Tablet-In-Cup Drug Delivery Device – Drug Release Modification By Tablet Geometry

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INTRODUCTION

Release modification is a common task in pharmaceutical technology in order to increase drug efficacy or to reduce side effects, dose frequency or toxicity [1]. Conventional approaches are predominantly based on release control by diffusion through matrix or membrane systems. Such systems often require intensive formulation and process development because critical factors like surface area and osmotic activity are changing during dissolution of the dosage unit. With the special geometrical design of the newly developed tablet-in-cup (TIC) device, disadvantages of conventional drug release systems can be over-come by keeping the surface exposed to the dissolution media constant over time. The design of TIC devices is characterized by a non-dissolving, non-swelling, non-porous and inert outer "cup" surrounding one or two flat single- or multiple-layer core tablets containing the drug.

Figure 1. *Photo of TIC device*

AIMS

- Development of TIC devices
- Elaboration of the potential of the TIC design for drug release modification
- In-silico simulation of TIC drug release

MATERIALS AND METHODS

Caffeine and duloxetine were used as model drugs to develop TICs with different geometries. Factorial design experiments were carried out with the help of DOE software in order to optimize the TIC design. Core-tablets and cups as well as the final TIC devices were produced on a Medelpharm Styl'One single-punch press with multiple-layer option and dry-coating device. Dissolution was carried out on a SOTAX AT7 dissolution tester (USP apparatus II) with online UV spectrophotometrical analysis. *In silico* simulations were done using F-CAD software, which is based on three-dimensional cellular automata and massively parallel computing [2].

RESULTS AND DISCUSSION

TIC devices with caffeine showed zero order kinetics with fairly constant release rates from beginning to end. Dissolution speeds depended on the intrinsic dissolution rate of the drug and its surface exposed to the medium. It was possible to modify release rates by changing the core-tablet diameters without changing the formulations of the cores or the cups.

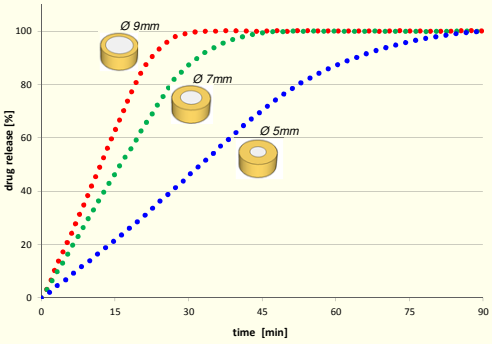


Figure 2. *Drug release of caffeine TICs with different core diameters but same doses (TIC type (a) according to figure 3)*

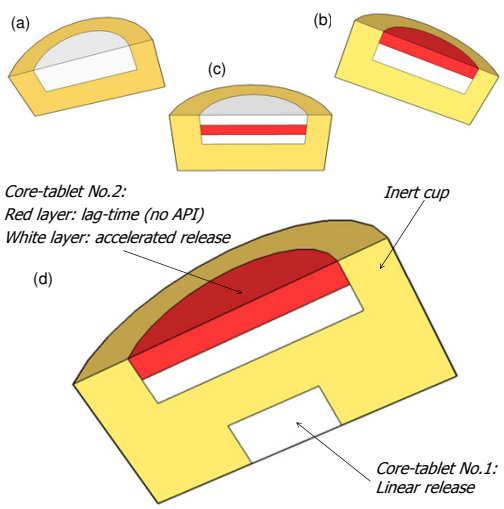


Figure 3. *Schematic cross-sections of different types of TIC devices (a) Linear release, (b) Delayed release (lag-time layer in red), (c) Dual-action pulsatile release, (d) End-accelerated release*

Delayed release tablets were produced by manufacturing dual-layer tablets with a drug layer and a lag-layer containing different amounts of polyvinyl alcohol (PVA).

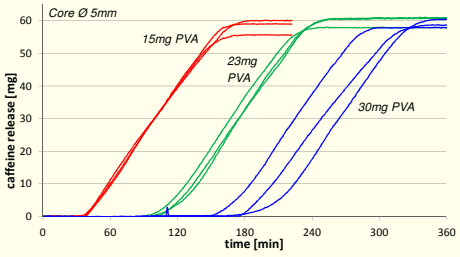
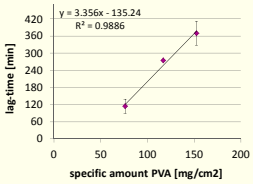


Figure 4. *Delayed release of TICs with different lag-layers (n=3)*



The resulting lag-times had a linear correlation with the specific amount of polymer in the lag-layer (red layer in TIC type (b) of figure 3).

Figure 5. *Correlation of PVA amount with lag-time in TICs type (b)*

In order to achieve pulsatile release, triple-layer core-tablets were manufactured consisting of a lag-layer in-between two drug layers according to TIC type (c) in figure 3. This resulted in two sequences of linear release, separated by a defined lag-time depending on the amount of polymer used for the lag-layer.

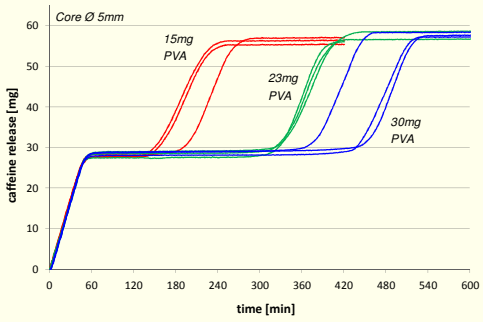


Figure 6. *Pulsatile release of TICs with different lag layers (n=3)*

TICs containing tablet cores with different sizes on both sides were developed in order to realize time-controlled change of the release speed. TICs according to type (d) in figure 3 provided end-accelerated release. During the dissolution of the small caffeine core (Ø 5mm), the lag-layer of the larger second core (Ø 9mm) is dissolving until the second caffeine layer accelerates release.

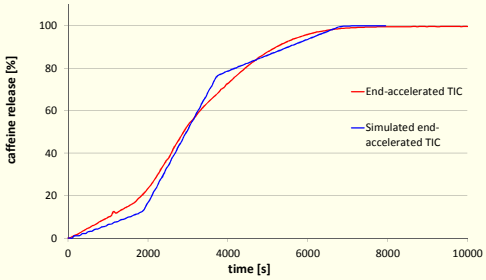


Figure 7. *End-accelerated TIC release real and simulated*

End-accelerated TICs were simulated with F-CAD showing good correlation to in vitro experiments, which allowed successful optimization of the dissolution kinetics in silico.

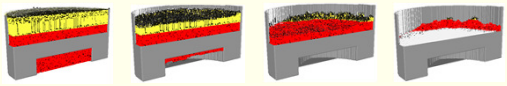


Figure 8. *Visualization captures of F-CAD during release simulation*

Trials with duloxetine showed constraints of the design: interactions between dissolution media and drug led to gel formation which caused non-linear release kinetics.

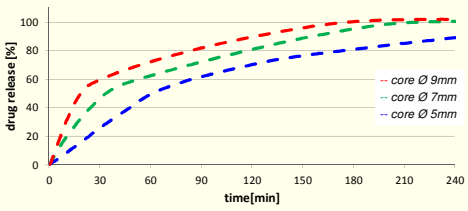


Figure 9. *Duloxetine release from TIC type (a) with different sizes*

CONCLUSION

The TIC drug delivery device represents a promising alternative to conventional oral drug delivery systems. TICs with complex release kinetics can be developed in relatively short time and optimized with the help of simulation software. Further investigations on the TIC design are suggested.

REFERENCES

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[2] Puchkov M, Tschirky D, Leuenberger H. 3D Cellular Automata in CAD of Pharm. Formulations in "Formulation Tools for Pharm. Dev." J. Aguilar, ed., Woodhead Publ. 2013.