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Challenges in the drug release testing of next-generation nanomedicines – What do we know?

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Abstract

Despite all advances in drug delivery, the limitations of the analytical technologies involved in the characterization of next-generation nanomedicines are still impeding further progress of an emerging market. Discriminating between different formulations and batches, drug release is one of the most important quality criteria in development and quality control of pharmaceutics. Unfortunately, there are only few methods available to sensitively measure this important parameter for nanosized carriers. With the development of the dispersion releaser (DR) technology our group has set up a dialysis-based technique that was tested with a number of nanocarrier and nanocrystal formulations such as liposomes and polymeric nanoparticles. By supporting formulation development with a more reliable methodology to assess the drug release from nanosized carriers, a first step has been made to improve future products.

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Keywords: Nanocarriers, QbD, release testing, dissolution, nanoparticles, liposomes

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1. Drug release testing of next-generation nanomedicines

Over the past decades nanomedicines have become increasingly important in global markets. With the emerging number of nanocarrier designs such as liposomes, nanocrystals and polymeric nanoparticles, there is also a need for advances in the analytical technology.

Today we know that many of the *in vitro* assays and tests that are applied to nanosized carriers interfere with the unique structures of such materials [1]. One good example is the separation technology that is used to assess the drug release from novel drug delivery devices. The poor sensitivity of the methods applied in development and quality control of nanocarriers may also be responsible for the lack of pharmaceutical quality and reproducibility of production processes which have been reported earlier [2].

Accordingly, the Food and Drug Administration of the United States of America (US-FDA) and the European Medicines Agency (EMA) have described the drug release to be an essential parameter in the regulatory procedures for liposomes [1,3]. However, after years of development, there is still no gold standard established. Commonly, the *in vitro* release of nanosized carriers is assessed with the help of 'sample and separate techniques' or dialysis-based procedures. Both technologies have their limitations with regards to with different carrier species.

The 'sample and separate' techniques utilize filtration [4,5], centrifugation [6] or solid phase extraction [7] for separation of the drug from the carrier material. More often, there is a certain risk of disrupting the carrier structure by subjecting these matrices to shear forces. Further, the adsorption to column or filter material may play a role in the sensitivity of the method.

Dialysis-based techniques are limited by the barrier properties of the dialysis membrane which is used for the separation. Speaking of drug release testing, more often a membrane sac is filled with the nanocarrier formulation which serves as a donor chamber releasing the drug through the membrane into the acceptor compartment. There are

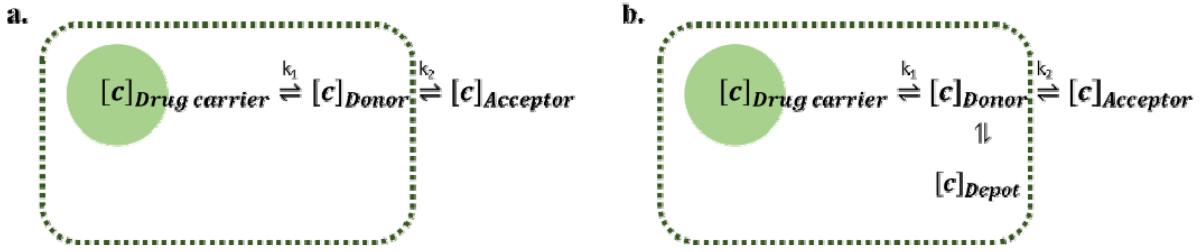

Fig. 1 (a) Schematic of the diffusion processes involved in the separation of drug and carrier material by dialysis (b) Schematic of the depot formation as a result of partitioning inside the acceptor compartment.

mainly two kinetics involved in the total release profile: the rate of the drug released from the carrier (k_1) and the permeation rate through the dialysis membrane (k_1, see Fig. 1b).

In the past mathematical models have been applied to calculate k_1 from the release profiles [8]. For this purpose, the rate constant of the membrane transport k_2 is calculated from a reference experiment using the free drug. This procedure is the more accurate, the faster the transport of the drug substance through the membrane during the dialysis experiment. An accumulation of the free drug in the donor compartment may result in crystallization or partitioning effects forming a drug depot (see Fig. 1b). The dialysis bag method has been utilized several times to determine the drug release. Unfortunately, the hydrodynamics inside the sac often slow down the membrane transport and make these partitioning effects more likely.

These limitations of the analytical technology undermine the sensitivity of the method for slight fluctuations in the release profile. It is widely known that Doxil®, one of the most successful liposome formulations of the past, releases almost 30% of the compound within the first hour after injection as indicated by its biphasic pharmacokinetic profile [9]. This early release also impacts the capacity of the nanocarrier system for a directed transport of the compound inside the human body. Implementing more sensitive release tests into the pipeline of

formulation development would also allow the prediction of such effects and could lead to a better understanding of the interplay between formulation design and therapeutic outcome.

2. Dispersion releaser technology

One important aspect in the implementation of quality standards in pharmaceutics was the harmonization of the equipment applied to dissolution and release testing between different countries. In nanomedicines, there are only few technologies available that take advantage of these compendial methods. Between 2011 and 2013 our group developed the dispersion releaser (DR) technology to deal with the issue of drug release testing of next-generation nanomedicines. There were several requirements defined during the early phase of this project. The release test should be based on the harmonized compendial equipment proposed by the European Pharmacopeia (EP), the United States Pharmacopoeia (USP) and the Japanese Pharmacopoeia (JP). Further, it should allow the testing of nanoformulations for different purposes: in biorelevant release tests which may be conducted during formulation development but also in quality control. With a first version of the dispersion releaser at hand we applied for patent in 2013 [10]. The DR is a dialysis cell (see Fig. 2) that is placed in the dissolution vessel of the apparatus 2 described by the USP. A constant stirring of the liquid in the donor chamber results in an increased membrane pressure and a directed flow of the medium to the dialysis membrane. The patent was licensed to Pharma Test Apparatebau AG (Hainburg, Germany) in 2016 and a commercial version of the equipment will be available soon. Up to now, we evaluated the technology with a number of drug formulations including polymer nanoparticles [11], microparticles composed of natural polymers [12] and liposomes [13] (see Fig. 3). Further, several biorelevant media were employed during these release tests to make sure that the medium composition does not interfere with the separation procedure. In future, further studies will be conducted to sensitively measure this essential parameter and to improve the design and composition of nanocarriers.

Fig. 2: Photograph of the dispersion releaser filled with nanoparticles loaded with an orange dye.

3. Progresses in nanomedicine

Assessing the drug release of nanocarriers is only one step on the road to more effective and safe nanomedicines. Since several regulatory authorities have implemented the “quality by design” paradigm into their frameworks, there was a growing interest in predictive markers that may be used to simulate the *in vivo* situation in an *in vitro* setup. More than other products, nanomedicines impact the biodistribution of drugs. Therefore, predicting the *in vivo* performance will require a combination of different methods including cell-based assays, release studies and also *in vivo* data. In a reflection paper on the data requirements for intravenous liposomal products, the EMA is pointing out that more *in vivo* studies will be required for nanomedicines than for other products, due to the poor predictive power of the existing *in vitro* assays. This issue will not solely be solved by the implementation of harmonized and more sensitive *in vitro* release tests. But there will be an improvement in the quality standards which also contributes to a more reliable nanotechnology. More research will be conducted to illustrate the value of these tools in formulation development and safety assessment of nanomedicines.

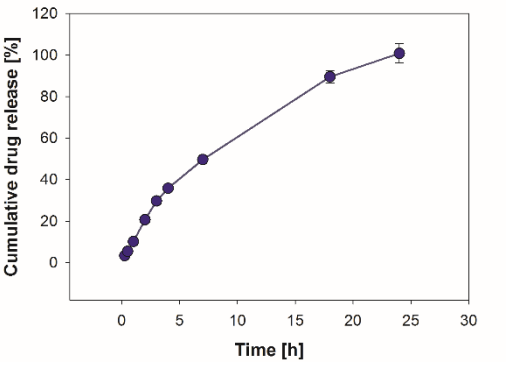

Fig. 3: Drug release test conducted with a PEGylated liposome formulation in the dispersion releaser setup (n=3) at pH 7.4 in presence of serum proteins.

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