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Studying the Propensity of Compounds to Supersaturate: A Practical and Broadly Applicable Approach

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ABSTRACT

Supersaturating drug delivery systems can enhance the oral bioavailability of poorly soluble drug compounds. Supersaturation of such compounds has been studied in many different ways; however, a more standardized method is required. The rationale of choosing suitable concentrations of supersaturation to study has previously been very inconsistent. This makes comparisons between studies and compounds difficult, as the propensity of compounds to supersaturate varies greatly. This study presents a standardized method to study the supersaturation of drug compounds. The method allows, both, for a ranking of compounds according to their supersaturation propensity and the effectiveness of precipitation inhibitors. The time—concentration profile of supersaturation and precipitation was studied *in situ* for 4 different concentrations for 6 model compounds (albendazole, aprepitant, danazol, felodipine, fenofibrate, and tadalafil) in the μDISS Profiler™ in fasted-state simulated intestinal fluid. A relation between the induction time of nucleation and the initial supersaturated concentration could be established based on classical nucleation theory. The model compounds had different propensities to supersaturate. The data show that a single degree of supersaturation or concentration would not have described the different systems adequately. The method could be used in early preformulation for characterization of supersaturation propensity of novel compounds or precipitation inhibitor effects.

Introduction

Many drug candidates in development today are challenged by low dissolution rate and poor aqueous solubility, which can result in low and variable oral bioavailability. To improve the bioavailability of these compounds and thereby their clinical effect, it is often necessary to use enabling formulation strategies. One such approach could be a supersaturating drug delivery system (SDDS).[1] The principle of SDDS is to increase the amount of compound in solution at the absorptive site and thus increase the bioavailability. This can be achieved by a number of formulation strategies,[2-4] for example, by the use of supersaturated self-nanoemulsifying drug delivery systems, enabling supersaturation in the intestinal fluids on digestion,[5] or amorphous drug delivery systems, allowing for a higher apparent solubility than the corresponding solubility of the crystalline form of the compound.[6]

In a supersaturated system, the concentration of a compound exceeds the thermodynamic equilibrium solubility. Hence, the system is by nature unstable and will, over time, revert to a more energetically favorable state (here the thermodynamic equilibrium solubility), by means of precipitation. Supersaturated solutions are often described by the degree of supersaturation (*DS*) that is defined as the ratio between the concentration (*C*) of the supersaturated system and the thermodynamic equilibrium solubility of the compound (Eq. 1):

$$DS = \frac{C_{\text{supersaturation}}}{C_{\text{equilibrium}}} \quad (1)$$

Compounds suitable for a SDDS formulation should be able to achieve an appropriate level of supersaturation over a sufficient

Abbreviations: SDDS, supersaturating drug delivery systems; DS, degree of supersaturation; t_{ind}, induction time; DMSO, dimethylsulfoxide; FaSSIF, fasted-state simulated intestinal fluid; FeSSIF, fed-state simulated intestinal fluid; FaSSGF, fasted-state simulated gastric fluid; SGF, simulated gastric fluid; FaHIF, fasted-state human intestinal fluid; FeHIF, fed-state human intestinal fluid; HGF, human gastric fluid; PI, precipitation inhibitors; HPMC, hydroxypropyl methyl cellulose; PVP, polyvinylpyrrolidone; C_{SS}, concentration of supersaturation.

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period of time, to enable an adequate dose of a drug to be absorbed. However, the supersaturation propensity is an inherent compound property and can vary greatly.

A theoretical insight into the thermodynamics of supersaturated systems will result in a better understanding of the important factors and mechanisms involved in the kinetics of the precipitation. A supersaturated system has an increased chemical potential (μ) compared with the corresponding saturated or unsaturated systems. The increased chemical potential makes the system thermodynamically unstable and acts as a driving force for precipitation. This can be described as in Equation 2 below[7]:

$$\Delta\mu = \mu_{\text{supersaturation}} - \mu_{\text{equilibrium}} \quad (2)$$

In a supersaturated system, $\Delta\mu > 0$ and precipitation will occur. Precipitation is a 2-step process. The first step is the formation of nuclei. This requires activation energy despite the thermodynamically unfavorable state of supersaturation. The required activation energy can be attributed to interfacial tension between the initial nucleus and the solvent. To overcome this, a certain size of the nucleus is required. Nucleus–embryos are continuously forming and disintegrating. At the critical radius (r^*), the nucleus–embryo has the highest interfacial energy. At this stage, the nucleus–embryo can either grow larger and form a nucleus, or disintegrate again. Once the nucleus radius (r) is larger than r^*, the activation energy for the second step, crystal growth, has been overcome. The crystal will hence grow without limitation until equilibrium has been reached (i.e., until $\Delta\mu = 0$). The critical radius (r^*) can be described from the Gibbs–Thomson equation[7]:

$$r^* = \frac{2\gamma\nu}{\Delta\mu} \quad (3)$$

where γ is the specific interfacial energy between the media and the nuclei, and ν is the molecular volume.

Classical nucleation theory describes a relation between the nucleation rate (J) of a system with spherical nuclei and the *DS*. The relationship can be described by Equation 4,[8-11] where k is the Boltzmann constant, T is the absolute temperature, and A is a pre-exponential factor influenced by several elements, such as the growth rate of nuclei–embryos ($r = r^*$) and the stability of the nuclei-embryos[10,12]:

$$J = A \exp\left(\frac{16\pi\nu^2\gamma^3}{3k^3T^3\ln(DS)^2}\right) \quad (4)$$

If the induction time for precipitation (t_{ind}) is assumed to be inversely proportional to the nucleation rate, then a linear relationship between $\ln(t_{\text{ind}})$ and $\ln(DS)^{-2}$ (Eq. 5) can be derived from Equation 4:

$$\ln(t_{ind}) = \alpha + \beta\ln(DS)^{-2} \quad (5)$$

Equation 5 has previous been used in similar context by, for example, Ozaki et al.[13] Whether classical nucleation theory can also be applied to amorphous precipitation is currently unknown.

Previous Work on Supersaturation in a Pharmaceutical Context

Supersaturation has often been studied by the solvent-shift method.[1] Here, the compound is dissolved in an organic and water miscible solvent where the solubility is high (e.g., dimethylsulfoxide [DMSO]). Supersaturation is induced by spiking a small volume of the organic solution into an aqueous medium to achieve a supersaturated solution. The method allows for a convenient way to investigate supersaturation using small amounts of compound, which makes it especially suitable in early drug development where the amount of compound is limited and small scale dissolution setups are routinely used. The challenging part of the solvent-shift method is to identify an appropriate *DS* to study, as the propensity of a compound to supersaturate is highly compound specific. Some compounds can stay in a supersaturated state with a high *DS* without instant precipitation, whereas other compounds readily precipitate at similar or lower *DS* values. Hence, a standardized method to investigate supersaturation is required, which includes a method to determine rational drug concentrations or levels of supersaturation to study.

Previous work (Table 1), using the solvent-shift method, has had different strategies in choosing concentrations of interest for the supersaturation studies: supersaturating the clinical dose,[14,15] using a fixed *DS* or drug concentration,[13,16-22] or adding a predefined volume of a 90 % saturated organic solution.[23] While in some cases, multiple concentrations have been studied,[13,16,19,20] only a single concentration has been studied in most cases.[14,15,17,18,21-23] Further considerations regarding the initial concentration are not discussed in these articles. Thus, there is a need to apply a systematic approach for choosing the *DS* for supersaturation studies in a preclinical setting, where the dose is unknown.

When studying solubility of poorly water soluble compounds, biorelevant media, such as fasted-state simulated intestinal fluids (FaSSIF), have been shown to have a higher predictability of actual *in vivo* solubility than simple pH-adjusted aqueous buffers. Therefore, FaSSIF is widely used during preformulation studies.[24,25] As solubility is a highly important factor in the study of supersaturation, it is relevant to use such a biorelevant medium in supersaturation studies.

Polymers are used as precipitation inhibitors (PI) and work by either slowing down nucleation (prolonging t_{ind}) and/or slowing down crystal growth rate. Therefore, PIs are often used as excipients in SDDS.[21,26] The effect of PI is, however, not defined by the polymer alone, but the effect can be different when used with different drugs or in different concentrations.[21,23] Therefore, the effect of a PI in a formulation is not easily predicted and should be studied case by case. The effect of PI on supersaturated systems has previously been studied by the solvent-shift method.

The aim of this study was therefore 3-fold: (1) to develop a small scale, standardized solvent, shift-based method that is broadly applicable for evaluating the propensity of a compound to supersaturate; (2) to apply the method to 6 model drugs; and (3) to evaluate the ability of the method to discriminate between the effectiveness of different PI.

Materials and Methods

Materials

SIF Powder Original was kindly donated by biorelevant.com (South Croydon, United Kingdom) for the preparation of FaSSIF. Aprepitant (Merck, Kenilworth, NJ), danazol (Sanofi Aventis, Paris, France), felodipine (AstraZeneca, London, United Kingdom), fenofibrate (Veloxis, Hørsholm, Denmark), and tadalafil (Eli Lilly, Indianapolis, IN) were provided from the respective companies.

Albendazole and monobasic sodium phosphate were purchased from Sigma-Aldrich (St. Louis, MO). Sodium chloride, sodium hydroxide, and DMSO were purchased from Merck Millipore (Darmstadt, Germany). Hydroxypropyl methyl cellulose (HPMC; Pharmacoat 606 6 cp) was purchased from Shin-Etsu (Tokyo, Japan), and polyvinylpyrrolidone (PVP, Kollidon 25 Ph.Eur grade) from BASF (Ludwigshafen am Rhein, Germany). Syringe Filter Q-Max RR 13-mm 0.22-μm Cellulose Acetate was purchased from Frisenette ApS (Knebel, Denmark).