A dialysis-based biorelevant drug release test using the dispersion releaser technology

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INTRODUCTION

Despite all advances, determining the release of drugs and drug candidates from micro and nanoscaled dosage forms with the existing methodology still remains challenging. Since the traditional 'sample and separate' techniques often subject drug carriers to strong mechanical forces which can disrupt the carrier structure, more often, these methods exhibit poor sensitivity and hardly discriminate the slight differences in drug release resulting from long-term storage or batch-to-batch variations in the production process.

In comparison, dialysis-based approaches are limited by the inherent barrier properties of the dialysis membrane used for the separation of the drug from the dispersed carrier. After a compound was released into the donor chamber, the drug permeates into the acceptor compartment.

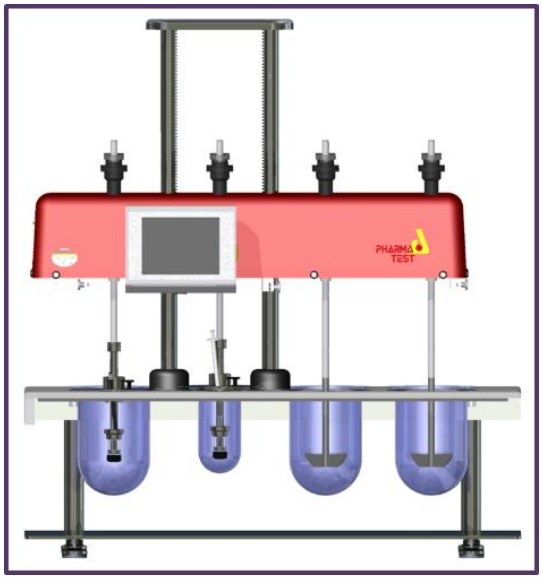

Fig. 1: 3D model of a USP apparatus 2 dissolution tester with a dispersion releaser system in standard vessel and mini vessel configuration.

Depending on hydrodynamics, the formation of immobile water layers can reduce diffusivity and delay the drug release measured in the acceptor compartment

In the present study, the dispersion releaser (DR) technology (see Fig.1) [1] was compared to a traditional 'sample and separate' approach. For this purpose, the drug release of flurbiprofen from polycaprolactone (PCL) nanoparticles was determined in fasted state simulated gastric fluid (FaSSIF) and fasted state simulated intestinal fluid (FaSSIF-v2).

These biorelevant media contain a high amount of proteins and emulsifying agents, resulting in a more difficult dialysis process. Afterwards, the release profiles measured with the DR technology were normalized using the four step model [1,2] to obtain real-time information on the in vivo drug release.

MATERIALS AND METHODS

Formulation

The nanoparticle formulations were manufactured at medium-scale using microfluidic technology as described previously [3]. A combination of polycaprolactone (PCL) and Pluronic F68 was employed. PCL was dissolved in acetone and mixed at defined rates with the aqueous solution.

Particle characterization

The particles were characterized for their particle size, polydispersity index, and zeta potential by dynamic light scattering. Additionally, number size distribution was determined by nanoparticle tracking analysis. The encapsulation efficiency was quantified as described previously [2].

Biorelevant in vitro drug release test

All particles were characterized for their drug release by syringe filtration (pore size 0.1 µm) as well as in the DR setup [1]. The suspension was filled into the donor chamber and released over a time period of 24 h. Samples were collected at predetermined time points and medium was replenished. A RC membrane (MWCO, 50 kDa) was used for the separation. A USP apparatus 2 (Pharma Test Apparatebau AG, Hainburg, Germany) was applied. All release tests conducted with the DR were normalized using the four-step model [1,2] with the help of R (www.r-project.org). For this purpose, reference experiments were conducted at elevated pH to determine the membrane permeation.

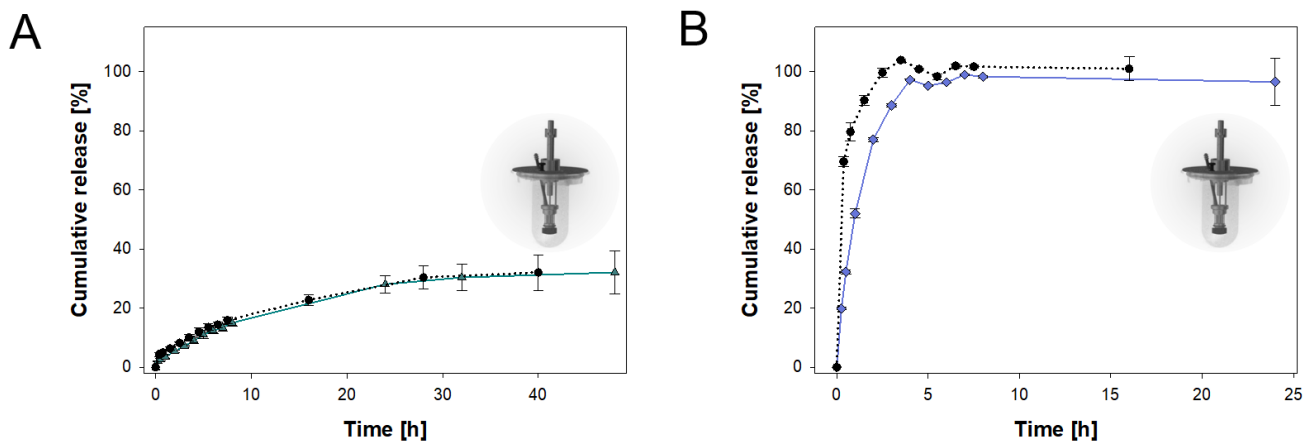

Fig. 2: Normalized (dotted line) and non-normalized (straight line) drug release profiles of a PCL nanoparticle formulation tested under non-sink conditions in FaSSGF (A) and sink conditions in FaSSIF (B).

RESULTS

To compare the DR technology with a syringe filtration method, a high-quality nanoformulation was manufactured using microfluidics as described previously [3]. The nanoparticles were loaded with flurbiprofen by nanoprecipiation and exhibited a high encapsulation efficiency of 96.24% ± 0.03%. Particle manufacture was highly reproducible and resulted in carriers narrowly distributed in size and with an average particle diameter of 197.0 nm ± 0.8 nm. The particle suspension remained stable even after exposure to biorelevant media.

Initially, the permeability coefficients of flurbiprofen were calculated from a reference experiment with each of the two biorelevant fluids. As a result of the forced dialysis approach, this important parameter was comparable to the one observed with buffer media when using the DR technology [1] ($2.15 \times 10^{-3} \pm 0.11 \times 10^{-3}$ cm²/h for FaSSGF and $2.34 \times 10^{-3} \pm 0.09 \times 10^{-3}$ cm²/h).

In presence of FaSSGF, a lowered solubility of flurbiprofen resulted in a sustained release of the drug from the nanoparticle formulation. Under these conditions, the membrane transport had only minor effect on the total release profile as indicated by the normalized profile (see Fig. 2 A). The plateau was reached at 32.1% ± 6.0%.

In FaSSIF-v2 a very rapid release of flurbiprofen from the nanoparticle formulation was observed (see Fig. 2 A). As the membrane permeation was rate-limiting, normalization revealed a more pronounced effect (see Fig. 2 B).

The filtration experiments led to similar results with regards to the total drug release of 27.3% ± 0.15% in FaSSIF and 91.0% ± 5.3% in FaSSIF-v2. However, for both media, the plateau was reached at the first sampling time point indicating a poor sensitivity for variations in drug release.

CONCLUSION

The DR technology offers great potential in the investigation of drug release properties of dispersed drug carriers. Even in presence of biorelevant media, the forced dialysis approach resulted in a reliable and highly reproducible release profile. Compared to the filtration method an enhanced sensitivity was confirmed. Ongoing research has to confirm the relevance of these differences for the *in vivo* situation.

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