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General Commentary

Non-Sink Dissolution Conditions for Predicting Product Quality and *In Vivo* Performance of Supersaturating Drug Delivery Systems

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ABSTRACT

With recent advances in the development of supersaturating oral dosage forms for poorly water-soluble drugs, pharmaceutical scientists are increasingly applying *in vitro* dissolution testing under non-sink conditions for a direct evaluation of their ability to generate and maintain supersaturation as a predictive surrogate for ensuring product quality and *in vivo* performance. However, the scientific rationale for developing the appropriate non-sink dissolution methodologies has not been extensively debated. This calls for a comprehensive discussion of recent research efforts on theoretical and experimental considerations of amorphous solubility, liquid–liquid phase separation, and phase transitions of drugs in a supersaturated solution when dissolution testing is performed under supersaturated non-sink conditions. In addition, we outline the concept of "sink index" that quantifies the magnitude of deviations from perfect sink dissolution conditions in the sink/non-sink continuum and some considerations of non-sink dissolution testing for marketed drug products. These factors should be carefully considered in recommending an adequately discriminatory dissolution method in the performance assessment of supersaturating drug delivery systems.

Introduction

Adequate absorption of orally administered medications involves solubilization of drug molecules in the gastrointestinal (GI) fluid and transport across the membrane of the epithelial cells in the human GI tract. Poorly water-soluble therapeutic candidates require enabling formulation approaches to develop oral solid dosage forms with enhanced solubility to reach the systemic circulation. Hence, Biopharmaceutics Classification System class II and IV drugs may be formulated as supersaturating drug delivery systems (e.g., amorphous solid dispersions [ASDs]) that are capable of generating a supersaturated drug solution during GI transit. Considering the strong dependency of the dissolution performance on the formulation, coupled with the complexity of solid-state characterization for these supersaturating systems, it is necessary to conduct both discriminatory *in vitro* dissolution testing and comprehensive physicochemical characterization (e.g., X-ray diffraction for determining drug crystallinity) to ensure product quality and *in vivo* performance.

Although many comprehensive reviews summarize underlying theories, preparation methods, product development, and physicochemical characterization of oral supersaturating dosage forms,[1-6] very few publications are dedicated to the assessment of *in vitro* dissolution testing in which the kinetics of drug release from the tablets or capsules based on ASD technology should be indicative of their ability to generate and maintain supersaturation *in vivo* with clinical relevance. In the context of solubility and bioavailability enhancement, oral supersaturating drug delivery systems are known to generate a transient but supersaturated drug solution in which the concentration is significantly higher than the equilibrium saturation of their crystalline counterparts. Advanced *in vitro* dissolution techniques have contributed to the real-time quantification of drug concentrations in a supersaturated state without the interference of undissolved or newly formed nano-sized particulates.[7-10] Thus, dissolution methods under non-sink conditions have become an increasingly important strategy in measuring the true performance of supersaturating formulations and drug products by assessing the extent of supersaturation that is generated as well as the

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associated crystal nucleation and growth kinetics. For this reason, concentration–time profiles generated from supersaturated drug delivery systems under non-sink conditions are generally recognized as a direct evaluation of their ability to achieve and maintain drug supersaturation.

Drug release kinetics based on diffusion, swelling, dissolution, or combination of aforementioned mechanisms have been well predicted.[11,12] Mathematical models of general validity have been proposed to describe diffusion-controlled drug release into a finite-volume medium.[13-15] However, supersaturating formulations can generate drug concentrations in the dissolution medium much higher than the equilibrium solubility, triggering nucleation and crystallization events in the dissolution medium under non-sink conditions. Additional modeling work has been performed to simulate dissolution and precipitation kinetics of formulations containing amorphous drugs based on a diffusion-controlled release mechanism into a finite-volume dissolution medium.[16] Although there appears to be an overall consensus in recent literature that recommends non-sink conditions coupled with mathematical modeling and simulation tools to characterize the dissolution behaviors of supersaturating dosage forms, the definition and use of the term "non-sink" has remained ambiguous.

In addition to dissolution testing, many other *in vitro* characterization tests such as powder X-ray diffraction,[17] spectroscopic analysis (e.g., IR, Raman),[18] thermal analysis (e.g., differential scanning calorimetry),[19] and solid-state nuclear magnetic resonance[20,21] have been developed and applied to detect the degree of crystallinity and to measure crystallization kinetics in ASD formulations. On one hand, when the amount of crystalline material is very low, it is quite challenging to quantify the degree of crystallinity in the ASD formulations during storage using common solid-state analytical methods. On the other hand, although it has been shown that the presence of crystal seeds can influence the physical stability of solid-state amorphous pharmaceuticals,[22-24] the potential impact of small amounts of crystal seeds on drug release, formation, and maintenance of a supersaturated drug solution during dissolution is still an area of active investigation. Therefore, the development of a clinically relevant dissolution method for amorphous pharmaceuticals is critical to ensure consistent quality and *in vivo* performance for both brand name and generic ASD drug products over their shelf-life. With this in mind, this commentary aims to highlight topics associated with developing appropriate dissolution methods under sink versus non-sink conditions and to stimulate further discussion of these issues among pharmaceutical scientists. Based on recent scientific understanding of oral supersaturating drug delivery systems, we will address issues related to theoretical considerations and experimental observations for characterizing dissolution and supersaturation behaviors under non-sink conditions, a proper definition of sink versus non-sink conditions, considerations for designing an appropriate dissolution method, and the need for future research in understanding *in vitro–in vivo* correlations for supersaturating formulations.

Theoretical Considerations for Characterizing Dissolution and Supersaturation Behaviors Under Non-Sink Dissolution Conditions

Supersaturation Ratio

A supersaturated solution is one in which the solution concentration exceeds the equilibrium solution concentration of the most stable crystalline form, at a given temperature in a particular solvent system. The degree to which a solution is supersaturated is an important parameter because it affects a number of kinetic processes including crystal nucleation, growth, and solute diffusion across a membrane. The extent of supersaturation in a solution can be expressed in different forms; however, the supersaturation ratio (S) is commonly used in the context of supersaturating oral dosage forms. This term is given by[25]:

$$\ln S = \frac{\mu - \mu^*}{RT} = \ln \frac{a}{a^*} = \ln \frac{\gamma c}{\gamma^* c^*} \quad (1)$$

where μ is the drug chemical potential, c is drug concentration, a is drug activity, γ is the drug activity coefficient, and * is the property at saturation (i.e., for a drug in a solution in equilibrium with the crystal). For dilute solutions in simple media, it can be reasonably assumed that γ/γ^* is 1, and thus, the supersaturation ratio, S, can be expressed as the relative concentrations:

$$S = \frac{c}{c^*} \quad (2)$$

Equation 2 is commonly used to determine the extent of supersaturation in the context of supersaturating dosage forms; however, it has been found that it does not accurately describe the supersaturation in complex media, such as solutions containing micelles (e.g., fasted-state simulated intestinal fluid [FaSSIF]) or cyclodextrins.[26]

Supersaturation and Passive Absorption

The current interest in supersaturating dosage forms stems from the improvements in passive absorption that are anticipated to result from the generation and maintenance of a supersaturated solution in the GI tract. It has been well documented with *in vitro* experiments, using both artificial and biologic membranes that flux across a membrane increases linearly with an increase in free drug concentration and continues to increase as the solution becomes progressively more supersaturated.[27,28] It has been further demonstrated that when the amorphous solubility of the compound is reached, the flux reaches a maximum value, and further increases in concentration beyond this value do not increase the rate of transport across the membrane.[29] Therefore, the amorphous solubility of a compound is an important value to estimate or measure because it marks the upper limit in flux improvement that can be practically achieved using a supersaturated solution. As will be discussed subsequently, formulations that exceed the amorphous solubility exhibit complex phase behavior, which needs to be considered in the context of dissolution testing.

Supersaturation and Crystallization

Supersaturation provides the driving force for crystal nucleation and growth. Therefore, using supersaturated solutions to enhance passive absorption *in vivo* is somewhat of a double-edged sword. On one hand, the higher the supersaturation, the higher the rate of membrane transport. On the other hand, the higher the supersaturation, the greater the likelihood of a phase transition that will deplete the supersaturation and lead to the formation of a new phase. Although the ability of classical nucleation theory to accurately describe the nucleation of experimental systems has been widely debated,[30] it provides a convenient means to understand the role of supersaturation as the thermodynamic driving force for the formation of a crystalline phase. Supersaturated solutions are metastable because clusters of a critical size need to form for crystal nuclei to survive; until these clusters form, crystallization is not observed. However, as the supersaturation increases, the size of the critical cluster decreases, and hence,