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Cover story

The lack of IVIVC for monoacyl phospholipid-based self-emulsifying drug delivery systems

Modern drug discovery has led to a large number of new drug candidates, but many of them have low water solubility and/or limited oral absorption to be clinically useful. Of the many strategies addressing the poor water solubility, amorphous and nanocrystalline drug delivery systems and lipid-based drug delivery systems (LbDDSs) have been successfully used for their simplicity to yield many clinical products. LbDDSs assist the oral absorption of drugs mainly by enhancing drug solubilization, permeability, and lymphatic transport. Among different types of LbDDSs, self-emulsifying drug delivery systems (SEDDSs) are especially useful to enhance oral bioavailability, due to usually low food effects and reduced inter- and intra-personal variations. It is often suggested that drug absorption should be related to the emulsion droplet sizes, colloidal structures formed during lipid digestion, and drug solubilization provided by the dispersion and digestion of the lipid at the absorption site. Since the formulation performance may dramatically be affected by the lipolysis process, *in vitro* lipolysis models have been used for a decade to predict the *in vivo* performance of lipid-based formulations before preclinical studies. Despite several variations, most *in vitro* lipolysis models use similar parameters simulating human conditions of lipid digestion. During each *in vitro* lipolysis assay, formulation scientists can characterize the colloidal systems and evaluate the capacity of the digested formulation to maintain the drug in solubilized form. Testing formulations in *in vitro* lipolysis models and then validating the absorption enhancement effect in an *in vivo* animal model is a common approach when developing new LbDDSs.

The paper published by the research group of Professors Anette Müllertz and Thomas Rades in this issue presents the traditional approach to develop SEDDSs containing monoacyl phosphatidylcholine (MAPC) by evaluating their performance in an *in vitro* lipolysis model simulating human condition and their *in vivo* performance in rats [1]. MAPC is a natural surfactant which has been recently used in SEDDSs to reduce the amount of synthetic surfactants [2]. Fenofibrate was selected as a lipophilic model drug. To study the effect of MAPC incorporation, two MAPC-containing SEDDSs were compared with two MAPC-free SEDDSs for the emulsion droplet size, extent of digestion, colloidal structure evolution and drug precipitation during *in vitro* lipolysis simulating human conditions of lipid digestion. Dynamic light scattering was used to measure emulsion droplet sizes formed during formulation dispersion and lipolysis in a simulated intestinal fluid. Interestingly, the Müllertz-Rades group used, for the first time, an *in vitro* lipolysis model coupled to an *in situ* synchrotron small/wide-angle X-ray scattering (SAXS/WAXS) to simultaneously study the kinetics of colloidal structure development and drug precipitation during the digestion. The drug precipitation profile during the lipolysis was confirmed by *ex situ* HPLC. After being tested in *in vitro* studies, four formulations were tested in a pharmacokinetic study in rats.

Adding MAPC increased the emulsion droplet sizes and polydispersity of dispersed SEDDSs. The kinetics of colloidal structure development was correlated to the digestion kinetics. The two MAPC-free SEDDSs generated lamellar phase structures (Lα) during *in vitro* lipolysis. Incorporating MAPC into these systems inhibited the formation of these lamellar phase structures. The amounts of precipitated crystalline fenofibrate from the four SEDDSs were similar during the first 15 min, but differed during the last 45 min of *in vitro* lipolysis. Although the four SEDDSs differed during the *in vitro* lipolysis in emulsification, digestibility, colloidal structure formation, and drug solubilization capacity during lipolysis, the *in vivo* pharmacokinetic data showed no significant differences between the SEDDSs. Thus, the *in vivo* data only correlated with the fenofibrate precipitation during the first 15 min of *in vitro* lipolysis. The fenofibrate absorption in rats was not correlated to the presence of MAPC, different emulsion droplet sizes and concentration of lamellar phase structures. This lack of correlation is possibly due to a discrepancy between the *in vitro* lipolysis and rat *in vivo* model. The *in vitro* lipolysis model may be very sensitive to minor differences in formulation characteristics, which, however, are not different enough to yield a significant impact *in vivo*. Rat intestinal fluids have lower enzyme activity and higher bile salt and phospholipid concentrations, and thus, provide better drug solubilization than human intestinal fluids. In addition, the *in vitro* lipolysis model might oversimplify the biological system that it simulates by neglecting the effect of gastric emptying and continuous absorption.

The *in situ* synchrotron SAXS/WAXS can provide details about the complex evolution of formulations during *in vitro* lipolysis, which are more accurate than combining other *ex situ* techniques. The crucial role of accurate characterization techniques and a predictive *in vitro* model is obvious in formulation development. As reported in the study by the Müllertz-Rades team, only the initial phase of the human *in vitro* lipolysis was predictive for the *in vivo* performance of the SEDDSs in rats. Thus, an *in vitro* model should be specifically designed to simulate an animal model to more successfully predict formulation performance. The importance of the study by the Müllertz-Rades group is their careful design of the experiments and their open mind of analyzing the data without any preconceived opinion. As important is their courage to present the so-called negative data. Many would have tried to use a portion of the data to make a story of positive correlation. The authors have shown how a good experiments can be done and how the data should be interpreted.

References

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