Mathematical Modelling and Spectroscopic Imaging of Multi-component Tablet dissolution

*J. Kimber, S.G. Kazarian, F. Štěpánek**

Department of Chemical Engineering, Imperial College London, South Kensington campus, London SW7 2AZ, United Kingdom
*Corresponding author: Tel.: +44 207 594 5608; Fax: +44 207 594 5638; E-mail: f.stepanek@imperial.ac.uk

Introduction

The dissolution characteristics of pharmaceutical tablets are key to determining the bioavailability of the active pharmaceutical ingredient (API) and it is therefore vital to understand the physical processes that affect drug release. As well as the API, tablets also consist of a supporting polymer matrix (known as the excipient) and other compounds such as fillers, binders, lubricants etc. The overall release of the API depends not only on the individual dissolution characteristics of the various components and their proportion in the formulation, but also on their interactions. Tablet microstructure and granule arrangement [1–4] within the tablet are also important. By understanding the tablet microstructure and dissolution properties of the various components, it will be possible to model how a tablet will release the API given a specific formulation, leading to better tablet designs.

Currently available models describing drug release from tablets tend to be empirical correlations that do not describe the underlying physical processes but rather provide an overall description of the drug release profile. Such models are of limited use for predicting tablet performance and for tablet design.

Complexities arise when dealing with phenomena-based modelling of interacting multi-component systems. In these cases, the physical properties of each component such as solubility and diffusivity is affected by the presence and concentration of the other species. Often the excipient is a swelling polymer (e.g. Hydroxypropylmethylcellulose or Microcrystalline cellulose) that can form a gel layer around the tablet during dissolution. This gel layer slows water ingress and drug diffusion also forms a macroscopic transport process as the swelling moves drug particles away from the tablet core. A computer model will need to take these processes into account if a tablet is to be modelled accurately.

Method

The tablet microstructure is encoded by the phase volume fraction method (Fig 1a). In this way, a value of unity corresponds to a completely solid voxel and a zero volume fraction voxel contains no solid. The overall tablet shape is discreetised using these voxels on a grid using Cartesian coordinates. The solubility of the components within each voxel is modelled using Noyes-Whitney first order equations and the diffusivity of each species is modelled using Fick's law. The diffusion of each species in solution is also simulated, considering concentration and porosity dependent diffusion coefficient. The domain is surrounded by a zero concentration boundary along with a

square boundary within the domain which is used to track the diffusing components. Components that have diffused beyond this boundary are considered "released" and thus enable a release curve to be obtained.

The main output of the simulation is a release curve, where normalised mass release is plotted against time. Given a set of parameters, the simulation gives release curves of differing characteristics. Examples of adjustable parameters include the volume fractions of the components, the random distribution of particles and particle size. In order to assess how parameters affect the shape of the release curve, points along the curve at 10%, 50% and 90% API release are noted. These points are then plotted against the varying parameter or parameters and from this, it is possible to determine how changes in one or more parameters affect the release time of the API or other component of interest.

The simulation results are validated using tablet dissolution experiments and Fourier Transform Infra-red (FTIR) imaging. The FTIR imaging system consists of a focal plane array of 64x64 IR detectors, obtaining spatial as well as spectral information. The tablets are compacted in-situ, dissolved and imaged using an Attenuated Total Reflection (ATR) crystal and a Golden Gate^{TM}(Specac) accessory. This non-invasive process along with the chemical specificity of IR enables concentration maps of each component within the tablet's bottom surface to be obtained throughout the dissolution process and has been used already to study drug release from swelling polymer tablets [5, 6]. Studies using this method also enable the determination of various parameters for the diffusivity and saturated concentration dependency equations as these are specific to the tablet composition.

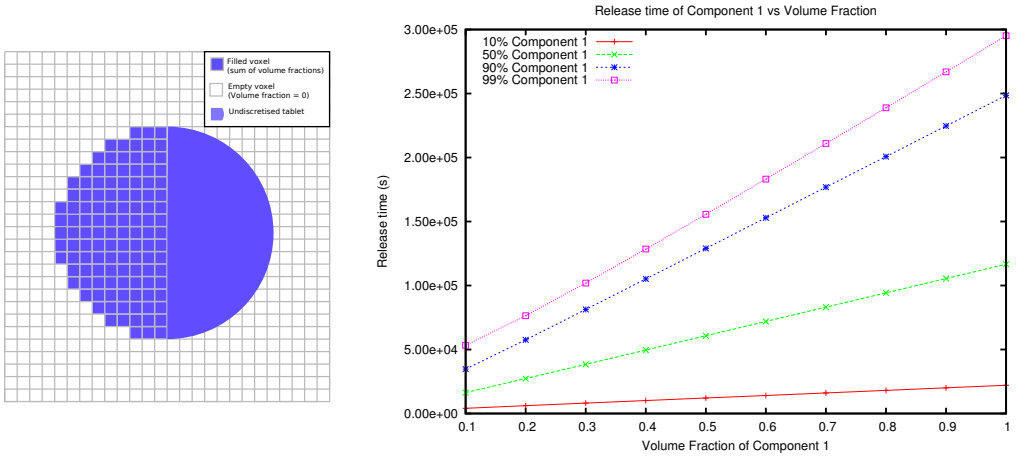

Fig. 1: a) Tablet discretisation method and b) parametric study results showing the effect of changing the volume fraction of component 1 on its release time

Results and Conclusions

The first set of results show release curves for a tablet containing an excipient shell (such that the API is only released after a time offset) (Fig 2a) as well as a tablet with with a random granular microstructure (Fig 2b). In all cases, component 1 is the API and component 2 is the excipient.

The first parametric study was a homogeneous tablet containing caffeine and lactose in varying volume fraction amounts. It was expected that by only changing the volume fraction of the components in the tablet, the dissolution time would change linearly between the dissolution times

of the pure components. This is seen in Fig 1b. It should be noted the dissolution time of the tablet is quite long due to the lack of porosity and the fact that the densities of the pure components were chosen as the densities of their crystalline forms, hence the tablet is more like a solid homogeneous crystal rather than a porous structure.

These types of parametric studies have a practical impact on tablet design such as the choosing of particle size, the blend homogeneity and the selection of excipients, binders and other "non-API" ingredients. This research also paves the way for the solution of the inverse problem, that is specifying a release characteristic (such as 50% API released after 60 minutes) and having the program find the appropriate composition and microstructure of the tablet to meet this criteria. This is a non-deterministic problem, as many different parameters could be varied to obtain a valid answer, but whose solution is an extension to the work on the parametric studies carried out so far.

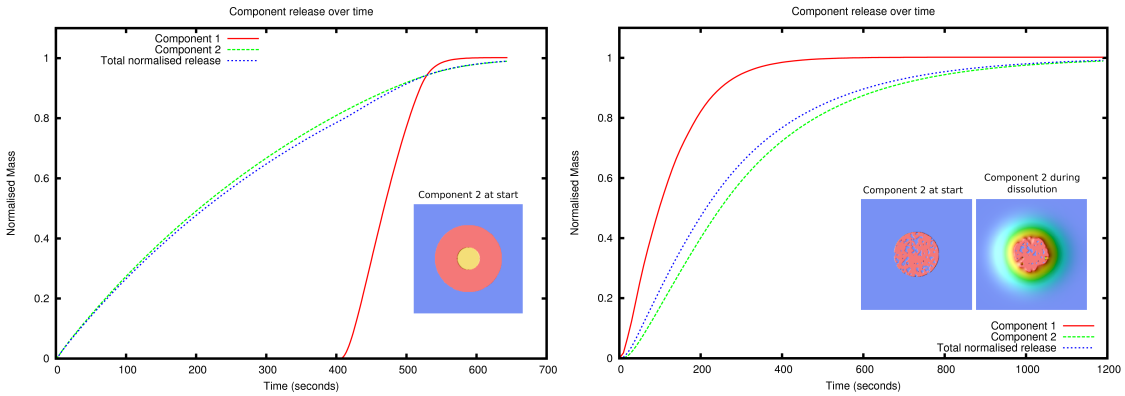

Fig. 2: Example tablet release curves and images of component 2 for a) Tablet with core of API and b) Tablet with randomly distributed API

References

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