (17). Thus, there is a progressive reduction of the transit rate from duodenum to the large intestine (31,32).

All above observations (16–32) substantiate the view that the flow is forced in the narrow and understirred spaces of the colloid nature contents of the lower part of the GI tract. Consequently, friction becomes progressively more important than intermolecular diffusion in controlling the flow as the drug moves down the intestine. The characteristics of this type of flow has been studied (33,34) with Hele-Shaw channels ensuring a quasi-two-dimensional space using miscible fluids of different viscosity. These studies revealed that when a less viscous fluid moves towards a fluid with higher viscosity (polymer solution or colloidal suspension) the interface ripples and very soon becomes extremely meandering (fractal). These viscous, fractal fingers have been observed in experiments mimicking the secretion of HCl and its transport through the mucus layer over the surface epithelium (35). Confirmation of this type of morphology ('channel' geometry) in the mucus layer has been provided by an *in vivo* microscopic study of the acid transport at the gastric surface (36). The results obtained with the dyes Congo red and acridine strongly suggest that secreted acid (and pepsin) moves from the gastric crypts across the surface mucus layer into the luminal bulk solution only at restricted sites (36).

In the light of these observations one can argue that the dissolution of sparingly soluble drugs (biopharmaceutic drug categories II and IV (16)) should be performed in topologically constrained media since the drug particles traverse the larger part or even the entire length of the intestines and attrition is a significant factor for their dissolution. However, one can anticipate poor reproducibility of dissolution results in topologically constrained media (37,38) since the dissolution of particles will be inherently linked with the fractal fingering phenomenon, Fig. 1. According to van Damme (34) fractal fingering is in many respects a chaotic phenomenon because it exhibits a sensitive dependence on the initial conditions. Although this kind of performance for a dissolution system is currently unacceptable, it might mirror more realistically the erratic absorption

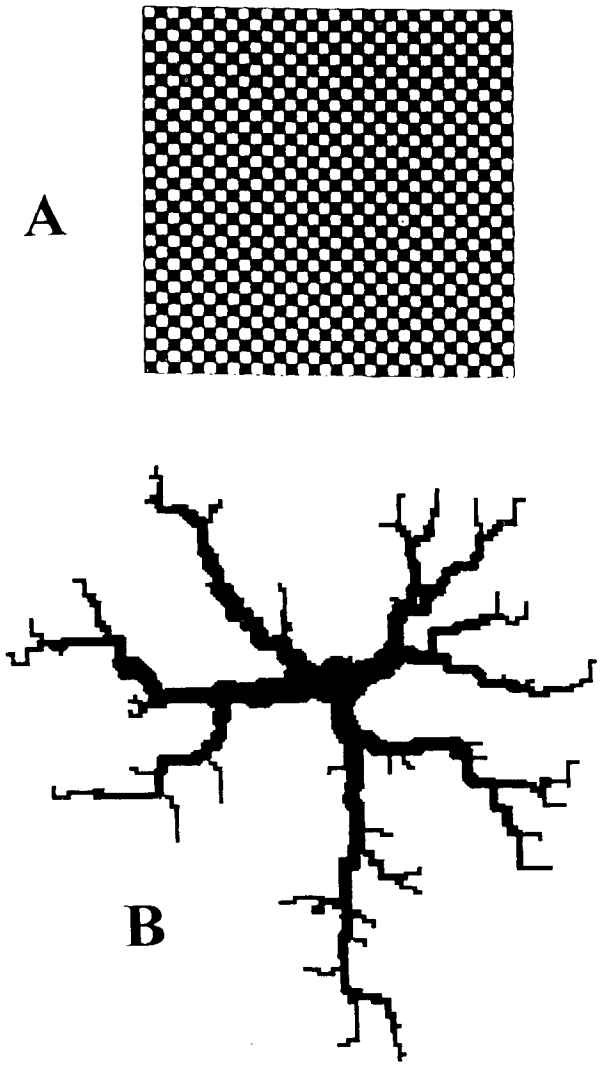

Fig. 1. Geometric representation of dissolution under homogeneous (A) and heterogeneous (B) conditions at a given time t. (A): All currently used well stirred dissolution media ensure at any time a homogeneous concentration of drug throughout their volume. Due to homogeneity a sample taken from a well stirred dissolution medium can provide the amount of drug dissolved (white squares) after separation of the undissolved drug (black squares). (B) Dissolution in topologically constrained media give rise to fractal fingering (see Figures in Refs 34, 37, 38). The tree-like structure shown here indicates the flow of liquid where dissolution takes place. This structure is generated via the modified DLA algorithm of Ref. 38 using the law $\rho = A(m/N)^{\beta}$. Here $N = 2000$, $A = 10$, $\beta = 0.5$, $\rho_c = 0.1$ and m is the number of particles sticking on the "downstream" portion of the cluster. This example corresponds to a radial Hele-Shaw cell where water has been injected radially from the central hole. Due to heterogeneity a sample cannot be used to calculate the dissolved amount at any time i.e. an average value for the percent dissolved amount at any time does not exist. This property is characteristic for fractal objects and processes.

of drugs with very low bioavailability, usually encountered with category IV drugs of the biopharmaceutics drug classification scheme (16).

Fractal-like Kinetics in GI Absorption? In spite of the complex nature of GI transit and *in vivo* drug dissolution, the derivation of the equations used in linear compartmental modeling rely on the hypothesis that absorption takes place from a homogeneous drug solution in the GI fluids and proceeds uniformly throughout the GI tract. However, for the reasons delineated above such an assumption is invalid.

The homogeneous GI absorption is routinely described by the following equation (39):

$$\text{Absorption rate} = FDk_a\exp(-k_at) \quad (1)$$

where F is the fraction of dose (D) absorbed, and k_a is the first-order absorption rate constant. Nevertheless, the maximum initial absorption rate (FDk_a) associated with Eq. 1 is not in accord with the stochastic principles in the transport of the drug molecules in the absorption process (39). Theoretically, the absorption rate must be zero initially and increase to reach a maximum over a finite period of time (39); this type of time dependency for the input rate has been verified in deconvolution and maximum entropy studies of rapid-release dosage forms (39–41). To overcome the discrepancies between Eq. 1 and the actual input rates observed in deconvolution studies, investigators working in this field have utilized a cube root-law input (42), polynomials (43), splines (41), and multiexponential (44) functions of time. In the same vein, but from a pharmacokinetic perspective, Yamashita and Amidon (45) have considered models for time dependent rate "constant" in oral absorption. Although these approaches (39,41–45) are purely empirical, their capability in approximating the real input function indicates that power functions of time can be of value in describing the GI drug absorption.

A more realistic approach to model drug absorption from the GI tract should take into account the geometrical constraints imposed by the heterogeneous structure and function of the medium. A diffusion process under such conditions is highly influenced, drastically changing its properties (6). For example, for a random walk in Euclidean space, the mean square displacement $\langle r^2(t)\rangle$ of the walker is given by Eq. 2:

$$\langle r^2(t)\rangle \propto t \quad (2)$$

while in disordered media $\langle r^2\rangle$ scales with t as

$$\langle r^2(t)\rangle \propto t^{2/D_w} \quad (3)$$

where D_w is the fractal walk-dimension (6). The value of D_w is larger than 2, typically $D_w = 2.8$ (2 dimensions), and $D_w = 3.5$ (3 dimensions), so the overall exponent is smaller than 1. Furthermore, in understirred media, where reactions or processes take place in a low dimensional space, the rate "constant" is time-dependent at all times (10). Hence, the transit , dissolution and uptake of drug under the heterogeneous GI conditions can obey the principles of fractal kinetics (10,46) in which rate "constants" depend on time. For these heterogeneous processes, the time dependency of the rate coefficient, k, is expressed by

$$k = k_1t^h \quad (4)$$

where k_1 is a constant while the exponent h is different than zero and is the consequence of two different phenomena: the heterogeneity (geometric disorder of the medium) and the imperfect mixing (diffusion-limit) condition. Therefore, k depends on time since $h \neq 0$ in nonhomogeneous spaces while in three dimensional homogeneous spaces $h = 0$ and therefore $k = k_1$ i.e classical kinetics prevail and the rate constant does not depend on time. For "ideal" drugs having high solubility

and permeability the homogeneous assumption ($h = 0$, GI absorption proceeds uniformly from a homogeneous solution) seems to be reasonable. In contrast, this assumption cannot be valid for the majority of drugs and in particular for these having low solubility and/or permeability. For these drugs a suitable way to model their GI absorption kinetics under the inhomogeneous GI conditions is to consider a time dependent absorption rate coefficient, k_a:

$$k_a = k_1 t^p \tag{5}$$

and a time dependent dissolution rate coefficient k_d:

$$k_d = k_2 t^d \tag{6}$$

In reality, the exponents p and d determine how sensitive k_a and k_d are in temporal scale and the kinetic constants k_1 and k_2, determine if the processes happen slowly or rapidly. The units of k_1 and k_2 are $(time)^{-(1+p)}$ and $(time)^{-(1+d)}$, respectively. Using Eq. 5, the absorption rate dQ/dt is:

$$\frac{dQ}{dt} = k_a Q_g = k_1 t^p Q_g \tag{7}$$

where Q is the quantity of drug in the body and Q_g is the dissolved quantity of drug in the GI tract. Since the change of Q_g is the result of dissolution and uptake which are both taking place under heterogeneous conditions ($p \neq 0$ and/or $d \neq 0$), Eq. 7 exhibits a non classical time dependency for the input rate. Thus, Eq. 7 provides a theoretical basis for the empirical power functions of time utilized in deconvolution studies (39,41–44).

The values of the parameters p and d for drugs exhibiting heterogeneous absorption kinetics are inherently linked with the physicochemical properties of drug, the formulation, the topology of the medium (GI contents) and the initial distribution of drug particles in it (10). It is worthy to mention that the initial conditions (the initial random distribution of the reactants: solid drug particles and GI contents) are very important in fractal kinetics (10). For all these reasons, population parameters for drugs having $p \neq 0$ and/or $d \neq 0$ are unlikely since the topology of the medium and the initial conditions are by no means consistent or controlled being subject-time dependent. Further analysis for the dissolution-uptake kinetics under heterogeneous conditions and the corresponding pharmacokinetic models will be presented elsewhere. For the sake of completion, one should add that under homogeneous conditions ($p = d = 0$) both k_a and k_d in Eqs 5 and 6, respectively are independent of time and therefore classical kinetics can be applied.

Implications. Relying on the above considerations one can argue that drugs can be classified in respect to their GI absorption characteristics into two broad categories i.e homogeneous and heterogeneous. The homogeneous drugs, have satisfactory solubility and permeability, are dissolved and absorbed mostly prior to their arrival to the large intestine, and exhibit low or moderate variability. It seems likely that the GI absorption characteristics of the homogeneous group of drugs is adequately described or modeled with the homogeneous approach i.e well stirred *in vitro* dissolution systems and classical absorption kinetics. In contrast, drugs with low solubility and permeability can be termed heterogeneous since they traverse the entire GI tract, are most akin to exhibit heterogeneous transit, dissolution, and uptake and therefore heterogeneous absorption kinetics. In this context, the following remarks can be pointed out for the heterogeneous drugs which exhibit limited bioavailability, high variability and most of them can be classified in category IV (16):

(a) Mean or median values should not be given for whole bowel transit since most of the dissolved and/or undissolved drug traverses the entire GI tract. The complex nature of transit involving normal and dispersive transport (27) as well as periods of stasis should be better expressed by reporting the range of the experimental values.

(b) Dissolution testing with the officially used *in vitro* systems ensuring homogeneous stirring conditions should be solely viewed as a quality control procedure and not as a surrogate for bioequivalency testing. According to the current views (16), limited or no *in vitro-in vivo* correlations are expected using conventional dissolution tests for the category IV drugs and the drugs of category II used in high doses. Since this "unpredictability" is routinely linked with our inability to adequately mimic the *in vivo* conditions, one should also examine if the chaotic character of *in vivo* dissolution is a valid hypothesis for the failure of the *in vitro* tests. It is advisable, therefore, to perform physiologically designed dissolution experiments in topologically constrained media (34,37,38) for drugs of categories II and IV (16) in order to determine potential cutoffs for dose and solubility values as well as flow characteristics for drug classification i.e homogeneous and heterogeneous drugs. These cutoffs will be further used for setting standards for *in vitro* drug dissolution methodology of drugs classified as heterogeneous.

(c) A notion which routinely accompanies oral absorption studies is that the mathematical properties of the underlying processes have a normal (Gaussian) distribution where the moments, such as the mean and variance, have well defined values. Relying on this notion, drugs and/or formulations are categorized as low or highly variable. Thus, any drug that generates an intra-subject coefficient of variation (CV) greater than 30% as measured by the residual CV (from analysis of variance) is arbitrarily characterized as highly variable. The use of a statistical measure of dispersion for drug classification is based on the law of large numbers which dictates that the sample means for peak blood concentration, C_{max}, and the area under the blood concentration-time curve, AUC, converge to fixed values while the variances decrease to non zero finite values as the number used in averaging is increased. The conventional assessment of bioequivalence relies on the analysis of variance to get an estimate for the intra-subject variability prior to the construction of the 90% confidence interval between 80 and 125% for AUC and C_{max}. The basic premise of this approach is that errors are normally distributed around the estimated mean values and two one sided t-tests can be performed. Although the validity of this assumption seems to be reasonable for drugs following classical kinetics concern is arising for the parameters C_{max} and t_{max} (time corresponding to C_{max}) when fractal-like kinetics governs absorption since for many fractal time processes (11,27) the mean and the variance may not exist. Under heterogeneous conditions, both C_{max} and t_{max} will depend on p and d and therefore mean values for these parameters cannot be justified when fractal kinetics is operating. Apparently, a significant portion of variability of the heterogeneous drugs can be mistaken for typical randomness and can

be caused by the time dependency of the rate coefficients of the *in vivo* drug processes. These observations provide a plausible explanation for the high variability in C_{max} values and the erroneous results obtained in bioequivalence studies (47). What is implicit from all above is that it is inappropriate to apply rigorous statistical tests in bioequivalence studies for heterogeneous drugs using parameter estimates for C_{max} and t_{max} which do not actually represent sample means. The recently suggested (48) comparison of the concentration-time curve profiles of test and reference products in bioequivalence studies seems to be in accord with the reservations of this study in using specific parameters for the assessment of absorption rate.

Finally, the analysis presented highlights the new insights that can be gained by the application of fractal concepts to biopharmaceutical problems. It is hoped that this work can pave the way for new levels of understanding heterogeneous phenomena in the field of biopharmaceutics and pharmacokinetics.

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