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Therapeutic Delivery

Are mathematical equations important for improving drug delivery devices performances?

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Drug delivery & mathematical modeling

Mathematical theories applied to drug delivery represent an extremely interesting field of increasing academic and industrial importance with tremendous consequences for the future due to the possibility of predicting and tuning the release of drugs [1,2]. Thanks to significant advances in computer science and electronics, the optimization of drug delivery systems using computational approaches can be expected to successfully improve the ease and accuracy of application [3,4]. Similar to what is happening in other disciplines that seem far removed from the drug delivery field, such as aviation or reactive systems, computational efforts are becoming fundamental to research into future improvements in pharmaceutical technology [5,6]. Taking into consideration the type of administration, the active principle of the cargo and the desired release kinetics, the predictions obtained from *in silico* studies can be used to estimate the optimized formulation, shape and manufacturing procedure of the dosage form to be produced. In this respect, mathematical models used in the optimization of drug delivery devices can help to save time and reduce expenses [7,8]. In fact, predictions obtained from theoretical studies can reduce the number of experiments needed to develop or optimize drug delivery devices. Furthermore, the correct knowledge of all the phenomena (mass and energy) that can take place in controlled drug delivery systems can be another key point in convincing the audience of the importance of this study. In particular, it could help to improve the safety and efficacy of new pharmaceutical therapies, which is a prerequisite for their development, underlining once again the importance not only from an academic but also from an industrial perspective [9]. It is indeed true that knowing what is happening in a system, instead of considering it as a 'black box', is fundamental in the whole decision-making process, starting from the laboratory formulation and procedures through good manufacturing practice (GMP) production to clinical trials and commercialization. This approach is fundamental in determining which device characteristics are critical to achieving the system performance required by medicine. In the last decades, many different models have been developed and are available in the literature [10–12], but most of them are still lacking in ease and accuracy of operation. The pioneer of theories applied to the transport of drug molecules through polymeric devices is Professor Higuchi (1918–1987), followed more recently by Professors Peppas and Siepmann [10]. In 1961, Professor Higuchi published his famous equation, which allowed an unexpectedly simple description of drug release using semi-empirical parameters depending on the geometry studied [13,14]. This was the beginning of understanding how drugs could be released from pharmaceutical forms.

To date, many different models have been described, including semi-empirical/empirical models and mechanistic realistic models. In the first case, the mathematics is purely descriptive and not strictly related to real natural, physical and/or chemical phenomena. As a result, these models provide only very limited insight into the mechanisms of delivery through the devices, and their predictive ability is very low. However, they can be useful if the information

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required is limited to a comparison between different delivery modes on a single parameter. Their use should be approached with great caution if mechanistic conclusions are drawn or predictions expected. In contrast, mechanistic mathematical models are developed considering real physical and/or chemical phenomena such as diffusion, swelling and degradation (erosion or bulk-based) [15,16]. Moreover, in the last years, strong attention was also dedicated to simulate what is happening in delivery systems where the release is driven by external stimuli like pH, enzymes or hydrolysis of cleavable bonds [17]. These different theories guarantee that system-specific parameters are obtained, which enable a good understanding of the mechanisms behind drug release. Their use can, for example, help to understand the relative importance of one of these phenomena compared with the others. Indeed, drug delivery devices are not treated as a 'black box' but as real physical delivery systems. During product development, these theories allow quantitative prediction of the role of material, formulation and process parameters on the resulting drug delivery. Therefore, information on the geometry, size and composition required to achieve specific device performances is predictable. In addition, problems encountered during device manufacture can be addressed knowing exactly what is happening in the delivery systems. When developing mathematical models to simulate and then predict the release of drug molecules from pharmaceutical devices, various aspects should be considered:

- In order to obtain an accurate mathematical model, it is generally necessary to increase the complexity, so as a rule, more phenomena are considered and more realistic predictions can be obtained as a result. However, great care should be taken to avoid overly complex models in which negligible mechanisms are also considered. This is because these theories are difficult to use as they require many parameters that are not easy to measure (from experiments). Therefore, when developing new theories, a great deal of effort should be put into understanding the system, and consequently only the physico-chemical phenomena that play a key role should be considered.
- It is necessary to compare the outcomes obtained from *in silico* studies with experimental results. There are two possible types of comparison: models fitted with experimental results or compared with results obtained from experiments independently of calculations. In the first case, some model parameters are optimized to minimize the discrepancy between models and experiments. This approach should be used with great caution because good agreement will be found even if the model is not well written and robust, especially when fitting many different parameters at the same time.

This can cause errors in the decision-making process because the predictions are not reliable. Therefore, to avoid this problem, it is strongly recommended to fit only one parameter at a time, using a minimum of 10 points obtained from experiments. If the fitting involved experimentally measured kinetic data, it is extremely important to take into account the entire profile and not only a portion (e.g. burst release, plateau or intermediate phase). The second case, which is much more reliable and generic, is the comparison between model predictions and experimental results, both obtained independently. In this framework, all the specific (physical and chemical) parameters of the system are fitted using different experimental results. When all the required parameters are known, the impact of formulation, microstructure and processing parameters are predicted *in silico* to tune device performance (e.g. drug molecule delivery kinetics). Consequently, the decision-making process can take place during the manufacture of a final device, where the predicted performance is verified by experiments and, if necessary, tuned;

- The absence of a generic model valid for all the controlled delivery systems. Depending on the assumptions made, some of them can be applied to a limited number of devices, while others can be applied to a wider range of them.
- Even if there is good agreement between independent results obtained from experiments and mathematical calculations, the advice is to be very prudent. Indeed, it is obvious that a mathematical model is a good simplification of a real system, and so it is fundamental to avoid oversimplification and try to use the same models for different systems (see advice on generic models above).

Can mathematical models improve the performance of drug delivery devices?

Mathematical models play a key role in the in-depth knowledge of all the transport phenomena that lie behind the release of active ingredients from controlled drug delivery systems. The proper design of controlled drug delivery devices is helped by the use of mathematical predictions, which can be derived from very simple and empirical models or from probabilistic or molecular models [18,19]. Indeed, starting from the use of transient descriptions and steady state of mass transport using Fick's law, the theories have considered micro-scale properties such as polymer

microstructure, relaxation of polymer chains, glass/rubber transitions, crystallinity of polymers and effect in the environment together with macro-scale device properties such as shape and geometry. One of the key gaps between experiments and mathematical theories that still remains in the field of drug delivery is the need to find and measure transport, thermodynamic and molecular properties with a high degree of accuracy. To solve this problem, efforts should be devoted to a fruitful collaboration between experimental studies (material and analytical) and theoretical ones, with the ultimate aim of filling this gap. In general, kinetic data from release studies are used to compare theory with experimental results.

These data represent the cumulative effect of various physical and chemical phenomena and polymer properties and structures. It therefore makes sense to validate the models against experiments that measure these microstructure, interaction and mass transport phenomena. In this context, for example, microscopy (scanning electron and transmission electron), nuclear magnetic resonance and mechanical properties should be used to measure polymer microstructures and compare them with mathematical models. The key weakness of this models is that they can properly simulate what is happening *in vitro* but to allow reliable prediction of what is happening *in vivo* also pharmacokinetics and pharmacodynamics contribution should be considered. These contributions complicate the theories and so the mathematical equation that should be used. A novel frontier is so represented by a proper consideration of all the mechanisms that take place within the human body when a pharmacological active ingredient is administered. In addition we should underline that the next generation of drug delivery systems will focus on the delivery of cargo to specific targets within cells to a lesser extent. These include the need to deliver pharmaceutics to organelles to regulate degenerative diseases, DNA to nuclei to tune gene expression and antigens to cytosolic sites as systems for vaccine delivery. For all these possibilities, there is a great need to understand the key players in the delivery phenomena of both the intracellular and extracellular compartments. Mathematical theories can so play a key role in improving the rational design of release systems that can deliver the right amount of their content at the right time and in the right place [20]. Today, many of the drug delivery models currently in use focus on the release of active ingredients with a low molecular weight, but the next frontier is the transition to biomolecules such as proteins or antibodies. Here, in-depth modeling activities are required to study and optimise their possible modification caused by manufacturing methods or interactions with the carrier during their release. To summarize, the correct use of mathematical models can optimise the number of experiments required and help develop formulations to improve the pharmacodynamic (efficacy) and pharmacokinetic (adsorption, distribution, metabolism and excretion) effects associated with new pharmacological therapies.

Author contributions

F Rossi wrote the first draft of the manuscript. F Pizzetti, G Perale and M Masi contributed to the final version of the manuscript. All authors provided critical feedback.

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