A Review on Pharmaceutical Nanotechnology for Poorly Water-Soluble (BCS -II/IV) Compounds

Rajesh Dumpala*, Chirag Patil
Research Scientist, Dept. F&D-(MS&T) Alembic Research Centre, Vadodara, Gujarat, India.

*Corresponding author’s E-mail: rdumpala64@gmail.com

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ABSTRACT
One of the biggest challenges faced by pharmaceutical scientists is poor solubility and bioavailability of new chemical entities (NCEs). According to BCS classification; approximately 25% of all compounds are classified as highly soluble and permeable. Nearly 40% of the new chemical entities currently being discovered are lipophilic so poorly water soluble drugs. BCS Class II and Class IV have low solubility. Aqueous solubility of any therapeutically active substance is a key property as it governs dissolution, absorption and thus the in-vivo efficacy. A surprisingly large proportion of new drug candidates emerging from drug discovery programs are water insoluble, and therefore poorly bioavailable, leading to abandoned development efforts. These so-called ‘brick dust’ candidates can now be rescued by Nanonization. Formulating the poorly soluble compounds as pure drug nanoparticles is one of the newer drug delivery strategies applied to this class of molecules. The present review deals in detail about the different techniques used for the improvement of the solubility and dissolution rate of poorly water soluble drugs with the use of nanoparticle as a drug delivery approach and characterization of nanoparticle.

Keywords: BCS, Pharmaceutical nanotechnology, Nanoparticle, Solubility, bioavailability, drug delivery.

INTRODUCTION

A large proportion of new chemical entities coming from drug discovery are water insoluble, and therefore poorly bioavailable. In biopharmaceutical classification system (BCS) (Table 1). Class II and Class IV have low solubility and low permeability. Class II drugs are now subdivided into class II a, where dissolution rate is the challenge, and Class II b, where apparent solubility of the drug molecule is low.

| Table 1: Biopharmaceutical Classification System |
|-----------------------------------------------|
| High permeability                              |
| High solubility Class I                        |
| Low solubility Class II                       |
| Low permeability                              |
| Class III                                      |
| Class IV                                      |

Drugs which are poorly soluble in water have a number of drawbacks such as high dosage administration frequency and the resultant occurrence of side effects are Major issues associated with poorly water-soluble compounds shown below.

- Poor Bioavailability
- Inability to optimize lead compound selection based on efficacy and safety
- Fed/fasted variation in bioavailability
- Lack of dose-response proportionality
- Suboptimal dosing
- Use of harsh excipients, i.e., excessive use of co solvents and other excipients
- Use of extreme basic or acidic conditions to enhance solubilization
• Uncontrollable precipitation after dosing
• Noncompliance by the patient, i.e., inconvenience of the dosage platform.

TECHNIQUES OF SOLUBILITY ENHANCEMENT

There are various techniques available to improve the solubility of poorly water-soluble drugs. Some of the approaches to improve the solubility are shown in Table 2. [8,9]

Table 2: Different techniques of solubility enhancement

| Physical modification | Chemical modification | Carrier/Delivery system |
|-----------------------|-----------------------|-------------------------|
| Pro-drug              | Salts                 | Co-solvents             |
|                       | Crystal engineering   | Polymeric systems       |
|                       | (polymorphs/co-       | Cyclodextrins           |
|                       | crystals)             | Micelles                |
|                       |                       | (Micro) Emulsions        |
|                       |                       | SMEDDS                  |
|                       |                       | Liposomes               |
|                       |                       | Micro-/Nanoparticles     |

Although all techniques mentioned above could enhance the solubility, the choice of the method will be based on its effectiveness as well as safety in terms of biocompatibility of excipients used. The solubility of poorly water-soluble drugs is increased by reducing particle size in drug. The size of solid particle influences the solubility because as particle becomes smaller, surface area to volume ratio increases. The larger surface area allows a greater interaction with solvent.

The present review deals in detail about the different techniques for improving solubility and dissolution rate of poorly water soluble drugs with reducing the particle size of drug in nano range, that is by forming nanoparticle of them. The major goals in designing nanoparticles are to control particle size, surface properties to increase the solubility of the poorly soluble drugs. [10]

NANOTECHNOLOGY APPROACHES [11]

Nanoparticles are typically defined as a discrete internal phase consisting of an active pharmaceutical ingredient having physical dimensions, less than 1 micron in an external phase and Nano crystal is a crystalline material with dimensions in nanometers. Nanocrystallisation is defined as a way of reducing drug particles to the size range of 1-1000 Nanometers. According to the size range nanoparticles are categorized as shown if Fig.1

- Coarse Particle cover a range between 10000nm to 2500nm.
- Fine particle is sized in range between 2500 to 100nm.

- Ultra Fine nanoparticles are sized between 1 to 100nm.
- Nanoclusters are those which have at least one dimension between 1 to100nm and have a narrow size distribution.
- Nanopowders are agglomerates of ultrafine particle, nanoparticle or nanoclusters.

The major goals in designing nanoparticles are to control particle size, surface properties to increase the solubility of the poorly soluble drugs. [10]

![Figure 1: Paths to Nanoparticle](image)

Advantages of nanoparticles [11,12]

1. Increase the stability of any volatile pharmaceutical agent, easily and cheaply fabricated in large quantities by a multitude of methods.
2. They offer a significant improvement over traditional oral and intravenous methods of administration in terms of efficiency and effectiveness.
3. Deliver a higher concentration of pharmaceutical agent to a desired location.
4. Choice of polymer and the ability to modify drug release from polymeric nanoparticles

Methods of Preparing Nanoparticle [10,11,12]

There are various ways in which nanoparticles of poorly water-soluble molecules are generated. Nanoparticles are formed by following methodologies.

In bottom up methods
• Precipitation method
• Cryo-vacuum method

In top down method
• Milling
• High pressure homogenization

Top down and bottom up spray drying

“Bottom up” technology begins with the molecule; active drug substance is dissolved by adding an organic solvent, and then, solvent is removed by precipitation. “Top-down” technology applies dispersing methods by using different types of milling and homogenization techniques. “Top down” technology is more popular than “Bottom up” technology; it is known as “nanosizing.”
Spray drying is also a method for preparing drug nanocrystals, which is faster and more practical compared to other methods.  

**Bottom up technology**

“Bottom up” technology relies on precipitation. The principle of this method is based on the dissolution of active drug substance in an organic solvent which is then added into a nonsolvent (miscible with the organic solvent). In the presence of stabilizers, thereafter, the nanocrystals are precipitated.  

**Precipitation method**  
Nanoprecipitation is also called solvent displacement method. In precipitation method a dilute solution is first produced by dissolving the substance in a solvent where its dissolution is good. The solution with the drug is then injected into water, which acts as a bad solvent, at the time of injection; the water has to be stirred efficiently so that the substance will precipitate as Nano crystals (Fig. 2) Nanocrystals can be removed from the solution by filtering and then dried in air.

Basic advantage of precipitation technique is that it is simple and has a low cost. Also, scale up is simple. This method has numerous limitations; it is very difficult to control nucleation and crystal growth to obtain a narrow size distribution. Often a metastable solid, usually amorphous, is formed which is converted to more stable crystalline form.  

**Cryo-vacuum method**

In this method the active ingredient to be nanonized is first dissolved in water to attain a quasi-saturated solution. The method is based on sudden cooling of a solvent by immersing the solution in liquid nitrogen (-196 °C). Rapid cooling causes a very fast rise in the degree of saturation based on decrease of solubility and development of ice crystals when the temperature drops below 0°C. This leads to a fast nucleation of dissolved substance at the edges of ice crystals. The solvent must be completely frozen before the vessel is removed from liquid nitrogen. Next the solvent is removed by sublimation in a lyophilization chamber where the temperature is kept at constant- 22°C and pressure is lowered to 10⁻² m.bar. Cryo-assisted sublimation makes it possible to remove the solvent without changing the size and habit of particles produced, so as to remain crystalline.  

**Top Down Method Milling**  
Nano suspensions are produced by using high shear media mills or pearl mills. The mill consists of a milling chamber, milling shaft and a recirculation chamber. Grinder chambers are made from stainless steel, porcelain or hard material. The milling media or grinding balls are made of ceramic-sintered aluminium oxide or zirconium oxide or highly cross-linked polystyrene resin with high abrasion resistance. For the purpose of making Nano size range particles the drug formulation is fed into mill containing small grinding balls/pears.  

As these balls rotate at a very high shear rate under controlled temperature, they fly through the grinding jar interior and impact against the sample on the opposite grinding jar wall. The combined forces of friction and impact produce a high degree of particle size reduction. Planetary ball mill is one example of equipment that can be used to achieve a grind size below 0.1μm.  

**Milling principles**- There are two basic milling principles - either the milling medium is moved by an agitator or the complete container is moved in a complex direction leading to movement of milling media to generate shear forces required to fracture the drug crystals.  

Key property of grinding media

- Size -Smaller the media particles, smaller the particle size of final product.  
- Density -the media should be denser than the material to be ground.
- Hardness -The grinding media needs to be durable enough to grind the material.
- Composition- various grinding applications have special requirements. Some of these requirements are based on the fact that some of the grinding media will be in finished product. Others are based on how the media will react with the material beingground.  

**Dyno Mill.**

For dispersion and wet grinding in the micron to nano range dyno mill is generally used.  

Features of dyno mill

1. Ideal for small scale production.  
2. Available for continuous or discontinuous operations.  
3. Ideal equipment for all type of product with the choice of widest possible range of material that come in contact with the product.  
4. Easy to operate.  

**Working of Dyno mill**

The milling chamber has a rotor fitted with disks that can be accelerated at the desired speed (500 – 5000 RPM). The rotation of disk accelerates/milling media...
radially. The product flows axially through the milling chamber where the shear forces generated and/or forces generated during impaction of milling media with the drug provides the energy input to fracture the drug crystals into nanometer-sized particles. The temperature inside the milling chamber is controlled by circulating coolant through the outer jacket. (Fig. 3). The process can be performed either in a batch mode or in a recirculation mode. The milled product is subsequently separated from milling media using a separation system. The mechanism of milling is fairly complex and does not lend itself easily to rigorous theoretical analysis due to its dynamic nature. According to particle nature nanorods could be produced by fracture. Smaller the grinding beads, higher is their number in a given grinding chamber volume. Higher the number of beads higher is the stress frequency. More grinding will occur and product of nanorange is obtained.

For the moldable and temperature sensitive materials porcelain or hard material beads of different size are available, low size beads generated heat by attrition which degrade the product and also heat causes fusion of nanoparticles which leads to increase in particle size thus low aqueous solubility. For aqueous solvent based suspension aluminium oxide and zirconium oxide beads should be used. For contamination sensitive products abrasion resistance highly cross-linked polystyrene resin beads should be used with small size range. Dyno mill is available in various series like DYNO-MILL ECM, DYNO-MILL KD shown in Fig. 5.

Guidelines about selection criteria for mill media:  
- Should be harder than the material to be ground.
- Should be denser than the material to be ground.
- Composition should not contaminate the product (Inert media for mineral industry).
- Should be competent by having a mechanical integrity.
- Make-up media size should be the smallest one required to grind the coarse particles.
- Should be cost-effective for the application & Should be easily separated from the finished product.

Homogenization  
Homogenization involves the forcing of drug solution under pressure through a valve having a narrow aperture. In this case, the drug solution is made to pass through a small orifice that result in a reduction of static pressure below the boiling of water, which leads to boiling of water and formation of gas bubbles. When the solution leaves the gap and normal air pressure is reached again, the bubbles implode and surrounding part containing drug particles rushes to the center and in the process collide, causing a reduction in particle size. Most of the cases require multiple passes or cycles through the homogenizer, which depends on hardness of drug, the desired mean particle size and required homogeneity.

- The major advantage of high pressure homogenization over media milling is that it can be used for both diluted as well as concentrated solution and also allows aseptic production.
- To produce a nanosuspension with a higher concentration of solids, it is preferred to start homogenization with very fine drug particles, which
can be accomplished by pre-milling.

**Hot homogenization**: Hot homogenization is carried out at temperatures above the melting point. First disperse/dissolve drug in the melted lipid and then add this mixture to hot aqueous surfactant solution using stirring device. The obtained pre emulsion is homogenized at higher pressure to get hot nano product. Finally the above solution is cooled to room temperature. In most cases 3-5 homogenization cycles at 500-1500 bar are sufficient. Increasing the homogenization leads to an increase of particle size due to particle coalescence which occurs because of high kinetic energy of particles.

The main drawback of this method is High temperature leads to degradation of active compound and Partitioning and hence loss of drug from the aqueous phase during homogenization.

**Cold homogenization**: Cold homogenization has been developed to overcome various problems associated with hot homogenization. First disperse/dissolve drug in the melted lipid and solidify the mixture using liquid nitrogen/dry ice. The solidified mixture is grinded to fine particles using powder mill and dispersed in a cold surfactant solution using stirrer. The obtained pre suspension is homogenized at higher pressure and at below room temperature to get nanoparticles.

- Compared to hot homogenization; larger particle sizes and a broader size distribution is typical of cold homogenized samples.
- Cold homogenization minimizes the thermal exposure of sample.

High pressure homogenization methods (Hot homogenization)

One of the methods used for size reduction is high-pressure homogenization.

The two - homogenization principles/homogenizer used is;

- Microfluidisation (Microfluidics, Inc.)
- Piston-gap homogenizers (e.g. APV Gaulin, Avestin, etc.)

**Micro fluidisation for production of drug nanoparticles.**

Micro fluidisation works on a jet stream principle where the suspension is accelerated and passed at a high velocity through specially designed interaction chambers. Frontal collision of fluid streams under high pressures (up to 1700 bar) inside the interaction chamber generates shear forces, particle collision, and cavitation forces necessary for particle size reduction. The Micro fluidizer processor keeps a constant feed stream that gets processed by a fixed geometry which produces high shear and impact necessary to break down larger particles. This process yields smaller particles with narrow particle size distribution with repeatability and scalability.

**Piston-gap technologies**

Using the micro fluidisation principle, an alternative technology based on piston-gap homogenizers was developed in the middle of 1990’s for production of drug nanoparticles. Homogenization can be performed in water (DISSOCUBES) or alternatively in non-aqueous media or water reduced media (NANOPURE).

Disso cubes technology employs piston-gap homogenizers in which drug powder is dispersed in an aqueous surfactant solution and subsequently forced by a piston through tiny homogenization gap (5 μm - 20 μm) depending upon the viscosity of suspension and applied pressure at a very high pressure (up to 4000 bar). Prior to entering the gap, the suspension is contained in a cylinder with a relatively large diameter compared to the width of following gap.

The resulting high streaming velocity of suspension causes formation and implosion of bubbles also known as cavitation which results in generation of shockwaves. **Fig.6** The drug particle gets reduced by these high shear forces, turbulent flow and powerful shockwaves. Another approach viz., Nanopure technology is useful for particle size reduction of thermolabile drugs because it uses low vapor pressure dispersion media for homogenization that helps in processing at low temperatures due to very little cavitation in homogenization gap.

**Top down and bottom up technology**

In “top down and bottom up” technology, both methods are used together. NanoEdge is a product obtained by such a combination technology. As can be inferred, precipitation is followed by high pressure homogenization in this technology

**Spray Drying**

One of the preparation methods of nanocrystals is spray drying. This method is usually used for drying of solutions and suspensions. In a conical or cylindrical cyclone, solution droplets are sprayed from top to bottom, dried in the same direction by hot air and spherical particles are obtained.

**CHARACTERIZATION OF DRUG NANOPARTICLES**

Following methods are used commonly for characterization of drug nanoparticles.

**Particle size and size distribution**

**Spectroscopy**

The appropriate method used to evaluate particle size distribution of submicron particle is photon correlation spectroscopy (PCS).
Laser Diffraction

The instrument is used for quantifying the amount of microparticles present, which is not possible using PCS. LD analyses the Fraunhofer diffraction in a laser beam. The first instruments were based patterns generated by particles on Fraunhofer theory which is applicable for particle sizes 10 times larger than the wavelength of light used for generating diffraction pattern.

Microscopy

Microscopy based techniques can be used to study a wide range of materials with a broad distribution of particle sizes, ranging from nanometer to millimeter scale. Instruments used for microscopy based techniques include optical light microscopes, scanning electron microscopes (SEM) transmission electron microscopes (TEM) and atomic force microscopes (AFM).

Thermoscopy (Hot Stage Microscopy)

HSM of pure drug, solid dispersions and for nanoparticles are conducted using Mettler Toledo hot stage microscope of 200 magnification using IM50 software

Solid-state properties

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) is used to determine the crystallinity of drug nanoparticles by measuring its glass transition temperature, melting point and their associated enthalpies.

X-ray powder diffraction (XRPD)

X-ray powder diffraction (XRD) is a rapid analytical technique primarily used for phase identification of a crystalline material and can provide information on unit cell dimensions.

FUTURE SCOPE OF NANOPARTICLES

Nanoparticle–formulation technologies have provided the pharmaceutical industry with new strategies for solving the problem of poorly soluble molecule. Nanoparticle formulation can be post processed into various types of patient friendly dosage forms that provide maximal drug exposure and bioavailability.

Nanoparticle formulation strategies provide a mean to incorporate old drug into a new drug delivery platform. For future drug –nanoparticle unfolds

many new approaches for drug targeting and permeation enhancement of different classes of drugs. Further advances are needed in order to turn the concept of nanoparticle technology into a realistic practical application as the next generation of drug delivery system.

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