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Review article

# Nanosizing techniques for improving bioavailability of drugs

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ABSTRACT

The poor solubility of significant number of Active Pharmaceutical Ingredients (APIs) has become a major challenge in the drug development process. Drugs with poor solubility are difficult to formulate by conventional methods and often show poor bioavailability. In the last decade, attention has been focused on developing nanocrystals for poorly water soluble drugs using nanosizing techniques. Nanosizing is a pharmaceutical process that changes the size of a drug to the sub-micron range in an attempt to increase its surface area and consequently its dissolution rate and bioavailability. The effectiveness of nanocrystal drugs is evidenced by the fact that six FDA approved nanocrystal drugs are already on the market. The bioavailabilities of these preparations have been significantly improved compared to their conventional dosage forms. There are two main approaches for preparation of drug nanocrystals; these are the top-down and bottom-up techniques. Top-down techniques have been successfully used in both lab scale and commercial scale manufacture. Bottom-up approaches have not yet been used at a commercial level, however, these techniques have been found to produce narrow sized distribution nanocrystals using simple methods. Bottom-up techniques have been also used in combination with top-down processes to produce drug nanoparticles. The main aim of this review article is to discuss the various methods for nanosizing drugs to improve their bioavailabilities.

## 1. Introduction

Advancements in combinatorial chemistry, high throughput screening, biology and genomics have led to an increase in the number of molecules which can be potential drug candidates. However, poor aqueous solubility and bioavailability has led to failure of more than 40% of these molecules during the drug development stages [1–4]. Regardless of excellent pharmacological activity, many of these Active Pharmaceutical Ingredients (APIs) fall under Class II of the Biopharmaceutics Classification System (BCS). The BCS system classifies drugs into four categories depending on their aqueous solubility and membrane permeability [5]. To overcome problems like poor aqueous solubility, the pharmaceutical industry and researchers have focused on developing formulation strategies for drugs classified under BCS class II (poor solubility and high permeability) and BCS class IV (poor solubility and permeability) [2,5]. A large number of approaches have been developed to improve oral bioavailability of these compounds by increasing their aqueous solubility and dissolution rates.

Conventional approaches for increasing the dissolution of drugs include formation of salts, use of solubilizing agents, complexing agents, etc. Previously, there was considerable difficulty with formulating a large number of compounds using conventional approaches. Currently, the use of conventional approaches is increasingly limited due to side-effects associated with salt formation, addition of co-solvents and requirements of large quantities of excipients in the formulation [1,6]. Other methods to improve the bioavailability of drugs include microemulsions [7], inclusion of cyclodextrins [8], melt extrusion [9], emulsions [10], liposomes [11], and solid dispersions [2,6]. All these methods have been successfully utilized in developing formulations for poorly water soluble drugs, especially for compounds which are highly potent. In addition to the above mentioned approaches, methods such as particle size reduction to the sub-micron size range, e.g. nanosizing of drug particles or nanosuspensions, have gained much attention in recent years [2,4,12].

Nanosizing is defined as a pharmaceutical process that involves reducing the particle size of the active pharmaceutical ingredient to the nanometre size range. It means achieving the particle size below the sub-micron range i.e. particle size $< 1$ μm [13]. Nanosizing techniques have become more popular as they can be applied to most compounds which have poor solubility issues. These techniques are referred to as 'non-specific techniques' to improve the bioavailability of poorly soluble drugs [13–15]. According to the Noyes-Whitney equation, a decrease in the particle size of a drug results in an increase in its surface area and thus the dissolution rate will increase proportionally which results in better absorption of poorly soluble drugs [3,4,13]. Recent advancements in nanosizing techniques have enabled the

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pharmaceutical industry and researchers to produce particles in the 100–200 nm range in a reproducible manner [3].

There are various approaches for nanosizing drugs and these are classified as top-down, bottom-up and combination approaches. Top-down techniques involve particle size reduction using high energy approaches such as media milling and high pressure homogenization. Currently, there are six FDA approved nanocrystal drugs in the market which have been prepared by top-down techniques [16]. All these processes are conducted in a liquid medium and thus they form nanosuspensions which are later processed into capsules or tablets or marketed as suspensions [3,17].

Nanosuspensions refer to colloidal dispersions of sub-micron drug particles which are stabilized by addition of a suitable polymer or surfactant, and are of a particle size below 1000 nm [4,13,18]. The dispersion medium can be aqueous e.g. water, or non-aqueous e.g. liquid polyethylene glycol and oils [13]. Bottom-up techniques are essentially a precipitation technique as the nanosized drug particles are obtained after precipitation from a supersaturated drug solution [16]. Bottom-up techniques offer many advantages such as being low energy processes and less expensive in comparison with other nanosizing methods, and produce particles with narrow size distribution. However, very few products prepared by bottom-up techniques have made it to market [19]. Bottom-up techniques have recently been used in combination with top-down techniques to obtain even smaller particles.

Although these techniques have been in use for at least a decade, very few nanocrystals with a particle size of 100 nm have been obtained. Various attempts have been made to develop particles of < 100 nm as it has been reported that drug nanocrystals of < 100 nm have novel physical properties and show improvement in permeation through various biological barriers [16]. Drug nanocrystals have improved the bioavailability of poorly-soluble drugs that are administered through a variety of routes including oral, dermal, ocular, buccal and pulmonary.

This review article will focus on various techniques for preparation of drug nanocrystals e.g. bottom-up techniques, top-down techniques and combination techniques. Case studies will illustrate the ways in which the particle size of certain drugs has been reduced to the submicron range by utilising various nanosizing techniques.

## 2. Biopharmaceutical classification system (BCS)

The BCS is a system which classifies drugs according to their aqueous solubility and intestinal permeability. Aqueous solubility correlates with in vitro dissolution and the intestinal permeability correlates with in vivo bioavailability of the drug particles [6]. According to the BCS, a drug is considered highly soluble if the highest strength of the drug is soluble in 250 ml of water and it is considered highly permeable if intestinal permeability of the drug is 90%. On the basis of BCS, all drugs have been classified into four categories i.e. BCS class I, class II, class III and class IV [6]. The BCS System classification is shown in Table 1 below:

The drugs in BCS class II and class IV have low solubility, therefore nanosizing of these drugs can increase their bioavailability. The BCS classification has been well accepted but a revised classification system, known as the Developability Classification System (DCS) has recently been introduced to classify drugs in a more relevant manner and it has been particularly useful in predicting critical factors related to in vivo performance as compared to BCS [20]. In some cases it has been found that drugs have such a low aqueous solubility that even the nanocrystals of that drug showed very low bioavailability [21]. For this reason, DCS classifies drugs according to whether they have dissolution rate-limited, solubility-limited or permeability-limited bioavailability. The dissolution rate-limited drugs are categorized under DCS class IIa and solubility-limited drugs are classified under DCS class IIb. Nanosizing of drugs has been found to be a suitable approach for dissolution-rate limited compounds i.e. DCS class IIa [21].

**Table 1**
BCS classification [6].

| | |
|---|---|
| **BCS Class I**<br>(high solubility and high permeability)<br>e.g. Metoprolol, Diltiazem | **BCS Class II**<br>(low solubility and high permeability)<br>e.g. Phenytoin, Danazol |
| **BCS Class III**<br>(high solubility and low permeability)<br>e.g. Acyclovir, Cimetidine | **BCS Class IV**<br>(low solubility and low permeability)<br>e.g. Furosemide, Hydrochlorothiazide |

## 3. Methods of nanosizing

As previously described, there are different nanosizing methods and these are classified as bottom-up techniques, top-down techniques and combination techniques [4].

## 4. Bottom-up techniques

Bottom-up techniques are also referred to as precipitation techniques as nanosized drug particles are formed by precipitation which can be in crystalline or amorphous form [13]. In this method, drug is precipitated from supersaturated drug solution, or by evaporation of solvent, or by mixing the drug with a non-solvent [4,14]. These techniques have not gained much traction in the pharmaceutical industry due to difficulties in controlling particle growth and the process [21]. However, bottom-up techniques are used in combination with top-down techniques to improve the effectiveness of the method. Some bottom-up technologies used are sonocrystallization, confined impinging liquid jet precipitation, high gravity controlled precipitation technology, and multi-inlet vortex mixing [13].

### 4.1. Precipitation by addition of liquid antisolvent

Precipitation of a drug from its solution by addition of an antisolvent is an effective method of obtaining nanosized particles. Moreover, the size of the particles and morphology of the finished product can be controlled [24]. In this method, a drug is dissolved in a solvent and then mixed with another solvent which is miscible with the first solvent but acts as an antisolvent (e.g. water) for the drug [16,25]. This results in increased super-saturation of the solution due to diffusion of solvent into the antisolvent and nucleation of the particles. During drug precipitation, particle growth and nucleation can compete by a process called “Ostwald ripening” but the process should be directed towards nucleation by the use of suitable excipients and stabilizers [24,26].

This method of obtaining nanosized drug particles is easy and cost-effective as compared to other methods of nanosizing [27,28] and it can be easily scaled up as it does not require any expensive equipment [29]. There are, however, some critical process parameters that affect the particle size and the physicochemical properties of the nanosized drugs such as the nature and selection of solvent and antisolvent, volume ratio of solvent and antisolvent, and their order of addition [16]. An antisolvent precipitation technique has been used to prepare drugs such as atorvastatin [30], taxifolin [31], amorphous amphotericin B [32], and danazol [33]. This method of nanosization can be divided into two types i.e. simple mixing and modified mixing methods [16].

#### 4.1.1. Simple mixing method using static mixer

In this method, nanosized drug particles are produced by mixing the drug solution and antisolvent using mixing forces. The solvent plays an important role in production of submicron particles as it should solubilize the drug and have a fast diffusion rate towards the antisolvent. The solvents used for preparation of drug solution can be organic e.g. ethanol, methanol, IPA, NMP, acetone etc., or co-solvents e.g.