REVIEW

Supersaturating Drug Delivery Systems: The Answer to Solubility-Limited Oral Bioavailability?

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ABSTRACT: Contemporary pharmaceutical pipelines are often highly populated with poorly water-soluble drug candidates necessitating novel formulation technologies to provide dosage forms with appropriate biopharmaceutical properties. The configuration of supersaturating drug delivery systems (SDDS) is a promising concept to obtain adequate oral bioavailability. SDDS contain the drug in a high energy or otherwise rapidly dissolving form such that intraluminal concentrations above the saturation solubility of the drug are generated. For the strategy to be useful, the formed supersaturated solution must then be stabilized to allow for significant absorption and eventually sufficient bioavailability. The stabilization of a supersaturated solution can be accomplished by adding precipitation inhibitors which may act through a variety of mechanisms. The goal of this review is to assess methods and excipients associated with the development of SDDS and provide some context for their use. In addition, the future directions and factors likely to contribute to or detract from optimal dosage form selection are assessed. This includes a discussion on the potential effect of the gastrointestinal physiology on the ability to attain and maintain supersaturation as this information is essential in designing useful formulations based on the supersaturating concept. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:2549–2572, 2009

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INTRODUCTION

A highly complex interacting system of parameters associated with absorption, distribution, metabolism, and excretion (ADME) determines the pharmacokinetic profile of orally administered drugs in relevant test species or in man. The absorption component of this cascade, a necessary but not sufficient step for drug bioavailability, can be assessed in the context of Fick's First law, where the flux (J) of a drug through the gastrointestinal wall depends on the permeability coefficient (P) of the gastrointestinal barrier for the drug and the drug concentration (C) in

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the gastrointestinal lumen (assuming sink conditions):

$$J = PC \tag{1}$$

This relation is the basis to classify drugs in the biopharmaceutical classification system (BCS) according to permeability and solubility criteria.[1]

For poorly water-soluble drugs (BCS class II and IV), the maximum achievable intraluminal drug concentration may limit absorption. As described by Lipinski and others, the introduction of high-throughput screening and combinatorial chemistry in drug development has resulted in a shift such that more new chemical entities suffer from limited aqueous solubility and/or poor dissolution properties.[2–4] Therefore, various approaches in drug formulation development have been directed at increasing the dissolution rate and improving drug solubilization in the gastrointestinal tract.[5] It should be recognized, however, that the intraluminal concentration of a drug is not necessarily limited by its solubility in gastrointestinal fluids. Drugs may be in solution at a concentration above their saturation solubility, that is, in a state of supersaturation. The degree of supersaturation can be expressed by the supersaturation ratio S:

$$S = \frac{C}{C_{eq}} \tag{2}$$

with C_{eq} representing the equilibrium solubility (saturation). An alternative way of expressing supersaturation is the relative supersaturation index σ, defined as

$$\sigma = S - 1 = \frac{C - C_{eq}}{C_{eq}} \tag{3}$$

A solution is defined as unsaturated, saturated or supersaturated based on the following relationships: $S < 1$ ($\sigma < 0$), $S = 1$ ($\sigma = 0$), or $S > 1$ ($\sigma > 0$), respectively.

As the chemical potential of a supersaturated system is increased compared to the equilibrium condition (saturation), a supersaturated drug solution is thermodynamically unstable and has the tendency to return to the equilibrium state (lowest chemical potential) by drug precipitation. If, however, a supersaturated drug solution exists in a metastable state in the gastrointestinal lumen for a time period sufficient for absorption, the increased intraluminal drug concentration can result in an enhanced flux across the intestinal wall.

The potential impact of supersaturation on the transport of drugs across biological membranes was first recognized by Higuchi.[6] Since then, the role of supersaturation has been most extensively studied in the field of transdermal drug delivery where the link between the saturation state of the drug substance in an applied vehicle and subsequent absorption is fairly well understood. By extension, drugs suffering from solubility-limited oral bioavailability may also profit from the generation of supersaturation in the gastrointestinal lumen.

This review focuses on the concept of supersaturation in the gastrointestinal tract as a strategy to enhance the intestinal absorption of poorly water-soluble drugs. We will discuss the approach of both generating and maintaining supersaturation and illustrate this with examples of supersaturating drug delivery systems. Next, the principles behind precipitation delay by excipients will be discussed more in detail. Finally, various issues regarding the *in vivo* relevance of intraluminal supersaturation and the biorelevance of supersaturation assays will be addressed.

THE SPRING AND PARACHUTE APPROACH

To exploit supersaturation as a strategy to improve intestinal absorption of poorly water-soluble drugs, two essential steps need to be considered: generation and maintenance of the metastable supersaturated state. Guzmán et al.[7,8] described this concept by using the term 'spring and parachute approach', as illustrated in Figure 1.

A thermodynamically unstable, supersaturated solution of a drug can only be generated starting from a higher energy form of the drug (as compared to the crystalline powder), that is, the "spring." A number of formulation options may induce the generation of supersaturated solutions in the gastrointestinal lumen, including the delivery of drugs in solution (e.g., cosolvent systems, lipid-based formulations) and the delivery of high-energy solid forms that provide an accelerated dissolution and/or a higher apparent solubility (e.g., amorphous forms, crystalline salt forms, co-crystals and the like). It should be noted that the term "apparent solubility" describes the apparent equilibrium between drug in solution and a solid whose structure is not in the most stable state.[9,10] Apparent solubilities should not