Journal of Pharmaceutical Sciences 105 (2016) 10–24

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Review

A Review: Pharmaceutical and Pharmacokinetic Aspect of Nanocrystalline Suspensions

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ARTICLE INFO

Article history:
Received 7 August 2015
Revised 23 September 2015
Accepted 25 September 2015
Available online 18 November 2015

Keywords:
nanocrystals
nanosuspensions
nanoparticles
solubility
dissolution
pharmacokinetics
food interactions
bioavailability
particle size reduction

ABSTRACT

Nanocrystals have emerged as a potential formulation strategy to eliminate the bioavailability-related problems by enhancing the initial dissolution rate and moderately super-saturating the thermodynamic solubility. This review contains an in-depth knowledge of, the processing method for formulation, an accurate quantitative assessment of the solubility and dissolution rates and their correlation to observe pharmacokinetic data. Poor aqueous solubility is considered the major hurdle in the development of pharmaceutical compounds. Because of a lack of understanding with regard to the change in the thermodynamic and kinetic properties (i.e., solubility and dissolution rate) upon nanosizing, we critically reviewed the literatures for solubility determination to understand the significance and accuracy of the implemented analytical method. In the latter part, we reviewed reports that have quantitatively studied the effect of the particle size and the surface area change on the initial dissolution rate enhancement using alternative approaches besides the sink condition dissolution. The lack of an apparent relationship between the dissolution rate enhancement and the observed bioavailability are discussed by reviewing the reported *in vivo* data on animal models along with the particle size and food effect. The review will provide comprehensive information to the pharmaceutical scientist in the area of nanoparticulate drug delivery.

Introduction

Recent advances in synthetic, analytical, and purification chemistry, along with the development of specialized tools such as high-throughput screening, combinatorial chemistry, and proteomics, have led to a sharp influx of discovery compounds entering into development. Many of these compounds are highly lipophilic, as the *in vitro* screening techniques place considerable emphasis on the interaction of compounds with defined molecular targets. In recent years, it has been estimated that up to 70% of the new drugs discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds. Poor aqueous solubility is one of the major hurdles in the development of new compounds into oral dosage forms, as absorption is limited by dissolution for these compounds.[1]

The well-known Biopharmaceutics Classification System (BCS) is frequently used to categorize pharmaceutical compounds. According to the BCS system, poorly soluble compounds belong to Class II (low solubility, high permeability) or Class IV (low solubility, low permeability). In another words, we can also say that Class II and IV compounds provide more opportunities for the development of newer technologies to overcome the solubility- or dissolution-related issues based on chemical and physical properties of the compounds. This perception is widely used and well established within the pharmaceutical industry. However, using the BCS system for guidance in formulation selection may sometimes oversimplify the complex nature of drug dissolution, solubility, and permeability. Poorly water-soluble compounds can possess such a low aqueous solubility that the dissolution rate, even from micronized particle, is very slow. In this case, it is not possible to reach sufficiently high drug concentrations in the gastrointestinal tract for an effective flux across the epithelial membrane. Other factors, such as efflux transport or pre-systemic metabolism, can also negatively influence oral bioavailability.

Therefore, it is recommended to classify compounds into slightly different categories, as they can show dissolution rate-limited, solubility-limited, or permeability-limited oral bioavailability. Butler and Dressman[2] designed the "Developability Classification System (DCS)," as another way to categorize compounds in a more bio-relevant manner. This system distinguishes

Conflict of interest: The authors report no conflict of interest.

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http://dx.doi.org/10.1002/jps.24694
0022-3549/

between dissolution rate-limited compounds (DCS Class IIa) and solubility-limited compounds (DCS Class IIb).

In order to select the right formulation approach and to address the compound-specific issues with a suitable formulation type, it is imperative to first understand the bioavailability limiting factors. Selection of the right formulation approach is one of the key activities for formulators in the pharmaceutical industry. Key factors include the physicochemical properties of active pharmaceutical ingredient (API), such as aqueous solubility, the melting point temperature, and chemical stability. In addition, the formulator needs information about the potency of the compound and the desired route of administration to determine the type of final dosage form as well as the required drug load. All these factors can be considered in decision trees, which are often used in the industry to guide the formulator.

However, there are some biopharmaceutical-relevant aspects that need more attention in order to avoid false negative results. In addition, it is also important to note that there is no uniform approach that solves all the formulation-related problems. Each technology has its own advantages and disadvantages. Depending on the formulator's understanding of the interplay between the physicochemical properties of the drug, the special aspects of the various formulation options and the required *in vivo* performance, the higher the chance that the optimal formulation approach will be chosen. This minimizes the risk of late failures in the human clinical trials, for example, due to insufficient or highly variable drug exposures. Compounds showing dissolution rate limited bioavailability may be referred to as DCS Class IIa compounds, but they represent only one part of the BCS Class II compounds. The extent of the oral bioavailability of such compounds directly correlates with their dissolution rate *in vitro*. The fraction of the dose that dissolves in the lumen is readily absorbed through the intestinal membrane. Consequently, the bioavailability of such compounds can be improved by any technique that increases the primarily the dissolution rate. Various formulation approaches are known to lead to increased dissolution rate and bioavailability, including salt formation, the use of cocrystals, particle size reduction, complexing with cyclodextrins,[3] microemulsions,[4] and solid dispersion technologies.[5,6] The formulator has to select the optimal formulation approach based on the properties of a specific drug molecule. However, all these technologies have certain limitations and cannot be used as universal formulation techniques for all the poorly soluble compounds, especially those which are insoluble in both aqueous as well as non-aqueous solvents.[7] To prevent the removal of poorly soluble compounds from the pharmaceutical pipeline, a broad-based technology is required for drug molecules that are insoluble or poorly soluble in both aqueous and non-aqueous solvents. This will have the tremendous impact in discovery sciences and will improve the performance of existing molecules suffering from formulation-related issues.[8]

In the last two decades, after the introduction of Nano crystal® technology, particle-size reduction approaches have grown to a commercial level. Several formulation approaches have been reported to formulate the nanoparticles, such as nanocrystalline suspensions, Poly Lactic-co-Glycolic acid(PLGA)based nanoparticles, nanospheres, and solid-lipid nanoparticles. By the virtue of their large surface area (SA) to volume ratio, nanocrystals provide an alternative method to formulate poorly soluble compounds. Nanosizing refers to the reduction of the APIs' particle size down to the sub-micron range. Nanosuspensions are sub-micron colloidal dispersions of discrete particles that have been stabilized using a surfactant and a polymer or a mixture of both.[9] Stabilized submicron particles in nanosuspensions can be further processed into standard dosage forms, such as tablets or capsules, which are best suited for oral administration.

It has been studied and observed that the reduction in particle size in the micron or nano range have a positive impact on the *in vitro* dissolution rate, which can be used to predict *in vivo* enhancement in bioavailability for poorly soluble compounds.[10] Compound-specific properties, such as high melting point, high log *p* value and poor aqueous solubility, are required to consider before the selection of this approach. Therefore, BCS Class II and IV compounds would theoretically be good candidates for the nanosizing approach, along with some exceptions, such as fenofibrate (FBT) (low melting point).[11] Drug nanocrystals exhibit many advantages, including high efficiency of drug loading, easy scale-up for manufacture, relatively low cost for preparation, and applicability to various administration routes, such as oral, parenteral, ocular, and pulmonary delivery (Table 1). All these advantages have led to successful promotion of drug nanocrystals from experimental research to patients' usage. The availability of several products on the market shows the therapeutic and commercial effectiveness of the approach.[12] The pioneering work of many academics and industrial researchers has laid the foundation for broad utilization and acceptance of this approach within the field of pharmaceutical sciences.

By definition, nanosizing is particle-size reduction to 1 and 1000 nm. Because of their small size, these particles can vary distinctly in their properties from micronized drug particles. Similarly to other colloidal systems, drug nanocrystals tend to reduce their energy state by forming larger agglomerates or crystal growth, which is why they are often stabilized with surfactants, stabilizers, or with a mixture of both. Reduction of the particle size to the nanometer range results in a substantial increase in SA (A), thus, this factor alone will result in a faster dissolution rate as described by Noyes–Whitney.[13] In addition, the Prandtl equation shows that the drug nanocrystals showed decreased diffusional distance "h". This further enhances the dissolution rate. Finally, the concentration gradient ($C_s - C_x$) is also of high importance. There are reports that drug nanocrystals have shown increased saturation/thermodynamic solubility (C_s). This can be explained by the Ostwald–Freundlich equation[14] and by the Kelvin equation.[15]

It is still not clear to what extend the saturation solubility can be increased solely as a function of particle size. Most probably the increased solubility of drug nanocrystals is a combined effect of nanosized drug particles and solid-state effects caused by the particle fractionation during the process. A number of authors have reported improvement from a 10% increase in saturation solubility

$\frac{dc}{dt} = \frac{AD(C_s - C)}{h}$	$\frac{\ln S}{S_0} = \frac{2MY}{\rho rRT}$	$h_H = k(\sqrt{L}/\sqrt{V})$
Noyes–Whitney Equation	Ostwald–Freundlich	Prandtl Equation
dc/dt = Dissolution velocity	S = Solubility at temp T	h_H = Hydrodynamic boundary layer thickness
A = Surface area	S_0 = Solubility of infinite big particle	k = Constant
D = Diffusion coefficient	M = Molecular weight	L = Length of surface in flow direction
C_s = Saturation solubility	ρ = Density	V = Relative velocity of flowing liquid
C = Drug concentration in solution at time t	U = Interfacial tension	
h = Thickness of diffusion layer	R = Gas constant	
	r = Radius	
	T = Temperature	