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Physical chemistry of supersaturated solutions and implications for oral absorption☆

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ABSTRACT

Amorphous solid dispersion (ASD) formulations are widely used for delivery of poorly soluble drugs for dissolution enhancement and bioavailability improvement. When administered, ASDs often exhibit fast dissolution to yield supersaturated solutions. The physical chemistry of these supersaturated solutions is not well understood. This review will discuss the concepts of solubility, supersaturation, and the connection to membrane transport rate. Liquid–liquid phase separation (LLPS), which occurs when the amorphous solubility is exceeded, leading to solutions with interesting properties is extensively discussed as a phenomenon that is relevant to all enabling formulations. The multiple physical processes occurring during dissolution of the ASD and during oral absorption are analyzed. The beneficial reservoir effect of a system that has undergone LLPS is demonstrated, both experimentally and conceptually. It is believed that formulations that rapidly supersaturate and subsequently undergo LLPS, with maintenance of the supersaturation at this maximum value throughout the absorption process, i.e. those that exhibit "spring and plateau" behavior, will give superior performance in terms of absorption.

Contents

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1. Introduction

It has been almost 20 years since Lipinski first proposed the "Rule of Five," outlining desirable physicochemical properties, i.e. drug-like properties, for efficient oral delivery of active pharmaceutical agents [1]. However, the percentage of insoluble compounds in discovery and development pipelines across the pharmaceutical industry continues to increase. While 40% of approved drugs are considered insoluble, nearly 90% of developmental compounds are poorly soluble [2]. Moreover, the extent of insolubility is also becoming worse. In the 1990's, an equilibrium solubility of 100 μg/mL might have been considered highly insoluble. Nowadays, pharmaceutical scientists feel fortunate to have drug candidates with an aqueous solubility of 10 μg/mL. Regardless of the reasons underlying the trends in suboptimal aqueous solubility of new chemical entitities (NCE), formulation scientists are tasked with designing formulations that deliver these intractable compounds to patients in an efficient and consistent manner. (See Table 1.)

Over the years, great advancements have been made in this area. Many formulation approaches have been explored and utilized to overcome the challenge of poor solubility. Since the pre-requisite of absorption is the presence of drug molecules in solution, many formulation approaches pre-dissolve the drug in the formulation using cosolvents or surfactant-lipid blends [3]. For most solubility enhancing approaches based on solid dosage forms, the theoretical basis is the Whitney–Noyes equation, coupled with the Nernst–Brunner diffusion layer model, which describes the dissolution of a solid:

$$\frac{dM}{dt} = \frac{DS}{h}(C_s - C) \approx \frac{DSC_s}{h} \quad (1)$$

where M is the mass of solute dissolved, dM/dt is the dissolution rate, D is the diffusion coefficient of solute, S is the surface area of the exposed solid, h is the thickness of the diffusion layer, C_s is the solubility of solute in dissolution medium, and C is the concentration of solute in the dissolution medium. Under sink conditions where C is approximately zero, the right hand side of the equation can be simplified.

Two parameters in Eq. 1, D and h, are dictated by the molecule and human gastrointestinal tract (GIT) conditions and are consequently difficult to influence by formulation. However, both surface area and solubility can be readily manipulated by formulation. Particle size reduction of the active pharmaceutical ingredient (API) using various milling techniques, direct generation of small API particles by rapid precipitation or supercritical fluid technology, has been widely used to facilitate dissolution. More recently, size reduction of the API to the nanometer range has seen application in the delivery of insoluble compounds [4,5]. Many approaches, such as co-formulating with solubilizing agents, using salts, co-crystals, and amorphous solids as the API, and amorphous solid dispersions (ASD), have been employed to enhance solubility.

In the past decade, there has been increasing realization that simply increasing the dissolution rate or solubilizing the API is often insufficient to achieve the desired bioavailability. Consequently, interest in delivery systems that lead to supersaturation has burgeoned. In this context, ASDs, where the API is typically molecularly mixed with or, less commonly, physically suspended in a hydrophilic polymer matrix, are commonly employed. When ASD formulations are administered, dissolution in the gastrointestinal fluids often leads to supersaturation, which drives rapid and sustained absorption. The application of ASDs has gained much attention in the recent years as a result of fundamental work on amorphous pharmaceutical systems [6–15] and experience gained through development and launch of commercial products [16–18]. Other formulation approaches or inherent molecular properties may also lead to supersaturation in vivo. Solubilizing components, such as surfactants, that are added to the formulation, or present in vivo, change the thermodynamic properties and phase behavior of supersaturating systems, resulting in complex systems that are not well understood. The physical chemistry of these supersaturated solutions and the implications for oral absorption are the subject of this review.

Table 1
Comparison of percentages of absorption at residence times of 4 h or 8 h.

	Residence time (h)	
Case	8	4
1	100	65
2		
2a	23	17
2b	46	27
2c	71	52
3	30	11
4	13	6

2. Theoretical considerations

2.1. Crystalline solubility

The solubility of the crystalline solid is a solid–liquid equilibrium (SLE) and is the concentration in solution following attainment of

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