# PhD thesis 2018 by Cecilie Maria Madsen

## Abstract

During the discovery and development of a potential new drug compound, it is desired to know about potential pitfalls in regard to its developability. *E.g.* if the aqueous solubility of the compound will limit the bioavailability of the compound after oral administration, then knowing about this limitation early will enable studies of different formulations strategies which might compensate for the poor aqueous solubility. The purpose of this thesis was to develop small-scale physiologically relevant physico-chemical tools for the assessment of key properties of a compound important for its performance after oral administration.

The solubility at the site of absorption after oral administration, *e.g.* in the proximal small intestine, is critical for the bioavailability of compounds with poor aqueous solubility. If the compound is not in solution at the site of absorption, it cannot be absorbed sufficiently into the body and will not be effective. The fluid of the human proximal small intestine, where a compound should be dissolved, varies in composition both within and between individuals. Different components of the human intestinal fluid (HIF) can influence the solubility of compounds with poor aqueous solubility significantly. In this thesis work, a design of experiments (DoE) was set up, to study the extent of variation in solubility of poorly soluble compounds in differently composed simulated intestinal fluids (SIF), and to learn which components of HIF influences the solubility of different compounds. The solubility of six model compounds (aprepitant, carvedilol, felodipine, fenofibrate, probucol, and zafirlukast) were analysed in SIF media simulating different HIF compositions. The composition of the SIF for this study was designed by MODDE, a design of experiments software. Five factors were varied across 21different DoE SIF media: pH, bile salt concentration, phospholipid concentration, osmolarity and buffer capacity. The solubility data of the six model compounds was analysed with MODDE. A model describing changes in solubility for each compound could be fitted ($R^2$ = 0.999-0.924 and $Q^2$ = 0.997-0.819). The changes in pH, bile salt concentration, and phospholipid concentration was overall important for the solubility of all compounds. It was found that changes in osmolarity and buffer capacity did not influence the compound solubility to a high degree and these factors could be excluded from the six models with little influence on the model fits ($R^2$ = 0.987-0.826 and $Q^2$ = 0.980-0.726). From these data, a smaller DoE was suggested, where only three factors were varied in the SIF media: pH, bile salt concentration, and phospholipid concentration. This reduced DoE, with 11 different media, was tested on danazol. A model could be fitted ($R^2$ = 0.956 $Q^2$ = 0.945), describing changes of danazol solubility in differently composed SIF. It was shown that the resulting model could predict danazol solubility in HIF.

For poorly soluble compounds, a supersaturating drug delivery system (SDDS) can be employed as a strategy enabling a possible higher bioavailability. An experimental setup, the standardized supersaturation and precipitation method (SSPM), was developed for the evaluation of a compound's propensity to supersaturate. The SSPM was developed from studies of six model compounds (albendazole, aprepitant, danazol, felodipine, fenofibrate, and tadalafil) and was found to be broadly applicable. Several concentrations of supersaturation were studied for each compound, allowing for an easy comparison of supersaturation behaviour between compounds. The effectiveness of two precipitation inhibitors (PI), polyvinylpyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC) was tested in the SSPM setup. The supersaturation behaviour of danazol was also tested in the 11 different SIF media, from the reduced DoE. It was found that changes in supersaturation behaviour of danazol in differently composed SIF media correlated with the changes seen in solubility of danazol in the same SIF.

One way of obtaining an SDDS-formulation for oral delivery, is to prepare a solid formulation with the amorphous form of a compound. When the amorphous compound dissolves, it will, in most cases, result in a supersaturation. The supersaturation will allow more compound to be available for absorption, compared to a solution obtained from a corresponding crystalline form. Zafirlukast is a poorly soluble compound and the amorphous form of zafirlukast has been marketed as . Accolate® has to be administered without food, due to a known negative food effect. It is well known that co-administration of a formulation with food, in many cases, can affect the

bioavailability of an administered compound significantly. It was interesting to investigate if a negative food effect, as seen for Accolate®, could possibly be explained or have been predicted by a small scale *in vitro* study of amorphous zafirlukast. The dissolution of amorphous zafirlukast in fasted state SIF resulted in a supersaturation, followed by a rapid precipitation of the crystalline monohydrate form of zafirlukast. The addition of PVP or HPMC, which are both excipients in Accolate®, prolonged the duration of supersaturation for zafirlukast. PVP was found to be most effective at inhibiting precipitation of the two PI, prolonging the supersaturation from approx. 20 min to >20 h and increasing the concentration of zafirlukast during supersaturation. The supersaturation of zafirlukast was studied in different fed state SIF, and it could be concluded that lipolysis products had a negative effect on the duration of supersaturation. A negative effect on the duration of supersaturation was also clear, even in the presence of PVP. Hence, it was concluded, that the negative food effect could possibly be explained by a negative influence of lipolysis products on the duration of supersaturation. Interestingly, the supersaturation concentration of zafirlukast was higher in the fed state SIF which could also have been interpreted as a positive food effect. Consequently, this experimental setup would not be suitable to predict food effects, but was useful to understand food effects and effects of excipients as PI.

In conclusion, two broadly applicable tools, a DoE for solubility assessment and the SSPM, suitable for preclinical discovery work has been presented, as well as an experimental setup for investigations of food effects. These methods can possibly be used for the assessment of key properties of new compounds under development.