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## Q1 Physical chemistry of supersaturated solutions and implications for oral absorption<sup>☆</sup>

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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.

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## 86 1. Introduction

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

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

$$112 \frac{dM}{dt} = \frac{DS}{h} (C_s - C) \approx \frac{DSC_s}{h} \quad (1)$$

112 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

t1.1 **Table 1**  
t1.2 Comparison of percentages of absorption at residence times of 4 h or 8 h.

t1.3	Case	Residence time (h)	
		8	4
t1.4	1	100	65
t1.5	2		
t1.6	2a	23	17
t1.7	2b	46	27
t1.8	2c	71	52
t1.9	3	30	11
t1.10	4	13	6
t1.11			

solid,  $h$  is the thickness of the diffusion layer,  $C_s$  is the solubility of solute  
113 in dissolution medium, and  $C$  is the concentration of solute in the disso-  
114 lution medium. Under sink conditions where  $C$  is approximately zero,  
115 the right hand side of the equation can be simplified. 116

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

130 In the past decade, there has been increasing realization that simply  
131 increasing the dissolution rate or solubilizing the API is often insufficient  
132 to achieve the desired bioavailability. Consequently, interest in delivery  
133 systems that lead to supersaturation has burgeoned. In this context,  
134 ASDs, where the API is typically molecularly mixed with or, less  
135 commonly, physically suspended in a hydrophilic polymer matrix, are  
136 commonly employed. When ASD formulations are administered, 136  
137 dissolution in the gastrointestinal fluids often leads to supersaturation,  
138 which drives rapid and sustained absorption. The application of  
139 ASDs has gained much attention in the recent years as a result of funda-  
140 mental work on amorphous pharmaceutical systems [6–15] and experi-  
141 ence gained through development and launch of commercial products  
142 [16–18]. Other formulation approaches or inherent molecular proper-  
143 ties may also lead to supersaturation in vivo. Solubilizing components,  
144 such as surfactants, that are added to the formulation, or present  
145 in vivo, change the thermodynamic properties and phase behavior of  
146 supersaturating systems, resulting in complex systems that are not  
147 well understood. The physical chemistry of these supersaturated  
148 solutions and the implications for oral absorption are the subject of  
149 this review.

## 150 2. Theoretical considerations

### 151 2.1. Crystalline solubility

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

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