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A Review on Evaluation and Development of Supersaturatable Formulation of Poorly Water Soluble Drugs

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ABSTRACT:

Past decade has witnessed the increasing number of poorly water-soluble compounds in contemporary drug discovery pipelines, the concept of supersaturation as an effective formulation approach for enhancing bioavailability is gaining momentum. This is intended to design the formulation to yield significantly high intraluminal concentrations of the drug than the thermodynamic equilibrium solubility through achieving supersaturation and thus to enhance the intestinal absorption. The major problems faced by scientists developing supersaturatable formulations include degree of supersaturation and controlling the rate with the application of polymeric precipitation inhibitor and maintenance of post-administration supersaturation concentration. Scientific publications associated with characterization of supersaturatable systems and related preclinical and clinical pharmacokinetics (PK) studies are reviewed and studied. Precisely, this review will address issues related to assessing the performance of supersaturatable systems including: various approaches for developing supersaturatable formulations, in vitro test methods to evaluate supersaturatable formulations, and in vivo PK study cases which have demonstrated direct relevance between the supersaturation state and the exposure observed in animal models and human subjects.

KEY WORDS: Bioavailability, poorly water-soluble drugs; supersaturation.

1. INTRODUCTION

With the increasing number of poorly water-soluble compounds in modern drug discovery pipelines, the concept of supersaturation as an effective formulation approach for enhancing bioavailability is gaining energy. This is proposed to design the formulation to yield significantly high intraluminal concentrations of the drug than the thermodynamic equilibrium solubility through achieving supersaturation and thus to enhance the intestinal absorption that will ultimately increase the ability to provide clinically reproducible, safe, and efficacious response upon administration[1,2].

For this enhanced intestinal absorption to take place, supersaturation must be obtained and maintained in the gastrointestinal environment for a sufficient long period of time. In vivo induction of supersaturation can be achieved through various formulation approaches. Different approaches to induce supersaturation have recently[2]. The metastable state of supersaturation has to be sustained for a time period sufficiently long in order to improve intestinal absorption. Maintenance of the supersaturated state has been the subject of research of various academic and industrial laboratories recently. It has been demonstrated that application of functional excipients (polymers, surfactants, etc.) can effectively minimize and/or delay drug precipitation in a highly

supersaturated state and this stabilizes supersaturation as shown by appropriate in vitro tests[1-3]. The awareness that supersaturation in the intraluminal environment could enhance intestinal absorption has urged implementation of high throughput precipitation screening methods to evaluate the supersaturation potential during lead selection/optimization and to guide excipient selection during formulation development. As it can be expected that the gastrointestinal environment induces drug precipitation in vivo, in vitro evaluation of supersaturation requires careful consideration of biorelevant test methods simulating physiological environments.

Scientific publications associated with characterization of supersaturatable systems and related preclinical and clinical PK studies are reviewed and analysed. Precisely, this review will address issues related to assessing the performance of supersaturatable systems including:

1. Various approaches for developing supersaturatable formulations

2. In vitro test methods to evaluate supersaturatable formulations, and

3. In vivo PK study cases which have demonstrated direct relevance between the supersaturation state and the exposure observed in animal models and human subjects.

2. Characterization of supersaturated state and precipitation kinetics in vitro

2.1 Biorelevant In Vitro Dissolution Tests

The most commonly used in vitro tests are United States Pharmacopeia (USP) compendial dissolution tests. The goal of such tests is to ensure complete release and dissolution of formulations under sink conditions. Such tests can be of enormous value for many drug products when the important parameters for evaluation are disintegration of the formulation and/or the rate of dissolution of different forms or particle sizes[4]. However, the compendial dissolution tests do not adequately address some important changes (e.g., pH change) and dynamic aspects that an oral formulation undergoes in GI luminal environment. A more physiologically relevant in vitro dissolution measurement is especially important for poorly water-soluble drugs formulated into supersaturatable systems where precipitation/crystallization of drug in GI tract is of a concern. Supersaturation and solution-mediated phase transformation of the drug may result from pH-induced precipitation (e.g., free-base from salt/ionized form), precipitation from solution formulations (e.g., cosolvents, lipids), or amorphous/metastable to stable polymorph/hydrate phase, transformations (e.g., crystallization of an amorphous solid dispersion). Therefore, assessing supersaturatable formulations with the use of biorelevant in vitro dissolution tests which can better represent in vivo conditions is more meaningful and highly desirable.

Various noncompendial dissolution methods have been developed to assess supersaturation under physiologically relevant conditions. Augustijns et al.[5] explored the use of human intestinal fluids as in vitro test medium for supersaturation. The authors revealed that the extent to which precipitation inhibition could be acquired appeared to be compound and excipient dependent. Experiments using intestinal fluids from volunteers in the fasted or fed state evidenced that the nutritional state did not significantly affect the extent of excipient-mediated precipitation inhibition. The usefulness of simple simulated intestinal fluids representative for the fasted or fed state as dissolution media to predict excipient-mediated precipitation inhabitation in human intestinal fluids appeared to be limited. However, the aqueous buffer or simulated intestinal fluids could readily determine the absence of supersaturation stabilization by a given excipient[6].

Artificial stomach and duodena model (ASD) was developed to mimic the process of gastric emptying and potential drug precipitation in the intestinal compartment in biorelevant manner[7]. In this method, a formulation is dispersed in a stomach chamber (20–70 mL) and transferred at a controlled rate to the duodenum chamber and mixed with simulated intestinal fluid (SIF). During this process, fresh gastric fluid and SIF were continuously infused into each chamber. By measuring drug concentration–time profile in the duodena compartment, the dynamic process of drug dissolution, precipitation, and recrystallization can be studied. The in vivo relevance of ASD dissolution profiles is based on the assumption that the concentration of dissolved drug in the simulated duodenum is proportional to its bioavailability. The use of ASD system for the evaluation of supersaturation-based formulations has been reported[8]. Miller el al[9] recently reported a dual pH–dilution test (or a simplified ASD method based on the same concept) for evaluating amorphous solid dispersions

of drug candidate with poor aqueous solubility. The test involves a serious dilution of the formulations using biorelevant dissolution media (pH 4 HCl and FaSSIF), physiologically based dilution factors and transit time simulating the rat GI transit (from stomach to duodenum, jejunum, ileum, cecum, and colon). In vitro drug concentration–time profiles obtained from the pH–dilution method were further used as inputs for PBPK modeling using GastroPlus® to predict in vivo oral plasma concentration profiles[10].

3. SEDDS/Lipid Formulations

Zhang et al.[11] studied the effect of polymers on drug precipitation from self-emulsifying drug delivery systems (SEDDS) formulations of carbamazepine (CBZ) when in contact with water. Their results show that 2% PVP K90 effectively prohibited drug precipitation from a SEDDS formulation for over 24 h (1 g of S-SEDDS in 50 mL 0.1 N HCl at 50 rpm mixing). Addition of 2% PVP K30 or PVP K60 in these formulations also prolonged drug precipitation to 4 h, while hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), and carboxymethyl cellulose (CMC)–Na showed no benefit on preventing drug from precipitation[12,13].

Shi et al.[14] utilized a biphasic in vitro release test method to evaluate three distinctly different celecoxib (CEB) formulations including SEDDS formulation, a solution formulation, and a marketed capsule formulation. Release profiles of CEB observed in the aqueous phase of the biphasic test from the solution and S-SEDDS formulations were comparable. However, their corresponding drug–concentration profiles in the octanol phase differed significantly and this was presumably attributed to different free drug concentrations in the aqueous phase of these two formulations. Due to the high level of surfactant in the solution formulation, CEB was mostly associated with surfactant micelles in the dissolution medium, resulting in a less amount of free CEB in the aqueous phase. In contrast, a substantial lower level of surfactant was utilized in the S-SEDDS formulation which led to the generation of highly supersaturated state of CEB. It is worth noting that CEB release profiles in the aqueous phase exhibited little relevance to the pharmacokinetic observations (e.g., Cmax and area under the curve (AUC)). However, a rank-order correlation was obtained between in vitro drug release profiles in the octanol phase and in vivo PK exposures and Cmax values among the three CEB formulations As the biphasic test permits a quick partition of drug into the organic phase, the amount of drug in the organic phase represents the amount of drug accumulated in systemic circulation in vivo[15].

4. Amorphous Solids

William et al.[16] proposed a mechanism regarding how supersaturation levels are maintained upon dissolution of amorphous particles as illustrated in Fig. 1. Amorphous particles may dissolve to form metastable highly supersaturated solutions. Drug may precipitate from these metastable solutions to lower the free energy depending upon the rate of nucleation to form particle embryos followed by growth via either condensation or coagulation. The growing particles may crystallize as less soluble crystalline form than the amorphous form. Condensation of dissolved molecules onto these crystals will deplete supersaturation[12]. The rate of growth by condensation is directly proportional to the excess surface area of undissolved particles. Growth by coagulation is dependent on the number of particles for a given stability ratio. The authors evaluated supersaturation of itraconazole (ITZ) particles of low to high surface areas when in contact with aqueous medium. To mimic the pH transition from stomach to intestine, the ITZ/hydroxypropylmethyl cellulose particles were exposed to pH 1.2 medium then shifted to pH 6.8 medium. A slow decrease in supersaturation was observed with the medium surface area particles. While the high surface area particles showed fast dissolution and high supersaturation followed by a rapid precipitation with supersaturation reduced from 12 to 4 in only 20 min. The study showed that medium surface particles offered an optimum balance between favorable rapid dissolution and unfavorable nucleation and growth out of solution. This work discovered that the dissolution rate of the drug from related formulations is a critically important factor in dictating the generation and duration of the supersaturated state. A rapid dissolution that generates a high degree of supersaturation may not be optimal to sustain the supersaturation state since it may induce rapid crystallization.

5. Mechanism on Polymeric Precipitation Inhibitor

Augustijns et al.[17] investigated excipient-mediated precipitation inhibition upon induction of supersaturation of five poorly water-soluble drugs (etravirine, ritonavir, loviride, danazol, and fenofibrate) in aspirated human

intestinal fluids at both the fed state and fasted state (FeHIF and FaHIF) and compared with those in simple aqueous buffer, FeSSIF, and FaSSIF. To study polymer effect on precipitation inhibition, supersaturation was induced in test media in the presence of 0.05% (w/v) predissolved polymers (HPMCAS, HPMC-E5, HPMC-E50, HPMC-E4M, HPMC-P, and PVP) at degree of supersaturation (DS) of 20 using a solvent shift method. The polymer effects on supersaturation stabilization appeared to be compound dependent. Etravirine, loviride, and danazol were sensitive to excipient-mediated stabilization of supersaturation. In contrast, these excipients showed insignificant or essentially no effect on ritonavir and fenofibrate. Cellulosic polymers such as HPMC-E5 and HPMCAS showed significant precipitation inhibition, whereas PVP K25 appeared to have no stabilizing effect. In general, the authors reported that excipient-mediated precipitation inhibition was less pronounced in HIF compared to simple aqueous buffer or FaSSIF/FeSSIF.

Talyor et al.[18] proposed two mechanisms that can negate the dissolution advantage of amorphous solids by either crystallization of the amorphous solid on contact with the dissolution medium or through rapid crystallization of the supersaturated solution as shown in Fig. 2. Polymer additives can retard both of these crystallization routes, leading to the generation of supersaturated solutions. Using felodipine as a model compound, the authors reported that PVP was a poor crystallization inhibitor. In contrast, both HPMC and HPMCAS were able to inhibit the crystallization of felodipine and maintain the drug solubility above 7 and 10 µg/mL for at least 4 h, respectively. Indomethacin concentration in the solution upon initial dissolution from amorphous solid decreased rapidly due to solution-mediated crystallization on contact with dissolution medium. Addition of a small amount of either PVP or HPMC at 250 µg/mL in the dissolution medium effectively inhibited the crystallization of drug from supersaturated state for at least 4 h. In another study of the same model drug by the same group, felodipine and related amorphous solid dispersions[19], the authors revealed that the amount of polymer relative to drug has a significant impact on the dissolution behavior of ASDs during dissolution. At low (10%) to moderate drug loading (50%), the solubility of the drug obtained from solid dispersions was similar to that of pure amorphous drug[20].

6. Bio-availability improvement associated with superstation-based formulation

GI factors play a significant role in determining bioperformance of supersaturatable formulations in vivo. These factors include gastric emptying rate, pH variation in different regions (e.g., stomach vs. small intestine), the presence or absence of food, the level of bile salts, and residence times in the region, etc. These factors certainly affect the rates of dissolution and generate a “local super supersaturatable state” that may be highly un-uniform with induced nucleation and precipitation. The GI fluid volume and composition coupled with pH variation and the level of bile salts have been established to affect the apparent solubility of drug in each region and thus impact the in vivo dissolution and ultimately the product performance. Common species used to evaluate drug formulations are rat, dogs, and monkeys. The utilization of animal models to assess bioavailability of supersaturatable formulations is of importance in formulation development with implication to oral absorption in humans. However, the complexity of physiological factors associated with human subjects considerably increase when species differences are considered in the preclinical in vivo PK screening studies.

7. In Vivo Study in Animal Models

A study was reported by Augustijns et al.[21] on the relationship among the drug release rate, the rate of achieving supersaturation, and corresponding biopharmaceutical performance from mesoporous formulations of fenofibrate. The relevance to the in vivo situation of the aforementioned effects is demonstrated by the PK profiles in rats. The authors emphasized the qualitative agreement between the in vitro release experiments conducted under supersaturating conditions and the in vivo data. As PK profiles in the fasted state, FFB:SBA-15-A exhibits a significantly lower exposure than those of FFB:SBA-15-B and FFB:MCM-41. This indicates that a short-lasting supersaturation due to rapid release from FFB:SBA-15-A did not yield optimal in vivo performance. Similarly, FFB:MCM-41 exhibits both the highest AUC and highest Cmax in the rats in fasted state, indicating that the slower release rate resulted in a more sustained supersaturation in intestinal media (as demonstrated in vitro). As these authors concluded that the decrease in drug release rate is accompanied by a decrease of the supersaturation rate and it is beneficial to the absorption of fenofibrate. These data suggest that it is

essential not to "dump" the entire drug load instantaneously, but instead release it in a gradual fashion such that absorption can take place while the drug is being released.

8. CONCLUSIONS

Supersaturatable formulations are intended to generate a supersaturated drug solution in vivo upon contact with GI fluids and maintain sufficiently long supersaturated state with the use of polymeric precipitation inhibitor. Supersaturated state created from appropriate supersaturatable formulations has been demonstrated to significantly improve intestinal absorption of poorly soluble drugs.

In this review, we attempted to summarize important formulation factors that affect the therapeutic performance of supersaturatable formulations from an in vitro and in vivo viewpoint. As we learned from these excellent scientific publications, it is of critical importance to gain understanding of the physiological factors associated with the GI tract and their relevance to absorption of weakly acidic and basic drugs. Therefore, we consider it necessary to apply appropriate biorelevant dissolution tests to examine these systems and acquire knowledge of the interplay between formulation and physiological factors. In addition, with the assistance of theoretical modeling and simulation approaches for PK profile, understanding of superstaturation and its impact on improvement of oral absorption in vivo will be imposed. The selection of a predictive animal model for testing the bioavailability of formulations should be made on a case-by-case basis, where the anticipated physiological rate-determining factors will dictate the selection of the species that is most analogous to humans for testing the specific compound. We anticipate that the advancement of characterization of supersaturated state by appropriate means and establishing their relevance to oral absorption in vivo will greatly facilitate the development and commercialization of supersaturatable formulations.

Conflict of interest

The authors reports no conflict of interest

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Figure 1. Mechanisms for depletion of supersaturation in solution where m is mass of drug in solution; A total particle surface area, C drug solution concentration, Csat drug solubility, Npert number of drug particles per volume, Kr rate constant, Nemb number of embryos per volume, Asp specific surface area (area/mass), and dpert diameter of the particle[16]

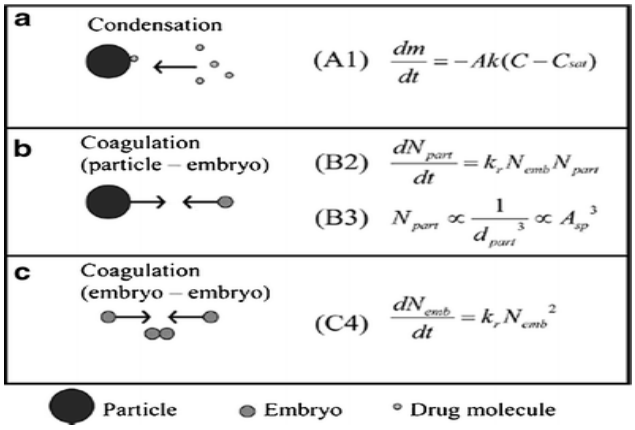

Figure 2. Schematic illustration of the competition between dissolution and crystallization via solid or solution state of amorphous systems[18]