Review Article

A review: Enhancement of solubility and oral bioavailability of poorly soluble drugs

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Abstract

Drug solubility can pose a great challenge for the development of novel formulations and impacts a wide spectrum of drugs with poor solubilities. Drug efficacy is known to be proportionally related to the solubility of a drug. Poor solubility of a drug leads to low dissolution rate and in turn to low absorption in the gastrointestinal tract following oral administration. Pharmaceutical particle technology is often used to improve poor aqueous solubility of drug compounds that limits in vivo bioavailability owing to their low dissolution rate in the gastrointestinal fluids after oral administration. This review discusses various particle techniques employed for improving the solubility of poorly water soluble drugs. The particle technology involves several approaches from the conventional size reduction processes to the newer novel approaches. The conventional methods of size reduction involve mechanical micronization techniques that are simple and convenient methods to reduce drug particle size and increase the surface area and thus enhance the solubility of poorly soluble drugs. The conventional particle technologies pose limitations for some drugs due to their low efficiency hence novel particle technologies are used to overcome these issues of the conventional methods. Novel particle technologies modify the solubility properties of the drugs and produce a solid, powdered form of the drug that is easily soluble in aqueous media and can be formulated into various dosage forms without difficulties.

Keywords: Drug solubility, Bioavailability, Particle technology, Poorly water soluble drugs, Solubility enhancement, Dissolution, Nanosuspension, Micronization, Particle size reduction

Introduction

Solubilization of poorly soluble drugs is a major challenge in screening studies of new chemical entities and their formulation development. When a drug is administered orally, its solubility plays a key role in the absorption of the drug. In recent years, many insoluble drug candidates have been discovered but more than half of these candidates demonstrate poor aqueous solubility. Two common molecular characteristics that impact drug solubilization are high lipophilicity and strong intermolecular forces (Lindenberg et al., 2004).

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Solubility is usually expressed in terms of concentration (mass/ volume) to describe a solute's ability to homogenously dissolve in a solvent. The solubility of a drug molecule may be dependent on many factors such as: solvent used (ACN, MeOH, Water), temperature (˚C or ˚K), and/or pressure of the system (Savjani et al., 2012). The extent of solubility of a substance in a specific system is measured as the saturation concentration, after that point more solute does not increase the concentration of the system (Lachman et al., 1986). Solubility equilibrium is achieved only when the two processes proceed at a constant rate. Equilibrium solubility may be exceeded under certain condition and form metastable solution known as supersaturation solution (Myrdal and Yalkowsky, 1999).

U.S. Pharmacopeia (USP) and British Pharmacopeia (BP) classify the solubility of compounds qualitatively shown in table 1.

Table 1. USP and BP solubility criteria

Description	Part of solvent required per part of solute
Very Soluble	Less than 1
Freely Soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

Solubility importance in oral drug ingestion

Oral administration is the most common and convenient route of drug delivery due to various benefits of oral ingestion such as: high patient compliance, manufacturing cost effectiveness, low sterility risk and rapid development of dosage form (Krishnaiah, 2012). Currently, more than 80% of drugs are administered orally. Drug absorption, distribution, bioavailability, and pharmacokinetic profile of orally administered drugs are dependent on the solubility of the compound. Low solubility drugs commonly require high or frequent doses in order to reach therapeutic plasma concentration after oral administration. Therefore, solubility enhancement is critical for the formulation development of such drugs (Chaudhary et al., 2012). Solubility enhancement techniques are normally selected based on the certain attributes of a drug based on the nature of selected excipients, route of administration, and pharmacokinetic profile for clinical efficacy.

Variations in availability or insufficient bioavailability are mainly dependent on the poor solubility and low dissolution rate of poorly water soluble drugs in aqueous gastrointestinal fluids. Drug solubility has been established into separate classes, Biopharmaceutics Classification System (BCS) I-IV and describe a molecules solubility and permeability as demonstrated in table 2 (Gandhi, 2016; Kadam et al., 2013). Typically for BCS class II drugs, solubility may enhance the bioavailability and dissolution rate of a drug in the gastrointestinal fluids. Examples listed in BCS Class II, solubility in the gastric fluid is rate limiting step; not the permeability (absorption into the system). Furthermore, when a drug's solubility is increased, the bioavailability also increases for this particular class of drug (Kumar et al., 2011; Sharma et al., 2009). Research costs, time to market launch, lack of efficacy, toxicity, compatibility with other components are only some of challenges commonly seen in the successful development of poorly soluble drugs (Di and Kerns, 2015).

Table 2: Biopharmaceutics classification system (BCS) with characteristics of drugs

BCS Class	Solubility	Permeability	Absorption pattern	Examples
I	High	High	Well absorbed	Metoprolol, Diltiazem, Propranolol
II	Low	High	Well absorbed	Phenytoin, Nifedipine, Danazol, Neteglidine
III	High	Low	Variable	Cimetidine, Acyclovir, Captopril
IV	Low	Low	Poorly absorbed	Hydrochlor-othaizide, Taxol, Furosemide

Process of Solubilization

The mechanism of solubilization involves breaking inter-ionic / intermolecular bonds of the solute (Tk and Jasti). This separation of the solvent molecule provides space for the solute; which initiates an intermolecular force between the solvent and solute molecule. Solubilization processes are described in below Figure 1.

During the solubilization process, a breakdown of solvent bonds takes place and holes can be seen as shown in Step-1. When the solubilization process occurs intermolecular bonding of the solute (solid) molecules break away due to external kinetic energy as described in Step-2. In the presence of external kinetic energy free solute (solid) molecule is integrated in the solvent as shown in Step-3.

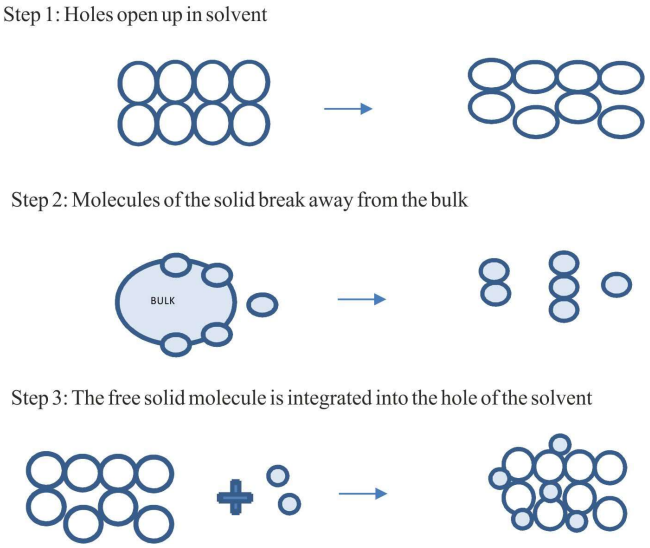

Figure 1. Process of Solubilization (Patil et al., 2011)

Factors affecting Solubilization

The solubility of a compound depends on the physical state (solid, liquid, or gas), composition of solvent medium, temperature, and pressure of the system (James, 1986).

Particle Size

The particle size of a solid material is a major factor that influences a drug's solubility. Particle size is inversely proportional to the solubility of a compound. When particle

size decreases, the solubility increases due to the surface area to volume ratio. As the surface area of particle increases it causes greater interactions with the solvent. The effect of particle size on solubility can be described by the following formula below:

$$log \frac{S}{S_0} = \frac{2 \gamma V}{2.303 R T r}$$

Where S_0 is the solubility of infinitely large particles, **S** is the solubility of fine particles, **V** is molar volume, **γ** is the surface tension of the solid, **r** is the radius of the fine particle, **R** is the gas constant and **T** is the temperature.

Temperature

Temperature plays an important role in the solubility of a compound. As the temperature of a compound increases, energy in the form of heat can be transferred causing the interactions between solute and solvent to more rapidly interact. If the temperature of a solution were to decrease, the lost energy would then decrease the solubility due to less rapid molecular interactions. Most solids follow this process but not all solids. In fact there are some solids that are more soluble with decreasing temperature. For all gases, solubility decreases when the temperature of a solution increases (Lindenberg et al., 2004).

Molecular Size

Molecular size is another important factor that impacts the solubility of a compound. Solubility tends to decrease when molecules have higher molecular weights and size since larger molecules have more difficulty to be surrounded by the molecules of a solvent. For organic compounds, carbon branching increases the solubility because branching reduces the size of the molecule (Singhal and Curatolo, 2004).

Nature of the Solute and Solvent

The concentration of the solute is depends on the nature of the solute and solvent. Only 1 gram of lead (II) chloride or 200 grams of zinc chloride can be dissolved in 100 grams of water at room temperature.

Pressure

Pressure has a different effect on the solubility of gaseous, solids and liquid solutes. For solids and liquid solutes, changes in pressure almost have no effect on solubility. On the other hand, when pressure in gaseous solutes increase, their solubility increases.

Polymorphs

Almost all crystals can change into different forms or polymorphs. Certain characteristics such as melting point typically change with their respective polymorphs. Since the melting point a solid is proportionally related to its solubility; polymorphs can have different solubility from their respective crystalline forms. Normally, the difference in solubility between a crystal compared to their different polymorphs is different from approximately 2-3 fold due to relatively small differences in free energy (Pinnamaneni et al., 2002).

Polarity

Theoretically, non-polar solute molecules dissolve in non-polar solvents and polar solute molecules dissolve in polar solvents. This is due to the polar nature of solute molecules; which have a positive and a negative charge. Additionally, if the molecule is polar, then only positive ends of solvent molecule will attract the negative ends of solute. This type of intermolecular force known as dipole-dipole interaction. Due to London dispersion forces, positive nuclei from the solute molecule attract the negative electrons from the solvent molecules. Furthermore, polarity of the solute and solvent play significant role in solubilization process (Singhal and Curatolo, 2004).

Various Techniques of Solubility Enhancement

Solubility and permeability of a compound are major factors for the in-vivo absorption of orally administered drugs. These processes may be altered or modified by various enhancement techniques (Brahmankar, 2009; Parve et al., 2014).

1. Physical Modification

1.1. Particle Size Reduction

1.1.1. Micronization

1.1.2. Nanosuspension

- Homogenization
- Wet milling

1.1.3. Sonocrystallization

1.1.4. Spray drying

1.1.5. Novel particle approaches for improved bioavailability

1.2. Modification of Crystal Habit

- Polymorphs
- Pseudo polymorphs

1.3. Drug Dispersion in Carriers

1.3.1. Eutectic mixtures

- Hot plate method
- Solvent evaporation method
- Hot-melt extrusion

- Melting-solvent method

1.3.2. Solid dispersions

1.3.3. Solid solutions

1.4. Complexation

Use of complexing agents

- Inorganic coordination
- Chelates
- Metal-olefin
- Inclusion
- Molecular complexes

1.5. Solubilization by Surfactants

- Microemulsions
- Self-micro emulsifying drug delivery systems

2. Chemical Modification
    - Soluble prodrugs
    - Salt formation

3. Other Techniques
    - Co-crystallization
    - Co-solvency
    - Hydrotropy
    - Solubilizing agents
    - Nanotechnology approaches

Particle size reduction

The bioavailability of poorly soluble drugs is directly related to drug particle size. Reduction in particle size, increases the surface area of a particle which allows a greater interaction with the solvent thus causing an increase in solubility which can improve the dissolution properties of a poorly soluble drug. This allows a wide scope of formulation approaches as well as delivery technologies (Chaumeil, 1998; Persky and Hughes, 2012).

Sucessful particle size reduction can achieved using various techniques such as: micronization, nanosuspension, sonocrystallization, spray drying and some novel approaches such as solid self-emulsifying drug delivery system, polymeric micells, freeze-dried liposomes, solid lipid nanoparticles.

Various theories have been published to describe these size reduction techniques (Patel et al., 2014):

- Griffith theory: Amount of force to be applied is dependant on the crack length and focus of stress at the atomic bond of the crack apex.
- Kick's law: Size reduction of a given quantity of material is constant for the same reduction ratio regardless of the original size.
- Rittinger's law: Particulate size reduction is directly proportional to the new surface produced.
- Bond's law: Reduced particle size is proportional to the square root of the diameter of the particle produced.

Mechanism of Particle Size Reduction

The mechanism demonstrates that stresses of varied nature are required in order to achieve size reduction. When various modes of stress are applied on a powder, particles may get strained. This stress-strain relationship is shown in figure 2. The common modes of size reduction are explained in table 4.

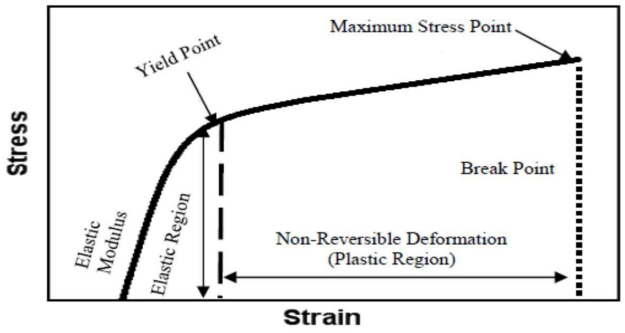

Figure 2. Stress strain curve for a solid (Williams et al., 2005)

1. Micronization

Micronization may enhance the dissolution rate of a drug through increased surface area and not equilibrium solubility. This reduction of drug particle size leads to an increased surface area thus improving the rate of dissolution. The Micronization of drugs may be done by various milling techniques such as: jet mills, rotor stators, colloid mills, ball mills, etc (Blagden et al., 2007).

Table 3. Mechanisms of Particle Size Reduction

Method	Examples	Approximate particle size (µm)
Cutting	Scissors Shears Cutter mill	100-80,000
Compression	Roller mill Pestle-Mortar	50-10,000
Impact	Hammer mill Disintegrator	50-8,000
Attrition	Colloidal mill Roller mill	1-50
Impact and attrition fluid energy mill	Ball mill	1-2000

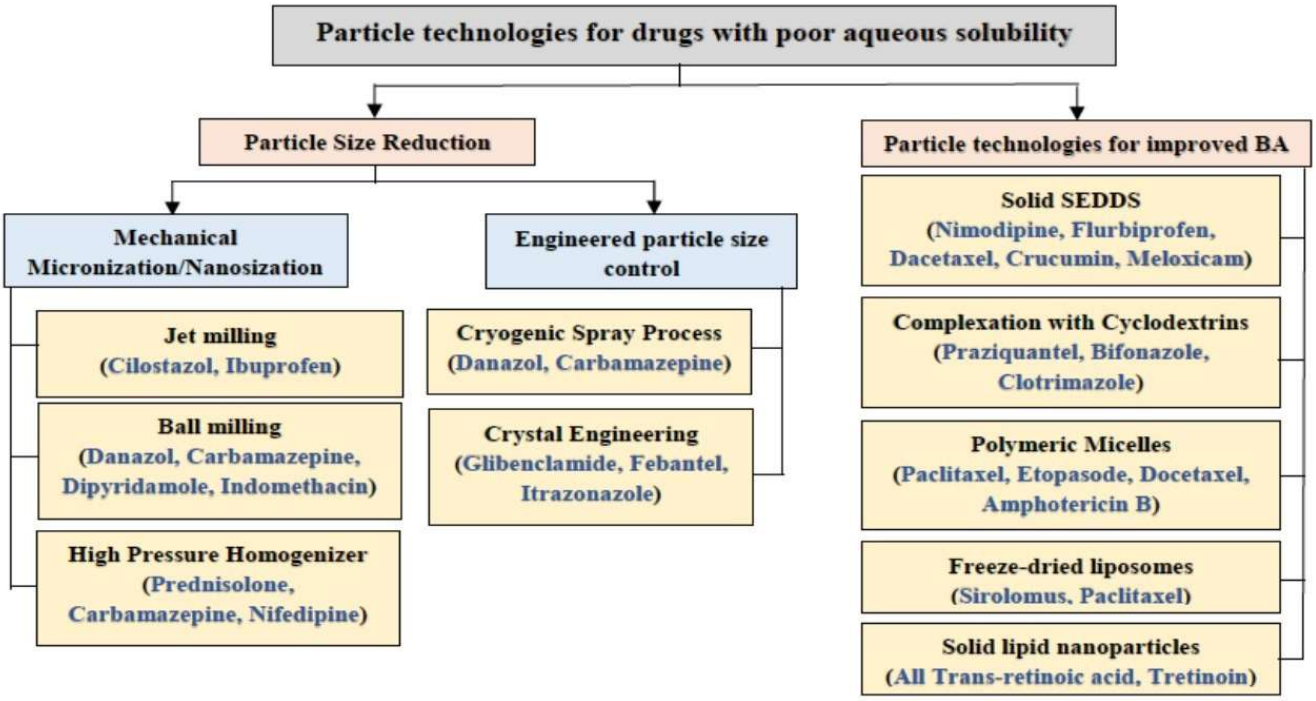

Figure 3. Particle size reduction techniques with drug examples

Jet mill

Jet mills are the most common and widely accepted industrial practice for reducing particle size.

Principle: Jet mills operate on the principles of impact and attrition by generating high viscosity collisions between particles that are suspended in nitrogen gas or a compressed air stream. The resulting impacts cause the particles to break down into smaller fragments. Centrifugal forces in the jet mill cause large, heavy particles to separate from smaller and lighter particles. The smaller particles are carried in the fluid stream towards the center of the milling chamber, where they are discharged into a collection unit. Larger particles remain in the milling chamber where they recirculate, causing them to breakdown, creating a uniform particle size distribution. Jet mills are commonly used for particle size reduction because it elimiates the need to use a grinding media, which could negatively impact the formulation.

(http://www.catalent.com/index.php/offerings/A-Z-Offerings/Catalent-Micron-Technologies/Particle-Size-Reduction-Services).

Advantages: (1) Production of very fine particles possible, (2) relatively little equipment space required, (3) grinding of hard products with a reduced equipment wear, (4) low operating temperature, (5) contamination-free process, and (6) no moving parts and foundation required.

Disadvantages: (1) Small process capacity, (2) high energy requirements, and (3) high maintenance costs (Saravacos G.).

Rotor stator colloid mill

Principle: Colloid mill works on the rotor-stator principle. This method breaks down particles by creating a dispersion of material in liquid. Shearing takes place in a narrow gap between a static cone (the stator) and a rapidly rotating cone (the rotor).

Factors that influence the degree of milling: (1) Homogenization intensity and duration, (2) viscosity of the continuous phase, (3) shear forces within the gap between the spinning rotor, and stationary stator and (4) clearance rate between the rotor and stator are the key factors which impact the particle size reduction (Remington et al., 2006).

Advantages: (1) Wide use of applications including comminution of slurry-fluid materials, (2) pressure less ionization, (3) easy to clean and assembly, (4) simple construction, (5) high capacity with lower maintainence requirements, and (6) low machine noise level.

Disadvantages: (1) No fine grinding, (2) higher energy requirement, and (3) no wide application for solid materials.

Ball Mill (Pebble mill/Tumbling mill)

Principle: Ball mill works on impact and attrition in a fluid energy mill. The Ball mill consists of a hallow cylinder containing balls; mounted on a metallic frame such that it can be rotated along its longitudinal axis. The balls which could be of different diameter occupy 30 - 50% of the mill volume and its size depending on the feed and mill size. The larger balls tend to break down the coarse feed materials and

the smaller balls help to form a fine product by reducing void spaces between the balls.

Factors that influence the degree of milling: (1) Residence time of the material in the mill chamber, (2) nature of the balls (type of metal), (3) feed rate and feed level in the vessel, (4) size, density and number of the balls, and (5) rotation speed of the cylinder are some of the key factors that influence the degree of milling (Sud Sushant, 2013; Williams III et al., 2011).

Advantages: (1) Ability to run continuous and easy for a scale up process, (2) simple structure and easy installation, (3) reliable operation and simple maintenance, (4) suitable for toxic material because of completely enclosed process, and (5) milling highly abrasive materials.

Disadvantages: (1) Relatively long and tedious process, (2) difficult to clean and to assemble, (3) high machine noise level when metal used as hollow cylinder, and (4) higher chance of contamination due to the continuous process.

2. Nanosuspension

A nanosuspension is a colloidal dispersion of nano-sized drug particles. They are normaly produced by a suitable method and stabilized by specific stabilizer. In nanosuspension technology, the drug is maintained in the crystalline state with reduced particle size, to enhance the dissolution rate and therefore improve bioavailability. The Nanosuspension formulation approach is most suitable for the compounds that are insoluble in water with higher log P value, higher melting point and high doses. This technology can be used for drugs which are insoluble in both aqueous and organic solvents (Li et al., 2011). In nanosuspension, particle size distribution of solid particles are usually less than 1 micron with an average particle size ranging between 200 nm to 600 nm (Chingunpituk, 2011). Nanosuspension may alter the pharmacokinetics of drug which can improve drug safety and efficacy from enhanced absorbtion. Drug particle size reduction leads to an increase in surface area and consequently in the rate of dissolution as described by the Nernst-Brunner and Levich modification of the Noyes-Whitney equation (Müller et al., 2001).

Additionally, an increase in saturation solubility is postulated by particle size reduction due to an increased dissolution pressure explained by the Ostwald-Freundlich equation.

Advantages of nanosuspension drug delivery:

- Oral administration of nanosuspension provide rapid onset, reduced fed/fasted ratio & improved bioavailability
- Increased dissolution velocity and saturation solubility of the drug
- Improved biological metabolism performance
- Increased resistance to hydrolysis and oxidation
- Increased physical stability to agglomerate formation
- Reduction in injection volumes; essential for intramuscular, subcutaneous, & intraocular/ ophthalmic drug administration
- Increased excipient compatibility
- Ease of manufacture and scale-up
- Long-term physical stability and versatility
- Increased oral absorption
- Improved dose proportionality
- General applicability and simplicity of model to many other drug molecules
- Administration of drugs used for only one particular treatment modality to novel routes
- Possibility of surface-modification of nanosuspension for site specific delivery
- Possibility of scale up, the prerequisite for the introduction of delivery system to the market

Disadvantages for nanosuspension drug delivery:

- Uniform and efficacious doses cannot be achieved
- Improper dose administration or location
- Special care must be taken during handling in a manufacturing plant and material transportation
- Physical stability, sedimentation and compaction are common drawbacks.

Nanosuspension preparation methods

For manufacturing nanosuspensions, there are two common approaches: 'Bottom-up' and the 'Top-down' technologies. The 'Bottom-up' technologies refers to an assembly method which goes from normal sized molecules to nanosized particles. These include microprecipitation, microemulsion, and melt emulsification method just to name a few. 'Top Down Technologies' refer to the disintegration methods from large particles and microparticles to nanoparticles. The later is a more suitable method since this is used to alter the properties of an existing drug product. Additional 'Top Down Technologies' are: Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in non aqueous media (Nanopure), and Combination of precipitation and High-Pressure Homogenization (Nanoedge) methods (Lakshmi and Kumar, 2010). Emulsion as templates and microemulsion

as templates are also used for preparing nanosuspensions (Banavath et al., 2010). Many of these methods used for nanosuspension preparation are cost effective and technically simple for poorly soluble drugs and may yield a more physically stable product compared to a liposomal encapsulation approach.

List of all major technique for nanosuspension preparations:

- Bottom-up technology (Precipitation)
- Top-down technology
  - Media milling (Nanocrystals)
  - High pressure homogenization in water (Dissocubes)
  - High pressure homogenization in non aqueous media (Nanopure)
  - Combination of precipitation and high-pressure homogenization (Nanoedge)
- Emulsions as templates
- Microemulsions as templates
- Supercritical fluid method
- Melt emulsification method
- Dry co-grinding
- Nanojet technology

2.1. Bottom-up technology (Precipitation)

Process starts on the molecular level, and goes via molecular association to the formation of a solid particle.

Process: Initially a drug is dissolved in a solvent. Then, the solution is mixed with a miscible antisolvent (normally water) in the presence of surfactants. Rapid addition of a drug solution to the antisolvent generate supersaturation state of drug in the mixed solution, and generation of ultrafine crystalline or amorphous drug solids. This process involves two phases: nuclei formation and crystal growth. High nucleation rate but low crystal growth rate is required for manufacturing of stable suspension with the minimum particle size.

Advantages: (1) Economic process equipment and simplistic process, (2) more suitable for compounds with higher saturation solubility, and (3) ease of scale-up.

Disadvantages: (1) Solvent residues need to be removed, which increase production costs, and (2) preserving the particle character is challenging. In general, this process is follwed up a second consecutive process performed for particle preservation such as spray drying or lyophilization.

Limitations: (1) The solvent needs to be miscible with at least one non-solvent. (2) the drug needs to be soluble in at least one solvent.(Dey, 2012; Patel et al., 2011; Shid, 2013)

2.2 **Top-down technology**

2.2.1. **Media milling (nanocrystals)**

This patent-protected technology was developed by Liversidge et al. (1992)(Myerson, 1992). Formerly, this technology was owned by a company named "NanoSystems" but now this patent was transferred to "Elan Drug Delivery". In this method, drug nanoparticles are obtained using high-shear media milling. The media mill consists of a milling chamber, milling shaft, and a recirculation chamber. The milling chamber is filled with the milling media, water, drug and stabilizers. The the milling media (pearls) is then rotated at a high shear rate in order to break down the drug particle size. Temperature is critical and has to be closely monitored and controlled throughout the process.

Principle: Large amounts of energy and shear forces are generated as a result of the milling media crashing into the drug particles providing the energy input to break the microparticulate drug into nano-sized particles. The milling medium is composed of glass, zirconium oxide or highly cross-linked polystyrene resin. This process can successfully create micronized and non-micronized drug crystals (Patravale and Kulkarni, 2004). This type of mill is suitable for batch production and continuous operation. Particle sizes of < 200 nm have been achieved using this process in previous work (Reddy and Anilchowdary, 2012).

Advantages: (1) Drugs with poor solubility in both aqueous and organic media can be formulated into nanosuspensions, (2) batch to batch variations are less and easy to control upon scale-up, (3) simple and convenient technological concept, (4) lower processing costs regarding the milling operation, and (5) a final product with a narrow particle size distribution can be achieved using this method.

Disadvantages: (1) Chances of product contamination from potential erosion of the milling material, (2) duration of the production is longer compared to other techniques, (3) potential microbial growth in water phase during longer milling processes, (4) high amount of homogenization cycles, (5) time and production costs are a major concern (6) separation of milling material from the drug nanoparticles in parenteral sterile products (Buchmann et al., 1996; Pandey et al., 2010).

2.2.2. **High pressure homogenization in water**

Dissocubes technology was developed by R.H. Muller. The patent rights of Disso Cubes were initially owned by Drug Delivery Services GmbH. Later, the patent was transferred to Skype pharmaceuticals. The suspension of a drug is

created to pass through a small orifice resulting in a reduction of the static pressure below the boiling pressure of water, leading to the boiling of water and formation of gas bubbles. When the suspension leaves the gap and normal air pressure is reached again, bubbles implode and the surrounding parts containing the drug particles rush into the center forming colloids with a reduction in particle size. The preferred method is to start with the micronized drug (particle size < 25 μm) for production of nanosuspension to prevent blocking of the homogenization gap. Before subjecting a drug to the homogenization process, presuspension of the micronized drug is recommended in a surfactant solution using high-speed stirrers. During the homogenization process, the drug suspension is passed through the homogenization gap in order to achieve nano-sizing of the drug.

Principle: Particle collisions due to High shear forces and pressure cause the particle size to be reduced. In some cases, viscosity enhancers may be added in order to increase the viscosity of a nanosuspension. Two key parameters using this method are: Homogenization pressure (higher the homogenization pressure leads lower the particle size) and number of homogenization cycles (can be optimized by particle size and polydispersity index of the drug after each cycle) affecting on the quality of the product.

Advantages: (1) Easy scale up process and less batch to batch variations, (Grau et al., 2000) (2) uniform size distribution in the final product, (3) potenitial for aseptic production of nanosuspension used for parenteral administration, (4) poorly soluble drugs in aqueous and organic media can be formulated, and (5) formulation of diluted or highly concentrated nanosuspensions.

Disadvantages: (1) Must have a micronized drug particles to start, and (2) need a stable suspension using high-speed mixers before subjecting it to homogenization.

2.2.3. **High pressure homogenization in non aqueous media (nanopure)**

Nanopure is a suspension that is homogenized in water-free media or water mixtures. Patents covering disintegration of polymeric material by high-pressure homogenization mention that higher temperatures of about 80ºC promote disintegration, which are not suitable for thermolabile compounds. In this technology, drug suspensions in the non-aqueous media were homogenized at 0 ºC or below the drugs freezing point; which was named "deep-freeze" homogenization after the low temperature processing (Venkatesh et al., 2011).

2.2.4. **Combination of precipitation and high-pressure homogenization (nanoedge)**

The basic principles of this technique are the similar to that of precipitation and homogenization. Combination of these two techniques result in smaller size particle with better prodcut stability in a relatively quick successive session. In the precipitation technique, crystal growth and long term stability are major drawbacks. Both problems can be resolved by the Nanoedge technology. In this technique, the precipitated suspension is further homogenized; leading to a reduction in particle size and avoiding crystal growth. Precipitation is performed in water using water-miscible solvents.

2.3. Emulsions as templates

Emulsions are normally used as s drug delivery vehicle but may also be used as templates in order to produce a Nanosuspension. There are two ways of preparing drug nanosuspensions by using the emulsification method.

An organic solvent or mixture loaded with a drug is dispersed in the aqueous phase containing suitable surfactants with high speed homogenization to form an emulsion. The organic phase is then evaporated under reduced pressure so that the drug particles precipitate instantaneously to form a nanosuspension. Particle size of the nanoemulsion as well as drug loading capacity in the emulsion can be control by using the optimum surfactant concentration. In other methods, partially water miscible solvents use as the dispersed phase instead of hazardous solvents (Trotta et al., 2001). The emulsion is manufactured by conventional method and the drug nanosuspension is obtained by just diluting the emulsion. Due to water miscible solvent as disperse phase, dilution of the emulsion with water causes complete diffusion of the internal phase into the external phase, leading to instaneous formation of nanosuspension.

Advantages: (1) No specific required instrumentation needed for manufacturing, (2) particle size can be controlled by modifying the size of emulsion droplets, and (3) ease of manufacturing scale-up processes.

Disadvantages: (1) Drugs poorly soluble in both aqueous and organic media can not be eficently created using this particlar method, (2) require ultrafiltration for purification of the drug nanosuspension, which increases production costs, (3) safety concerns from the use of hazardous solvents, and (4) the large quantities of surfactant/stabilizers required for processing compared to other production techniques.

2.4. Microemulsions as templates

Microemulsions are thermodynamically stable and is an

isotopically clear dispersion of two immiscible liquids, such as oil and water, stabilized by an interfacial film of suitable surfactant and co-surfactant (Eccleston, 1994). The method of preparation uses an organic solvent or solvent mixture added with the drug dispersed in an aqueous phase containing suitable surfactants to form an emulsion. The organic phase is then evaporated under reduced air pressure to make the drug particles precipitate instantaneously forming a nanosuspension. Another method uses partially water-miscible solvents as the dispersed phase instead of hazardous solvents. Oil in water (O/W) microemulsions are preferred for this purpose. The drug can be loaded into the internal phase or pre-formed microemulsions can be saturated with the drug by continuous mixing. Both manufacturing methods are identical as described earlier in Emulsion as template preparation. Microemulsions have a long shelf-life, high drug solubilization and can be scaled up during manufacturing. The manufacturing process of a microemulsion is identical to the emulsion manufacturing. Advantages and disadvantages of this processing method are similar to the described Emulsion as template method.

Industry applications: Nanosuspension formulations of poorly water-soluble and poorly bioavailable antifungal drug such as griseofulvin using microemulsion as templates method; significantly increased the dissolution rate of the drug when compared to the commercial product. However, this technique is still under observation and needs additional testing to determine the pharmacological impact and bioavilibility compared to the finished products performance in-vivo (Trotta et al., 2003).

2.5. Supercritical fluid method

The various methods attempted for manufacturing are rapid expansion of supercritical solution (RESS) process, supercritical anti-solvent process, and precipitation with compressed anti-solvent (PCA). In rapid expansion of supercritical solution technique, the drug solution is expanded through a nozzle into supercritical fluid, resulting in precipitation of the drug as fine particles by loss of solvent power of the supercritical fluid. The supercritical anti-solvent process uses a supercritical fluid in which poorly soluble drug and compatible solvent that is also miscible with the supercritical fluid. In this process, the drug solution is injected into the supercritical fluid and the solvent gets extracted as the drug solution becomes supersaturated.

Example: The drug, griseofulvin, was successfully prepared by Chattopadhyay et al. using this method (Young et al., 2000).

Disadvantages: (1) High amount of hazardous solvent needed for extraction, and (2) particle nucleation overgrowth which may result in the development of amorphous or another undesired polymorphs.

2.6. Melt emulsification method

Melt emulsification method is widely used to prepare solid lipid nanoparticles. In this method, a drug is dispersed in the aqueous solution with a stabilizer. The solution is heated at a temperature higher than the melting point of the drug, then homogenized by a high-speed homogenizer for emulsification. The temperature is set above the drug's melting during overall process to keep it solubulized. Finally, the emulsion is cooled to precipitate out remaining particles. The particle size of nanosuspension is dependant on various parameters such as: drug concentration, stabilizer concentration, type of the stabilizer, cooling temperature and homogenization speed during processing.

Example: Ibuprofen nanosupension was the first nanosuspension prepared using the this type of melt emulsification method (Kipp et al., 2003; Sutradhar et al., 2013).

Advantages: (1) No organic solvents used during the production process, (2) reduction in processing costs, (3) excellent for drugs that form impurities with other solvents.

2.7. Dry co-grinding

Dry co-grinding is a modern technique used to prepare nanosuspensions. Colloidal particle formation of poorly water soluble drugs such as: Griseofulvin, Glibenclamide and Nifedipine;can be obtained by grinding with Polyvinylpyrrolidone and Sodium dodecylsulfate. Many types of soluble polymers and copolymers have been used in conjunction with this method. Physical properties and dissolution of poorly water-soluble drugs are improved by co-grinding due to changes in the surface polarity and transformation from a crystalline to an amorphous drug form (Banavath et al., 2010; Itoh et al., 2003).

Advantages: (1) Simple process, (2) no organic solvents required during manufacturing process, and (3) short grinding times required.

Disadvantage: (1) Generation of residue from milling media and (2) limitations on formulation components.

2.8. Nanojet technology

This methods is also known as opposite stream technology. This technique uses a chamber where a stream of suspension is divided into two or more parts. Both streams collide with each other at high pressures during the process. These net high shear forces produced during processing results in a particle size reduction.

Example: Atovaquone nanosuspension was prepared by Dearns using the microfluidizer technique.

Disadvantages: (1) High number of passes through the microfluidizer and (2) product obtained contains a relatively larger fraction of microparticles (Dearn, 2003).

3. Sonocrystallization

Recrystallization of poorly soluble materials using liquid solvents and antisolvents is another method that sucessfully reduces particle size and improves the solubility of some drug molecules. In sonocrystallization, particle size reduction on the basis of crystallization achieved by ultrasound method (Patel, 2012).

4. Spray drying

Spray drying is a commonly used method for drying a liquid feed through a hot gas (normally air). Many times, Nitrogen gas is used in special cases in the processing of oxidation sensitive materials or solvents like ethanol require oxygen-free drying. This process of drying is a single step rapid process and eliminates the need for additional processing (Patel, 2012).

Example: Spray drying of the acid dispersed in acacia solutions resulted in as much as a 50% improvement in solubility of poorly water soluble salicylic acid (Kawashima et al., 1975).

5. Newer particle technologies to improve bioavailability

5.1. Solid self-emulsifying drug delivery systems (S-SEDDS)

This technique is suitable to lipophilic drugs and drugs with poor aqueous solubility typically in lipid based formulations. These formulations are typicaly oils, surfactant, dispersions, emulsions, SEDDS, solid lipid nanoparticles and liposomes (Tang et al., 2008) S-SEDDS are formulated by incorporating a liquid, semisolid self-emulsifying ingredients into powders, or nanoparticles by various solidification techniques. Solidification techniques are spray drying, adsorption to solid carriers, melt granulation and melt extraction techniques. SSEDDS are more desirable than regular liquid SEDDS.

Table 4. Marketed formulation using S-SEDDS drug delivery

Trade Name	Drug Used	Dosage Form	Company
Neoral	Cyclosporin	Soft Gelatin Capsule	Novartis
Norvir	Ritonavir	Soft Gelatin Capsule	Abbott Laboratories
Fortovase	Saquinavir	Soft Gelatin Capsule	Hoffmann roche

Limitations: (1) S-SEDDS such as strong adsorption and physical interaction of the drug with the carriers that causes retarded or incomplete release of the drug from the S-SEDDS.

Disadvantages: (1) Expensive processing costs and (2) limitations to as which materials can be used (Gandhi, 2016).

5.2. Complexation with cyclodextrins

Cyclodextrins are useful solubilizers for both liquid oral and parenteral dosage forms and can increase the solubility of the drug. Cyclodextrin inclusion complexation, which is the formation of host-guest inclusion complexes by weak intermolecular interaction (Loh et al., 2016). There are several methods are designed for the preparation of drug-cyclodextrin complex like freeze drying, spray drying co-precipitation of a cyclodextrin/drug solution, kneading, extrusion and grinding of slurry of drug in a mortar and pestle.

Table 5. Marketed formulation using complexation with cyclodextrins technique

Trade Name	Drug Used	Dosage Form	Company
Nitropen	Nitroglycerine/ βCD	Sublingual tablet	Nippon Kayaku
Nimedex	Nimesulid/ βCD	Oral Sachet	Novartis
Omebeta	Omeprazole/ βCD	Tablet	Betapharm

5.3. Polymeric micelles

Polymeric micelles are potential carriers for poorly soluble drugs by solubilizing them in their inner core. In a polymeric micelle, the hydrophobic fragments from the core of the micelle, while hydrophilic fragments form the micelle's corona. The nonpolar molecules are solubilized within the hydrophobic core while polar molecules will be absorbed on the micelle surface and the substances with intermediate polarity will be distributed along surfactant molecules in intermediate positions. Two core methods for drug loading into the polymeric micelles are used. The first method is the direct dissolution method; which is mostly employed for moderately hydrophobic copolymers. Marketed product from Lupin pharmaceutical using polymeric micelle technique to improve bioavailability of Paclitaxel drug.

The later method is the preparation of drug-loaded micelles by solvent removal which is employed for amphiphilic co-polymers.

5.4. Freeze-dried liposomes

Liposomes are phospholipid vesicles, comprising a phospholipid bilayer surrounding an aqueous compartment and can dissolve lipophilic drugs in their lipid domain.

One of the serious limitations with applicability of liposomes as drug delivery systems is associated with its poor stability during storage. The liposomal formulations can thus be stabilized by a freeze drying process in order to obtain dry powders with enhanced stability (Gandhi, 2016) Liposomal incorporation of poorly soluble drugs followed by freeze drying approach can produce powder form of the drug.

Table 6. Marketed formulation using freeze-dried liposomes technique

Trade Name	Drug Used	Company
Doxil	Doxorubicin	Sequus Pharmaceuticals
DaunoXome	Daunorubicin	NeXstar Pharmaceuticals
Abelcet	Amphotericin B	Liposome Company

5.5. Solid lipid nanoparticles (SLN)

Solid lipid nanoparticles is colloidal drug carrier system similar to nanoemulsions. The main difference from the later is the lipid nature in which the liquid lipid part of emulsion is replaced by a solid lipid at room temperature.

Various methods of SLN preparation have been developed such as cold and hot homogenization, breaking of o/w microemulsion, solvent injection, high shear homogenization, solvent emulsification diffusion and/or ultrasound dispersion. Among all of these methods, the high pressure homogenization method is considered to be the most effective method due to several key advantages such as: uniform particle size distribution, high particle content in the dispersions, avoidance of organic solvents and scale-up feasibility. Marketed product from US WorldMeds, LLC use solid lipid nanoparticles technique to improve bioavailability of Apomorphon drug.

Disadvantages: (1) Low drug loading capacity, and (2) formulation stability are biggest concerns (Gandhi, 2016).

Conclusion

For orally administered drugs, solubility is one of the rate limiting parameters to achieve their desired concentration in systemic circulation for pharmacological response. Drug solubility is the key factor that impacts the formulation and therapeutic efficacy of the drug. These particle size reduction technologies can be divided into two main categories: Conventional methods and the Novel approaches. The conventional size reduction techniques are simple and convenient methods that offer increase the surface area by the reduction of the drug particle size. Novel techniques include the basic particle size reduction principles but overcome many of the obstacles and limitations used with conventional methods. Various techniques described in this review may be used alone or in combination with other to enhance the solubility of poorly aqueous soluble drugs. Selection of a solubility enhancement technique is important to meet critical formulation attribites such as: good oral bioavailability, reduced dosing frequency, and better patient compliance, with a relatively low production cost. The method for selecting an appropriate solubility enhancement technique is dependant on drug characteristics including: solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behavior, dosage form requirements (tablets or capsules), drug loading, immediate or modified release, and maximum daily dose, regulatory, approved excipients, and analytical quantitation methods. Solubility enhancement of poorly solubility drugs is a challange and many drugs are affected to their bioavailability. Recent advancements in processing technolgoies have now made it possible to increase the solubility of poorly soluble drugs with the various techniques as described in this review article better than before.

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