Simulations of Drug Release Profiles as a Function of Different Geometrical Designs

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INTRODUCTION

For combination therapy, it is important to provide release modifications for the different compounds, in order to match therapeutic objectives for individual medication [1].The complexity of development of combination drugs lies not only in physicochemical properties but also in influences of simultaneous drug releases from different geometries. Hence, it requires optimization and development. Thus, the computer based modeling approach which can simulate release profiles of several drugs with different physicochemical properties is of importance. The possibility to model geometries and arrangements of different drugs in different geometries allows optimization and enhancement of therapeutic effects.[2]

AIMS

Explore simulated release profiles from complex geometries using discrete element calculation method based on 3-dimensional cellular automata.

MATERIALS AND METHODS

Intrinsic dissolution tablets, produced of an outer shell composed of ethylcellulose and Lubritab® granulated with EtOH and an inner core consisting of caffeine, were used for determination of material parameters in simulation. The tablets were produced on a Medelpharm Styl'One compaction simulator. Dissolution was carried out on a SOTAX AT7 dissolution tester (USP apparatus II) with online UV spectrophotometric analysis. In silico simulations were done using F-CAD 2.0 software (CINCAP GmbH, Switzerland), which is based on three-dimensional cellular automata and massively parallel computing. [3]

RESULTS AND DISCUSSION

Figure 2 shows the release of a bobbin-shaped geometry. In accordance to Noyes-Whitney equation, the dissolution rate is directly proportional to the surface area accessible to the medium. Therefore the release rate decreases linearly. At the end of the release, the rate decreases rapidly.

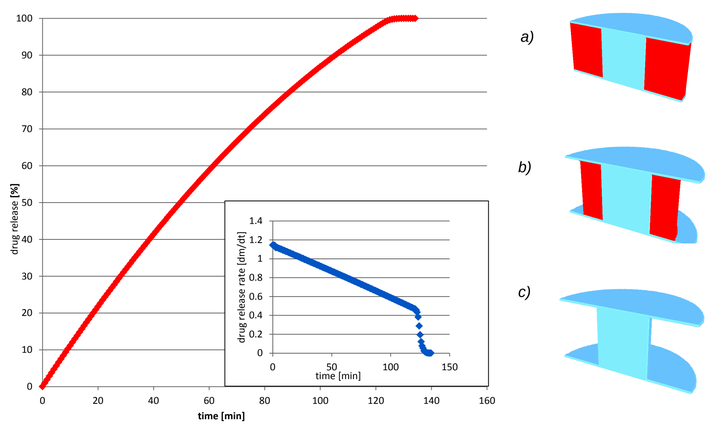

Figure 2. *Simulated release profile of a bobbin-shaped tablet*

After finding the correct parameters to simulate the caffeine release (with intrinsic dissolution tablets of 9mm core diameter), the release of intrinsic dissolution tablets with 7mm and 5mm core diameter were first simulated then experimentally confirmed. As shown in *Figure 1* the simulated and experimental release profile are the same in case of 9mm and 5mm. In case of 7mm core diameter, deviation is associated with possible cracks or deformation of the caffeine core during the production of the tablets. For all other geometric arrangements, simulations were carried out keeping these parameters constant.

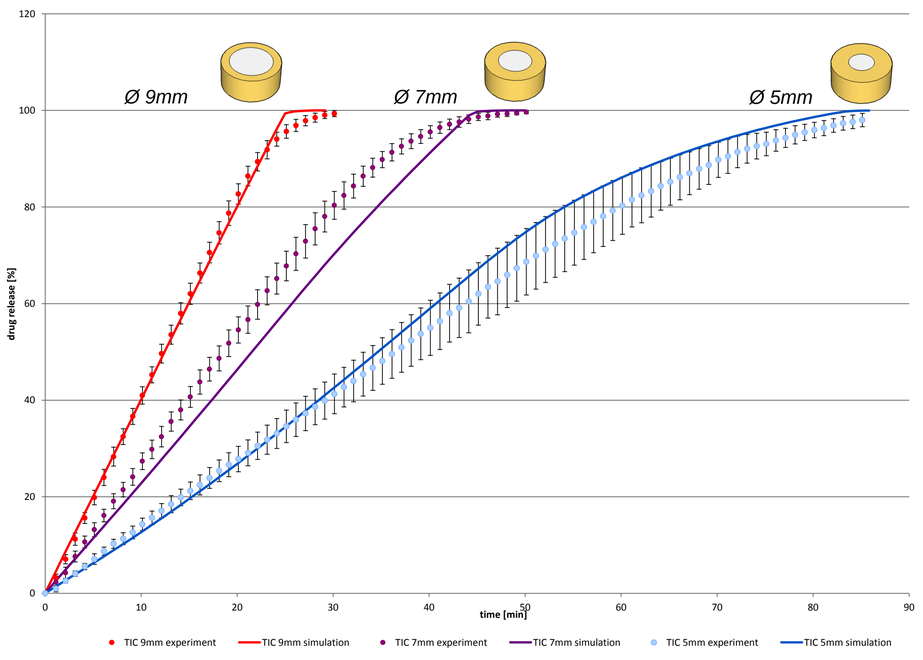

Figure 1. *Drug release of caffeine intrinsic dissolution tablets with different core diameters, but same doses. Simulated profiles (solid lines) and experimentally measured profiles (dots).*

The release profile of a lense shaped caffeine core is shown in *Figure 3*. The lense is accessible to the medium at six points. The release rate is constantly accelerating due to the increase of accessible surface area untill 70% drug is released.

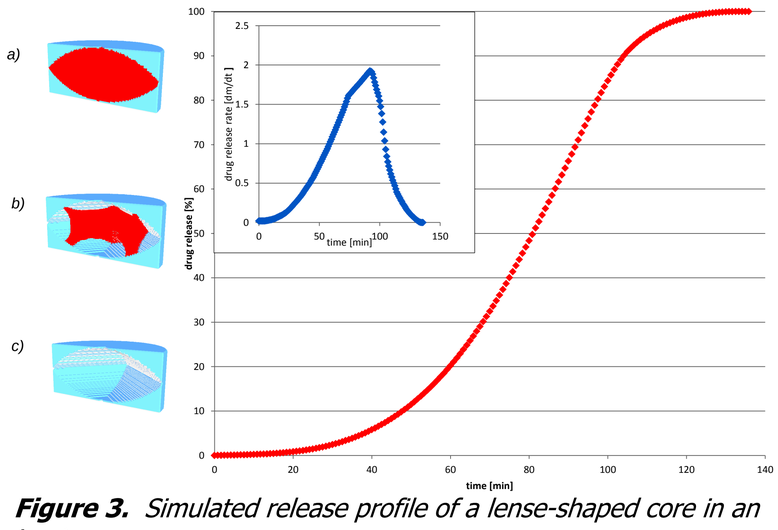

Figure 3. *Simulated release profile of a lense-shaped core in an inert cup*

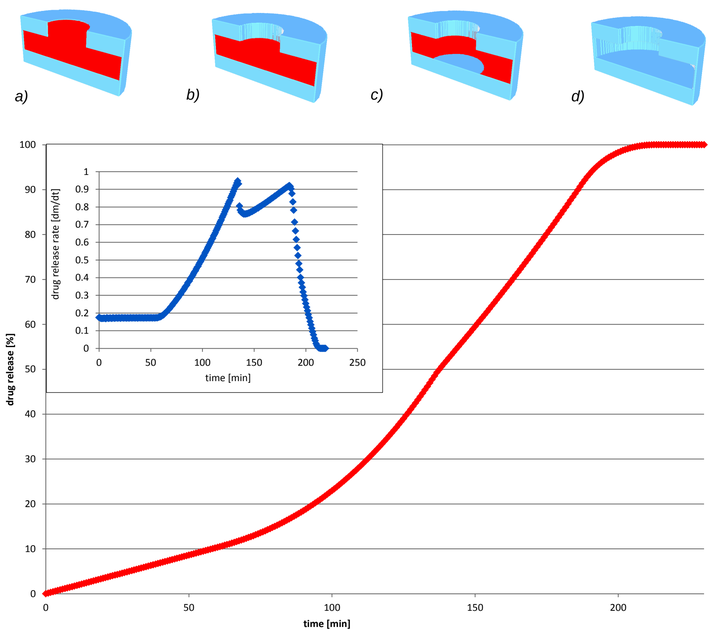

Figure 4. *Simulated release profile of double-cored tablet*

Figure 4 shows the release profile of a double-cored tablet, the lower core has a larger diameter. The small core yields in a linear release, hence the release rate is constant until the larger core starts to release. Inital increase due to surface increase is followed by a decrease in release rate. The rate increases again proportionally to the surface area of the inner cylinder (*see Figures 4 c)).* The end of this complex release rate pattern is characterized by a rapid decrease of the release rate, similar to the bobbin-shaped geometry.

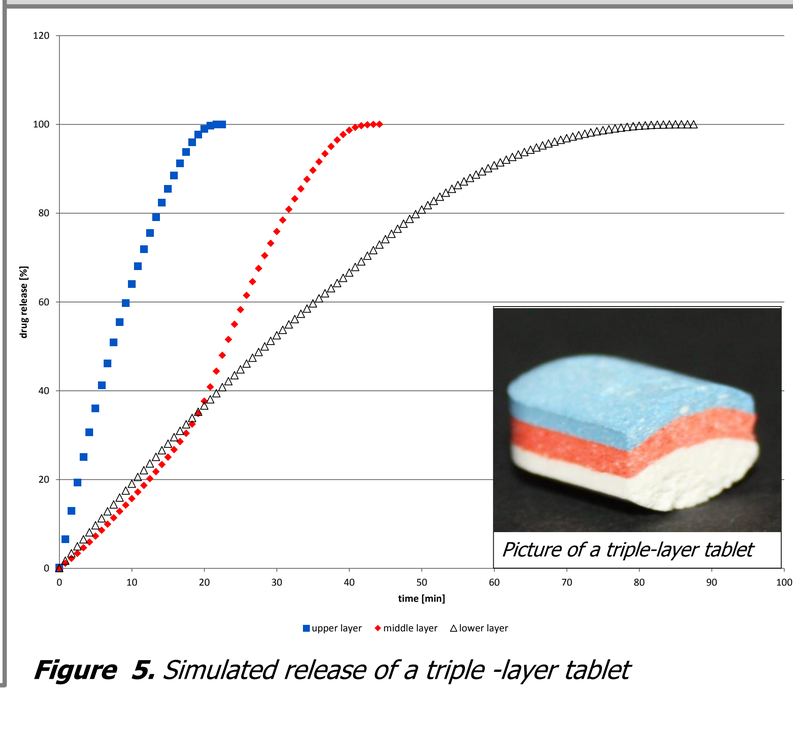

Figure 5. *Simulated release of a triple -layer tablet*

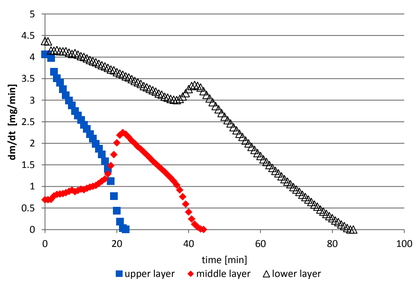

Figure 6. *Release rate (dm/dt) vs. time (min) of a triple layer tablet*

The release profiles of a triple-layer tablet with three drugs are shown in *Figure 5*. It is assumed that all the three layers have the same release behavior. As seen the kinetic is changing depending on the location of the layer. This is due to different surface area accessible at different time points during the dissolution process.

CONCLUSION

Despite the fact that the presented geometries are difficult to find in reality, an attempt to modulate the release behavior of different geometries requires special material for inert parts of the tablets. Such material needs to be pharmacologically inert, have excellent compactibility and compressability and allow modifications to achieve different dissolution rates (from 0 to highly soluble). The best candidate for this material seems to be functionalized calcium carbonate which could be hydrophobized or admixed with citric acid to either block or enhance the dissolution rate. [4] [5]

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