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Perspective

IVIVC of controlled release formulations: Physiological–dynamical reasons for their failure

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Controlled release formulations have been developed for many orally administered pharmaceutical compounds to replace the immediate release dosage forms. These formulations are developed for various reasons, including overcoming the limitations of short half-life of a drug, narrow therapeutic index, and site dependant absorption as well as for marketing benefits. The basic performance requirement of controlled release systems is that they release the drug *in vivo*, according to a specific, predefined delivery pattern. Ideally, the *in vivo* behaviour is assumed to match well with the corresponding *in vitro* behaviour. In other words, they are assumed to have a very good *in vitro–in vivo* correlation (IVIVC).

1. Controlled release formulations are linked to non-linear IVIVC

An important proportion of all research carried out in the field of biopharmaceutics is devoted on IVIVC studies. Most of these studies aim to demonstrate linear correlation between the *in vivo* and the *in vitro* experiments. A failure to produce the desired outcome, is often considered a negative result. The study then follows the fate of most of negative scientific results and remains unpublished. Despite the fact that most of these studies do not get published, some uncorrelated data [1], as well as non-linear IVIVC studies have appeared in literature [2]. It has also been suggested that the latter should be referred to as *in vitro–in vivo* relationships (ivivr) to specifically distinguish them from the linear cases [2]. One would expect that all of these non-linear IVIVC studies correspond to immediate release formulations of sparingly soluble compounds. Surprisingly, this is not true. A significant proportion of non-linear IVIVC studies concern controlled release formulations [3], although these are supposed to be engineered to perform well in that respect. This discrepancy is due to the dramatic differences of the *in vivo* conditions to any *in vitro* experiment, regardless of the efforts to simulate the former with the latter as realistically as possible. These differences are related to the properties of the gastric fluids, such as composition and pH. The distinction is especially notable, as these are spatially heterogeneous and are altered by the presence of food, the mechanical conditions imposed by the physiology, such as complex motility and hydrodynamic patterns, and also other factors like feedback mechanisms and the synergistic effects of the interplay of various factors (Fig. 1). Since what is important *in vivo* is not the release itself but the entire absorption process, factors that may not influence the release rate but influence the final pharmacokinetic profile also contribute to the observed variability and the discrepancies between the *in vitro* and the anticipated *in vivo* performance of controlled release dosage forms [4].

2. Anomalous diffusion-fractal/fractional kinetics

In the majority of cases, the release device controls the molecular diffusion of the drug molecules in and/or surrounding the delivery system. This category includes the following preprogrammed delivery systems: (i) polymer membrane permeation-controlled drug delivery systems; (ii) polymer matrix diffusion controlled drug delivery systems; (iii) polymer (membrane/matrix) hybrid-type drug delivery systems; and (iv) microservoir partition controlled drug delivery systems [5]. While under *in vitro* conditions, the performance of these devices is very reproducible and the variability observed is quite low, under *in vivo* conditions, under-stirring and the heterogeneous properties of the medium, change the topology of the environment and influence the diffusion in the matrix, altering the kinetics of drug release (Fig. 1). Unlike the well stirred *in vitro* experimental conditions, where the concentration of the medium is considered homogeneous, under *in vivo* conditions, due to the composition of the medium, a depletion zone may be developed around the device that alters the kinetics inside the device as well. It has been shown that in constrained, understirred spaces diffusion of materials follows different laws than the classic Fickian law. These give rise to the so-called anomalous kinetics to emphasise the deviation from the classic case [6]. Although anomalous kinetics have been used to describe the *in vitro* drug release inside the device [7], this type of kinetics may extend outside the device as well as in a space which is wrongly assumed to be well stirred. Anomalous kinetics has been described by employing concepts of fractal geometry to account for the fact that due to the prevailing conditions, the space appears as if it has a geometry of lower dimensionality than the Euclidean space [8]. In fact, Monte Carlo simulations have been used to study drug release for Euclidean and fractal geometries and found that the Weibull model provides an adequate description of the release process [9–18]. Under *in vivo* conditions, the topological differences of the medium do not remain constant for the entire process of release and they vary in time and along the different parts of the GI lumen. They are also affected by the presence of food and mechanical influences, such as the intestine motility, since this act as stirring. Efforts to describe mathematically the anomalous kinetics include fractal kinetics with power law and time dependant rate coefficients [8]. Also more recently, attempts with differential equations

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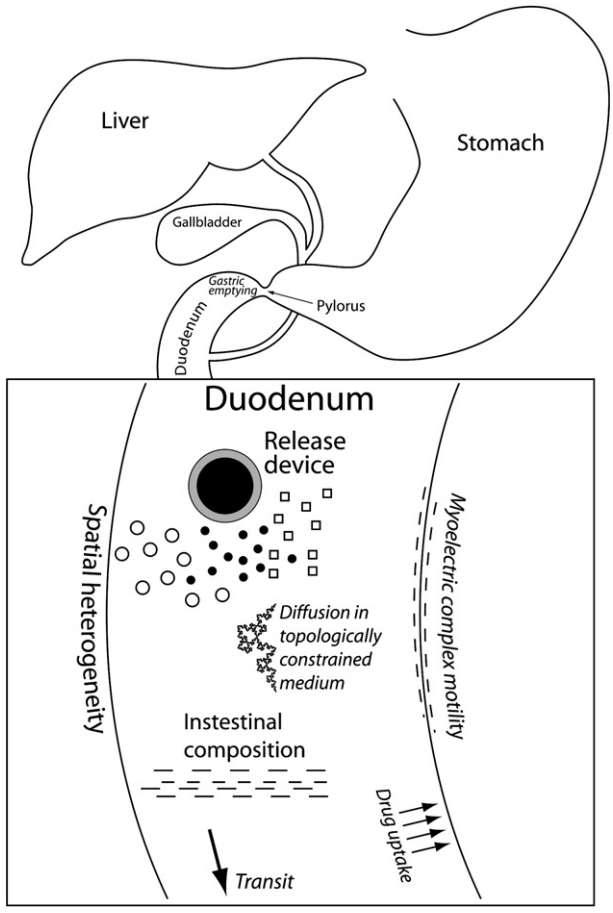

Fig. 1. A heterogeneous-dynamic picture of drug processes in the GI tract. Key: ●, dissolved drug molecule; ○, food components; □, bile salts. The three species (●, ○, □) compose a dynamical system. Gastric emptying which is controlled by the gastric migrating myoelectric complex can be chaotic [22]. Anomalous diffusion of drug species both in the device and in the lumen fluids is a result of under-stirring and low dimensionality. Intestinal composition changes spatially and temporally.

of fractional order, the so-called fractional kinetics, have appeared [19] to describe anomalous kinetics, where the fractional order of differentiation is also related to the geometry of the space. It is interesting to note that the fractional version of a constant rate process gives rise to a power law solution, when integrated [19]. Therefore, it is plausible that a process which appears to have a constant rate under well stirred *in vitro* conditions, becomes anomalous (power law) under constrained *in vivo* conditions. This could be described in the context of fractional kinetics simply by changing the order of the derivative in the differential equation.

3. Mechanical–dynamical factors cause variability

Further to the alteration of the release kinetics *in vivo* and due to the differences of the properties of the medium, mechanical properties imposed by the physiology and the anatomy are important. Apart from intestinal motility and its contribution to stirring of the GI contents, the hydrodynamic properties such as the flow, which determines the residence time of the device and also its location in the GI lumen, may be important [20] (Fig. 1). The presence of food delays flow and alters the entire transit profile. This is important, especially for drugs with site dependant absorption, as the residence profile of the device is altered which results in the drug being released in parts of the GI with limited absorption, including the stomach [20]. Although this altered transit profile may not influence the release pattern itself, it influences the pharmacokinetic profile and contributes to the observed variability and departure from the *in vitro* performance. In the same vein, gastric emptying can also have a role in the observed pharmacokinetic variability, especially since there is evidence of feedback mechanisms with some drugs [21] and also complex behaviour of the myoelectric complex controlling the function of the pylorus [22]. The latter has been also reported to exhibit chaotic behaviour [22].

4. Synergistic actions produce complex behaviour

It is common in a multifactorial system that the synergistic effects of its components may give rise to emergent behaviours that cannot be explained by the individual behaviours of the components. Studying these systems in the classic reductionist approach may result in missing some of its properties. It is the interactions of the different components that give rise to these additional properties of the system. There is evidence that the GI may present such properties and some of its components may form a dynamical system [4] with complex behaviour as a result of the interaction of these factors. We already mentioned that there have been reports of chaotic behaviour of the myoelectric complex. Another potential example of such a synergistic behaviour consists of three tightly interacting quantities: the drug concentration, food and biliary secretion (Fig. 1). It is well known that the consumption of a meal rich in fat, stimulates alterations in gastric pH, secretion of pancreatic enzymes, promotion of lymphatic transport and stimulation of biliary lipid release from the gallbladder. The basic components of biliary lipids, namely, bile salts, phospholipids and cholesterol promote the formation of colloidal species within the small intestine, which aid the solubilization of the poorly-water soluble products of lipid digestion, e.g., fatty acids as well as enhance the solubility of the poorly-water soluble drugs. The exact structure and function of the dynamical system food/biliary lipids/drug is unknown; however, a recent study [23] demonstrates that even relatively low quantities (2 g) of long chain lipids stimulated gallbladder contraction and elevated, variable intestinal bile salt, phospholipids and cholesterol levels. Although the variability was mainly attributed to classical randomness (subject to subject variation) the second reason quoted on the difficulties associated with effective duodenal sampling is most likely linked with the heterogeneous spatial composition of the intestinal fluids. Besides, the oscillatory nature of the concentration–time plots of the biliary derived lipids in the intestinal lumen might be indicative of the dynamics of the system. For all above mentioned reasons we believe that the *in vitro* measurements of drug solubility in food mimicking media or bile salts (biorelevant media) cannot capture the dynamics of the *in vivo* conditions. Due to the multiple interactions among the components of the system involved, a reductionist approach focusing exclusively on the drug/biliary lipids interaction cannot unveil the entire picture. Consequently, more carefully designed *in vivo* studies are required to shed light on the function of food/biliary lipids/drug dynamical system.

5. Conclusions

In conclusion, we believe that the variability of the GI can be explained at large by contribution from dynamical sources, such as feedback mechanisms and complex behaviour, resulting from the interaction of the different components. Also, the altered topological properties of the GI contents seem to be particularly important for controlled release dosage forms, as these properties change the release rate from the device. However, one thing is clear; there are still too many unknowns in the GI system. This is the main reason why the discrepancies between *in vitro* behaviour and the observed *in vivo* performance, together with the corresponding variability, are treated as random noise and little attempt is made to explain them systematically, in a mechanistic way. More research, with experimental studies with emphasis on *in vivo* techniques

and also applications of new theory with novel mathematical approaches is needed, to shed light on the processes of *in vivo* release, diffusion, transit and absorption, so that the discrepancies with the well described *in vitro* experiments can be explained. In parallel, investigators should be encouraged to submit for publication non-linearly correlated or uncorrelated *in vitro* and *in vivo* data. This will enable a better understanding of the factors involved in this exercise.

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