AUCTORES
Globalize your Research

Journal of Pharmaceutics and Pharmacology Research
Krishna Shailaja *

Open Access

Review Article

Review on Solubility Enhancement Techniques for Poorly Soluble Drugs

Krishna Shailaja*, M. Usha, P. Sankeerthana, R. Jaya Sri, S. Niharika and S. Madhuri

Department of Pharmaceutics, RBVRR Women's college of pharmacy, Affilated to Osmania University, Hyderabad India.

***Corresponding Author:** Krishna Shailaja, Department of pharmaceutics, RBVRR Women's college of pharmacy, Affilated to Osmania University, Hyderabad India.

Received date: April 03, 2023; Accepted date: April 15, 2023; Published date: April 26, 2023

Citation: Krishna Shailaja, M. Usha, P. Sankeerthana, R. Jaya Sri, S. Niharika and S. Madhuri (2023), Review on Solubility Enhancement Techniques for Poorly Soluble Drugs, *J. Pharmaceutics and Pharmacology Research*, 6(3); **DOI:**10.31579/ 2693-7247/126

Abstract

Solubility of the drug is important factor that control the formulation of the drug as well as therapeutic efficacy of the drug. Many techniques are used for enhancing the poorly soluble drugs.So, by enhancing solubility we can improve dissolution rate and further oral bioavailability. In this article solubility enhancement techniques were discussed in detail.

Key words: thymoquinone; vascular; health; vascular endothelial cells; cardiovascular diseases; vascular smooth muscle

Introduction

An important physiochemical property of drug substance is solubility,especially aqueous system solubility. To achieve therapeutic efficacy a drug should have a property of aqueous solubility. For drug to enter systemic circulation and exert a therapeutic effect it must be in a solution.Therefore, solubility defined as ''concentration at which the solution phase is equilibrium with solute at a stated temperature and pressure''. Solubility is the property of a solute (solid, liquid or gaseous) to dissolve in a solvent (solid, liquid or gaseous) to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used, temperature and pressure[1,2].

If the solubility of drugs substance is less than desirable, consideration must be given to improve its solubility. The methods to accomplish this, depends on chemical nature of drug and type of drug product under consideration. Chemical modification of drug into salt or ester form is frequently used to increase solubility. A drugs solubility is usually determined by the equilibrium solubility method, by whichan excess of drug is placed in solvent and shaken at constant temperature over a long period until equilibrium is obtained. [3,4].

Knowledge of the solubility of a drug is also important during manufacturing of solid dosage forms such as orally administered drugs, liquid dosage forms such as injectables and other dosage forms. Solubility enhancement remains one of the primary areas of focus during the formulation development phase, there are several situations that may require solubilityreduction and enhancement. [5,6].

Solubility Criteria As Per The Usp

Descriptive term	Part of solvent required per part of solvent
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Practically insoluble	10,000 and over

Importance of Solubility

- Poorly water-soluble drugs often require high dose in order to reach therapeutic plasma concentrations after oral administration.
- The improvement of drug solubility there by its oral bioavailability remains one of the most challenging aspects of drug development process especially for oral drug delivery system.
- Enhance bioavailability of poorly soluble drugs(BCS class II, class IV) a new drug with pH dependent, poor solubility(< 10ug/ml) at intestinal pH and low medium permeability this

results in poor drug bioavailability and precipitation in intestinal fluids.
With the cryo-spraying technology it was possible to formulate the drug as solid dispersion into amphiphilic lipid based micro spheres to improve dissolution profile.

- Controlled release of highly soluble BCS class I drugs.Metoclopramide is a highly soluble, highly absorbable drugs used to treat GI disorders and as antiemetic in chemo therapy treatment.
- Improve bioavailability of celecoxib. Celecoxib is considered in BCS class II drug which hasPoor drug solubility leads to sporadic. As other cox 2i, its cardio vascular toxicity limits its wider therapeutic application.
- In medicine: solubility plays a critical role in drug effectiveness. Without drug substance cannot be observed, leading to low bioavailability, poor solubility of drug lead to other issues such as challenges with metabolism or permeability, interactions with other drugs or the need to extend drug release. [7,8].

Factors Affecting Solubility Enhancement of Drugs

1.Temperature

2. Polarity of drug and solvent

3. PH

4.Drug particle size

5.Effect of pressure

6.Crystal structure

7.Nature of solvent

8.Molecular structure

9.Co-solvency

10.Molecular size

11.Common ion effect

1.**Temperature**:Most substances are endothermic, or absorb heat in the process of dissolution, meaning an increase in temperature from room temperature storage to oral consumption and moving into body heat results in an increase in solubility.

2.**Polarity of Drug And Solvent**: In addition, ion trapping is important for the drug to show its effect properly. In the stomach or intestines, the drug is non-ionized again to prevent it from going back to the GIT and to ensure it is absorbed by body. Lipid soluble substances contain non-ionized molecule(NaCl), and hydrophilic substances contact ionized molecules (Na+, CL-), meaning the more lipid soluble a drug is, the more absorption there will be. The more water soluble(hydrophilic) a drug is, the less absorption there is

3.**Ph Levels:** PH measures the amount of hydrogen content in a solution. The less Hydrogen ions the greater will be the Ph. Solutions with strong pH levels fully dissociate and those with weak pH levels only partially dissociates. The pKa value is used to determine the strength of an acid. A lower pKa value means the drug substance is a stronger acid, which more fully dissociatesin water.

4.**Drug Particle Size:** The solubility of the drug is directly tied to the particle size. Larger particles are less solubilized, especially if the temperature, pressure and polarity for the solutes is the same. The ability for a drug to be soluble allows for simple diffusion of the drug with no energy or carrier protein neededto enter and be absorbed by blood stream.

5.**Effect of Pressure**:In case of solids and liquids solutes there is no effect of pressure on the solubility but in case of gaseous solutes. When the pressure increases there is increase in the solubility and with decrease in pressure there is a decrease in solubility.

6.**Crystal Structure:** Amorphous form of drugs is more soluble than crystalline form.

Solubility: Solvates > Anhydrous > hydrates

Crystalline structure is the best mechanism to improve the solubility.

7.**Nature of Solvent:**The solubility of a solute in a solvent depends on the nature of solute and the solvent. The polarity of the solute and polarity of solvent effect the solubility. Examples:Polar solvents dissolve polar solutes whereas non polar solvents does the same.

8.**Molecular Structure:** Slight modification in the molecular structure of solids lead to marked changes in the solubility of a given solvent.

Introduction of hydroxy group increases water solubility.

Ex: Phenol and Benzene

9.**Co-solvency:**It is a systemin which water miscible or partially miscible organic solvent is mixed with water to form a modified aqueous solution known as co-solvency. Cosolvents have some degree of hydrogen bonding which accepts some hydrocarbon regions. This result in some of physical properties those are intermediate to pure organic solvent and water. It can be reduced by water-water interaction.

Ex: Cosolvents are Ethanol, Sorbitol, Glycerine.

10.**Molecular Size:** Solubility decreases as the molecular size increases. On the other side solvent molecules wrap around molecules of smaller size more easily increasing solubility of the substance.

11.**Common Ion Effect**: added to another ionic compound with a common ion, the solubility of substance decreases significantly. The common ion effect can be explained by LeChatelier's principle of chemical equilibrium. As the reaction of a drug shifts to left side.

Bcs -Biopharmaceutical Classification System

The bioavailability of an orally administered drug depends primarily on its solubility in the gastrointestinal track and its permeability across cell membrane this forms basic for biopharmaceutical classification system[9,10]. Based on intestinal permeability and solubility of drugs, developed biopharmaceutics classification system. The table shows approach employed to overcome formulation challenges in each class drug.

Class	Solubility	Permeability	Absorptionpattern	Examples
I	High	High	Well absorbed	Diltiazem, Propranolol, Metoprolol
II	Low	High	Variable	Nifedipine, Naproxen, Carbamazepine

III	High	Low	Variable	Insulin, Metformin, Cimetidine
IV	Low	low	Poorly absorbed	Taxol, Chlorothiazide, Furosemide

Table 1: BCS Classification of drugs

.

- **Class idrugs:**
- They are orally administered drugs.
- The solubility of drug is high.
- The permeability of drug is high.
- They are well absorbed orally. They have no limitation for solubility and permeability.
  Ex:Diltiazem, propranolol, metoprolol.

- **Class ii drugs:**
- They are orally administered drugs.
- The solubility of drug is low.
- The permeability effect of drug is high.
- They show variable absorption due to solubility limitation.
  Ex:Nifedipine, naproxen, carbamazepine.

- **Class iii drugs:**
- They are absorbed orally.
- The solubility of drug is high.
- The permeability effect of drug is low.
- They show variable absorption due to permeability limitation.
  Ex: insulin, Metformin,cimetidine.
- **Class iv drugs:**
- They are orally administered drugs.
- The solubility of drug is low.
- The permeability of drug is low.
- They are poorly absorbed because of low solubility and low permeability.

Ex: Taxol, chlorothiazide, furosemide.

The BCS classification depends mainly on solubility permeability, dissolution rate this corelate to respective dimensions such as dose number absorption number, dissolution number.

Determination of Solubility

For a pharmacist and pharmaceuticalpersonthe question of solubility is paramount importance. Solubility is not only necessary for dispensing and preparing of medicines but also the effect in separation of substance in qualitative and quantitative analysis. It is one of the best techniques for determining the purity.

Techniques of Solubility Enhancement

1)Physical methods

a)Particle size reduction

i) Micro-nization
ii) Sono-crystallization
iii) Super critical fluid process
iv) Nano suspension

b) modification of crystal habit

i) polymorphs
ii) pseudo polymorphs

c) drug dispersion in carriers

i) eutectic mixtures
ii) solid dispersions
iii) solid solutions

d) complexation -use of complexing agents

e) solubilisation by surfactants -microemulsion

2)chemical methods

i. Change of pH
ii. use of buffer
iii. derivatisation

3)Other methods

i. Co-solvency
ii. Co-crystallization
iii. Hydrotrophy
iv. Nanotechnology
v. Solvent deposition
vi. Solubilising Agents

Size reduction

Micronisation: Micronization is a process of reducing the size ofparticles from larger substance to 50 microns in diameter. Micronization increases the solubility by decreasing the surface area. Lower the particle size faster the solubility. Micronizationtechnology includes wide range of equipment and process to account for the range of material properties, size and shape requirements and other specifications needed for pharma products.

Micronization increases the rate of dissolution of drugs by decreasing drug particle size.

Micronization techniques:

1.Ball mill
2.Rotary cutter mill
3.Hammer mill
4.Fluidized bed jet mill
5.Super critical fluid

Ball mill:

Construction: Ball mill consists of a hallowcylinder, which is mounted on a metallic frame in such a way it rotates on its own axis. The cylinder is made of a metal and is usually lined with stainless steel or sometimes the cylinder is lined with rubber or porcelain. Balls occupy about 30-50% of volume and diameter of the ball in 12-125nm. Shell is rotated at a speed of 60-100rpm.The weight of the balls is kept constant.

Ball Mill

Advantages:

- It Provide very fine powder
- Ball mill suitable for both wet and dry grinding
- It is closed system such that sterility can be achieved
- In ball mill operating and labour cost is low.

Disadvantages:

- It is very noisy machine
- In ball mill soft tacky and fibrous material are not milled.
- It is a slow process. The rate at which energy applied is limited, it depends on acceleration of balls and which influenced by gravitational force.

Variants: Harding mill, continuous ball mills, vibrating ball mills.

Hammer mill:

Construction:. The rotor is rotated at a speed of 8000-15000rpm inside the drum while material is fed through feed chopper. In pharmaceutical industry different shapes are used for grinding dry materials, wet filter cakes, etc.

Two basic shapes are

1.STIRR UP.
2.BAR.

For tablet granulation bar shaped hammers are used widely. The hammer blades can be with flat edge or sharp edge or both on each side. Hammers may be rigid or swing type. The unit enclosed in chamber containing a grid or removable screen through which the material must pass. These screens are not oven type.

The fitness of the product can be regulated by altering:

- Rotor motor
- Feed rate
- Clearance between hammers and grinding plates
- Number and type of hammers
- Size of discharge opening(screen)

Uses: Fineto moderate grinding of may be obtained, depending on the speed of the hammer. The particle size may vary from 10 to 400 mm.

Advantages:

- Various type of feed stock can be handled using screen of different sizes.
- Hammer mill occupies small space.

Disadvantages:

- The screen may get clogged.
- Production of heat is more during milling so product degradation is possible.
- In Hammer mill sticky, fibrous and hard materials are mot milled.

Jet Mill: It is also known as fluid energy mill.

Principle: The principle involved in fluid energy mill is impact and attrition. In this fluid energy millwith high velocity the feed stock is suspended in air stream. Milling takes place between suspended particles with high velocity collisions.

Construction: The surface of mill is made up of soft stainless steel or tough ceramics. Mills are contructed with these materials so that they can easily removed when they are eroded and the contact surface area is more. Grinding nozzles (usually two to six) may be placed tangentially and /or opposed to the initial flow path of a powder.. Inert gases are used to control or eliminate the oxidation of compounds.

Jet Mill

Advantages:

- During milling heat is not produced because it does not contain any moving parts. Therefore, heat liable substances can be milled. Examples are sulphonamides, vitamins and antibiotics. Due to expansion of gases under pressure cooling effect is produced during milling.
- It is rapid and an efficient method for reducing powders to 30 mm or less.
- During milling there are no wear and tear, contamination is not possible.

Disadvantages:

- not suitable for milling of soft tacky and fibrous materials.

Super Critical Fluid Extraction

Principle: Super critical fluid extraction is the process of separating one component from another (the matrix) using super critical fluids as the extracting solvent.

- At certain temperature and pressure liquid and vapour phases of a substance become indistinguishable known as critical condition.
- Substances at critical point are called super critical fluids
  EXAMPLE:co2 It is widely used because it is low cost, nontoxic and low critical parameters.

Parts of sff:

- **Solvent pump:** solvent pump concentrated co2 pump delivers the fluid throughout the system
- **Modifier pump:** It is necessary for increasing polarity of solvent or super critical co2
  EXAMPLE: methanol in concentration 1-10%
- **Valves:** It helps in controlling process pressure, pump flow rate, chiles and temperature in every section
- **Extraction cell:** It is made up of stainless steel to withstand high pressure. Size ranges from 50-100ml
- **Refrigerated system:** It is designed to trap the most volatile compound

Super Critical Fluid Process

Advantages:

- Solvent recovery is easy
- Continuous process
- Oxidative and thermal degradation of active compounds solvent extraction and steam distillation methods
- Selectively controllable
- Contaminant free

Limitations:

- No polar substances are extracted
- High power consumption
- Very expensive and complex equipment
- Operating at elevated pressures.

Applications:

- Extractions of essential oils from black pepper, jojoba oil from seeds of Simmonds chinensis

Flavaniod Extraction: Quercetin from onion skin

- Rapid analysis of fat content
- Rapid analysis for pesticides in food
- Sources form where main bio actives are antitumor(18%)and antibacterial activity (10%)followed by antiviral, antimicrobial, anti-inflammatory and anticholinesterase.

.

Recycling of Sff Can Be Done By

1. **Reduction of pressure:** Super critical fluid unable to dissolve the solute, separation of solid under gravity and gas at low pressure is compressed back to super critical conditions.
2. **Reduction of temperature:** solute drops and recovery of solvent without compression.
3. **Pumping super critical fluid to expansion tank:** Where it becomes gas results in very less solubility i.e. separation of solute

Heat exchange are used to maintain temperature and prevent excessive cooling at throttling value called as Joule-Kelvin effect.

Sonocrystalization In Solubility Enhancement:

The novel approach for particle size reduction on the basis of crystallization by using ultrasound is Sono-crystallization.

Sonocrystalization In The Nucleation Phase: In nucleation, molecules gather together in cluster in a defined manner these clusters need to be stable under current experimental conditions to reach the critical cluster size or they will redissolve and it is the point in the crystallization process that defines the crystal structure.

- Ultrasound radiation is known to induce acoustic cavitation on liquids through the formation, growth and collapse of bubbles.

Applications:

- Control particle size, shape, crystallinity, polymorphism
- Eliminate problems associated with physical seeding.
- Improve batch consistency, filtration, isolation and drying
- Enhance dissolution of poorly soluble drugs.
- Increase CGMP compliance.

Nano Suspension

This method is mainly categorised into

Top-down process

1. Micronization
2. High pressure homogenisation
3. Micro-fluidisation

Bottom-up process

1. Solvent anti solvent
2. Super critical fluid process

High Pressure Homogenization

Homogenization is the process of emulsifying two immiscible liquids(i.e., liquid that are not soluble in one another) are uniformly dispersing solid particles throughout a liquid. The process of homogenization was

invented and patented by Auguste Gaudin in 1899 when he described process for homogenising milk. Gaudin's machine a three-piston thruster outfitted with tiny filtration tubes, was shown at the world fair in Paris in 1900.

THEORIES

1.Cultivation theory

2.Globule disruption by turbulent eddies

1.cultivation theory: The liquid encounters intense cultivation because of large pressure drops through the valve when the pressure drop is large enough, the vapour pressure of liquid exceeds the ambient pressure causing formation of vapour bubble (cavities in the liquid). When the cultivation bubbles implode (collapse of the cavities), shock waves are generated in the liquid. The shock waves break apart the dispersed droplets.

2.Globule disruption by turbulent eddies:.This theory predicts how the homogenising effect varies with the homogenising pressure.

High Pressure Homogenizer

Working: the nano homogenized product enters the valve seat at high pressure and low velocity. The intense release cause turbulence and localized pressure which tear apart the particles. The homogenized product impinges onthe impact ring and exit at a pressure sufficient for movement to the nextstep.

Advantages:

- Low risk of product contamination.

Disadvantages:

- Prerequisite of micronized drug particles.

Microfludization

Microfluidization is a method used for production of micro and nano scale materials. It is commonly used in pharmaceutical industry to make liposomal products emulsions, and in food industry to produce dairy products. A microfluidizer is used to create highpressure to disintegrate fibers, using shear forces. It is patent in mixing technology which uses the microfluidiser.

- The device uses a high-pressure positive displacement pump which forces the product through interaction channels which contain microchannels.
- The product flows through a micro channel on to an impingement resulting in a very fine particle or droplet size
- The aqueous and oil phase in an inline homogenizer to yield a coarse emulsion
- then it is further proceeds to microfluidizer to obtain a nano emulsion

Microfluidisation

APPLICATIONS

- parenteral delivery
- oral drug delivery
- topical drug delivery
- ocular and pulmonary delivery
- nanoemulsion and biotechnology

Solvent and Anti Solvent

It is used for preparation of nano particles of drug which have low aqueous solubility those are drugs which belongs to BCS class II and class IV. In this method we take a solvent in which drug is completely soluble. This solvent can be any organic solvent like acetone, ethanol, dichloromethane, as this name suggest we take an antisolvent which is usually aqueous medium such as water in which the drug is insoluble. Here the drug is having solubility in solvent and solvent is having more solubility in water

Procedure:

- Take the solvent and dissolve the drug in it, there the drug is completely soluble in solvent
- Now add solvent to antisolvent which is water
- As soon as we add solvent to antisolvent the solvent dissolves in water completely precipitating out the drug particles this is because solubility of solvent in the antisolvent is more than solubility of drug in the antisolvent
- To get this drug particles in nano sized range we need energy which can be provided either by simple stirring or by ProbeSonicator.
- This simple stirrer or Probe Sonicatorsplits the solvent in to small nano sized droplets which dissolves in water and the drug is precipitated in nano form

EXAMPLE: acetonitrile, ethanol, ethyl acetate, water.

Polymorphs

Among the various techniques used to enhance solubility of poorly soluble drugs are physical and chemical modification of drugs, and method such as particle size reduction, salt formation, solid dispersion, use of surfactants and complexation. Crystalline polymorphs have the same chemical composition, but different internal structure and therefore possess different physicochemical property because of the different lattice structure, different molecular conformations. Polymorphic forms of drugs can crew interesting for drug developers because their thermodynamic and physicochemical properties.

Polymorph screening

The process seeks to determine whether a given compound exist in polymorphic form. The concept of polymorphic screening was introduced by Pepinsky in 1955 and first applied by Schmidt in the context of covalent bond formation in solid state. Combinatorial chemistry and high through put screening used in drug discovery have resulted in an increase of poorly water-soluble drugs. .

Pseudopolymorphs

Pseudo polymorphs is the phenomenon where in aa compound is obtained in crystalline forms that differ in the nature or stoichiometry of included solvent molecules. The solvent can exist in different crystalline form called as pseudo polymorphs.

- Solvents are molecular complexes that have incorporated crystalizing the solvent molecule in the lattice position and in fixed stochiometric
- Estradiol form highest number of solvents with all 30 solvents
- Solids can be distinguished from polymorphs by observing bubbles of gas in silica oil upon heating

Complexing Agents

Complexation relies on relatively week forces such as van der wall forces, hydrogen bonding and hydrophobic interactions. It is of two types

1.Inclusion complexation 2. Staching complexation

Inclusion Complexation

This are formed by the insertion of the non-polar molecule or the non-polar region of one molecule into the cavity of another molecule or group of molecules. Cyclodextrins are most commonly used host molecules. Based on the structure and properties of drug molecule it can form 1:1 or 1:2 drug cyclodextrin complex.

Staching Complexation

Complexation formed by dissolving organic drug with water. it is squeezed out by strong water-water interaction force. It forms aggregates and reduce contact between non-polar hydrocarbon moieties and polar water moieties the larger non polar regions opposed by entropy and random arrangement was formed. The formed complexes stached can be homogenous or mixed. It is a self-association complexation. Ex: nicotinamide, Anthracene, Caffeine, theobromine[10].

Microemulsion

Microemulsion is defined as isotropic mixture of natural or synthetic oils, surfactant and co-surfactant. Microemulsions are liquid droplets in a diameter of 10-100nm. They are transparent translucent as the droplet diameter are less than one-fourth of the wavelength of light, they scatter little light.

Advantages:

- Ease of manufacturing and scale-up
- Useful in topical application

Disadvantages:

- Traditional dissolution methods donot work because this formulation potentially dependent on digestion prior to release of drug

Eutectic mixtures

A eutectic or eutectic mixture is a mixture of twoor more phases at a composition that has lowest melting point .it is a where the phases simultaneously crystalize from molten solution. Their formation occurs via non covalent forces mainly hydrogen bonding, ionic and Vander Waalsforces and aromatic interaction.This,systems can be considered as of physically blended with high thermodynamic functions. eutectic mixtures have been known for long time in pharmaceutical field. However, its potential as a system to improve the solubility and dissolution of poorly water-soluble drugs remains little explored. Recently the number of studies involved in the preparation of eutectic mixtures to improve solubility and oral bioavailability of poorly soluble drugs has increased considerably including drug carrier and drug-drug mixtures.in this review is discussed the potential of eutectic mixtures as an alternative pharmaceutical solid system to enhance drug solubility, dissolution rate or oral bioavailability[11].

Lovastatin is widely used to control hypercholesterolemia and is first line treatment of coronary artery disease and atherosclerosis which acts by inhibiting hydroxy glutaryl coenzyme A reductase.

Differential scanning calorimetry analysis

Differential scanning calorimetry curves of the obtained solid wereacquired using DSCQ 200 equipped with a TA refrigerator cooling system 90,using aluminium crucibles with 2mg of sample under dynamic nitrogen atmosphere and heating rate of 10 degrees per minute in the temperature from 40 to 200 degree Celsius

DSC is the primary technique used to identify eutectic formation hence it is applied to screen LOV and co -formers or excipients in binary mixture composition (1:1).

Solid Dispersion

In solid dispersion technique poorly-soluble drugs is dispersed in highly solid hydrophilic matrix which enhanced the dissolution of the drug and can yield molecular and non-molecular level mixing. Ex: PEG 4000 increases the rate of dissolution. Solubility of Griseofulvin, ketoprofen, Aceclofenac, Oxcarbazepine, Albendazole, bifonazole induced by solid dispersion technique.

It was prepared by

1.Hot melt method

2.Solvent evaporation

3.Hot melt extrusion

Hot Melt Method:

The excipients are heated to a temperature above its melting point and the drug is incorporated. A molecular dispersion can be achieved or not depends on the degree of saturation and rate of cooling used in the process. When drug and vehicle which is meant for melting it should contain low melting point and insoluble in organic solvents. It was cooled quickly and prepared for suitable dosage form

Hot Melt Extrusion

Hot melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of immiscible components leads to amorphous drug dispersed in crystalline excipient. The process has been useful in preparation of solid dispersion in single step. This method of choice in the polymer industry, but Speiser and Huttenrach were the 1st person to use this technology for pharmaceutical purpose. A melt extrusion consists of following section: an opening to feed raw materials, a heated barrel that consist of extruder screws to convey and mix the feed materials and an exit port, which consist of optimal die to shape the extruding mass. the active ingredient and the carrier are feeding to the extruder at aconstant rate. When a mixture of active ingredient and carrier is conveyed through heated screws, it is transformed into its fluid like state. This state allows intimate homogenous mixing by the high shear of extruder screws. An exit port which consists of optional die, shapes the melt in required form such as granules, pellets, films or powder. [12].

Hot Melt Extrusion

Advantages of solid dispersion:

- It has rapid dissolution rate.
- Increase absorption rate of drug.
- Improve bio-availability in water of a poorly water-soluble drug in a pharmaceutical.
- Decrease the crystalline structure of drug into amorphous form.
- Prepare rapid disintegration oral tablets.
- Mask the taste of drug substance.
- Avoid degradation or decomposition of drugs.

Disadvantages:

- Instability of solid dispersion.

By Change Of Ph

Poorly water-soluble drug may potentially dissolve in water by implementing a Ph change. To access the solubility the buffer capacity and tolerable Ph are important to be considered. Solubilized excipients that increase environmental pH with in the dosage form to a range higher than pKa of weakly acidic drugs increase the solubility of that drug,.

Advantage:

- Simple to formulate and analyse
- Uses small quantity of compounds, amenable to high through put evaluation

Disadvantage:

- Risk of precipitation may occur Intravenously this may lead to emboli, orally it may cause variability.
- Tolerability and toxicity both local and systemic related with use of a non-physiological Ph and extreme Ph should be considered.

For weekly acidic drugs

- Lower Ph -unionised form – insoluble ppt
- Higher Ph -ionized form -more soluble drugs

For weakly basic drugs:

- Lower Ph -ionised form -more soluble drug
- Higher Ph -unionised form -insoluble ppt

Use of buffer

They maintain the Ph of the solution overtime and it reduces or eliminate the potential for precipitation upon dilution.. Change of pH by onefold increase solubility by 10fold if it changes by one pH unit, that decrease ionization of the drug and solubility decreases by 10-fold.

Derivatization

It is a technique used in chemistry which transforms a chemical compound in to a product of similar chemical structure, called derivative. Derivatives have different solubility has that of adduct.

Co-Crystalization: Co-crystallization alters the molecular interactions and is considered to optimize drug properties as an alternative metho

Co-crystallization overcomes various physical, chemical, or physiological drawbacks of an API. Mechanism of co solvency favours the dissolution of a non-polar solute by lowering the interfacial tension. If one of the components is liquid and the other is solid then it is termed as cocrystals.Pharmaceutical co-crystals basically consist of two components that are the API and the co crystal formers[12].

Different techniques for co-crystallization:

- Solvent evaporation
- Grinding
- Slurry co-crystallization
- Solvent drop grinding(modification of grinding)
- High throughput co-crystallization
- Hot melt extrusion
- Sonocrystallization

Co-crystals characterization parameters:

- Solubility
- Maximum wavelength

- Stability
- Intrinsic dissolution
- Bioavailability
- Melting point
- Melt (hot stage microscopy)
- Scanning calorimetry (DSC)
- Vibrational spectroscopy

Co-Solvency: It has found its main use in parenteral dosage forms because of low toxicity of many cosolvent and relatively greater ability of co-solvents to solubilise nonpolar drugs. Commonly used cosolvents glycerol, propylene glycol, PEG 400, dimethyl sulfoxide, dimethyl acetamide, ethanol, n-octanol are the commonly used cosolvents

Advantages:

- Has large solubilizing capacity for poorly soluble drugs

Disadvantages:

- Toxicity and tolerability related with the level of solvent administration has to be considered
- The drugs which are extremely insoluble in water and do not readily redissolve after precipitation from the co-solvent mixture may have a potential risk for embolism and local adverse effects at the site of injection.[13].

Hydrotrophy:

It is a solubilization phenomenon where addition of a large amount of second solute results in an increase in the aqueous solubility of existing solute. Hydrotropic agents are ionic organic salts.

Aromatic anionics: sodium benzoate, sodium salicylate, sodium benzene-sulphonate, sodium benzene di-sulphonate, sodium cinnamate

- Aromatic cationic: para-amino benzoic acid hydrochloride, procaine hydrochloride, caffeine
- Aliphatic and linear anionics: Sodium Alkanoate.

Advantages:

- does not require emulsification.
- It only requires mixing of drugs with the hydrotrope with water and do not require chemical modification of lipophilicdrugs, use aromatic solvents, or preparation of emulsion system.
- Examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol and beta- naphthol and salicylates, alkaloids like caffeine, nicotine, ionic surfactants like diacids, SDS(sodium dodecyl sulphate) and dodecyl Benzene.

Mixed hydrotrophy: It is new, simple, cost effective, safe, accurate, precise method which involves the blends of hydrotropes which gives synergistic effect on solubility of poorly water-soluble drugs.

Nanotechnology:

It refers widely to study and use of materials and structures at the nano scale level of approximately 100 nm or less. Forvery low solubility, oral bioavailability many techniques are used such as enhancement by micronization which is not sufficient because micronized product has very low effective surface area for dissolution and further step taken was nanonisation which reduce the particle size from micro to nano. The methods of preparation like milling, high pressure homogenisation, vacuum deposition, high temperature evaporation may be used.

Advantages:

It results in production of the nano or micro sized spherical particles with smooth surfaces and narrow particle size distribution and high specific surface areas, consequently increasing the dissolution rate and solubility.

Disadvantages:

The agglomeration problem is inherent and difficult to overcome.

Solubulizing agents:

We use different types of solubilizing agents such as surfactants, Crospovidone, croscarmellose sodium and sodium starch glycolate etc. The aqueous solubility of the antimalarial agent halofantrine was increased by the addition of caffeine and nicotinamide[14].

Solubilization by surfactants: Most surfactants consist of hydrocarbon segment connected to polar group.

Microemulsion: The addition of surfactant, which predominately soluble in the internal phase when compared with co surfactant. It results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the internal phase is less than 0.1micron droplet diameter. The surfactant and the co surfactant alternate each other and form a mixed film at the interface, which contributes to the stability of microemulsion.

Non-ionic surfactants, such as tweens (polysorbates) and labrafil(polyoxyethylated oleic glycerides), with high hydrophile-lipophile balances are often used to ensure immediate formation of oil-in-water droplets during production.

Advantages:

- Ease of separation due to spontaneous formation.
- It hasThermodynamic stability.
- It gives transparent and elegant appearance.
- Through biological membrane it enhances the permeation.
- It Increases bioavailability and less inter and intra-individual variability in drug pharmacokinetics.

Solvent Deposition

Reduction of particle size remains the accepted method for increasing dissolution rates. However, upon micronization hydrophobic drugs have a tendency to form clump when exposed to the dissolution medium. Sekiguchi and Obi proposed that the incorporation of a microcrystalline or molecular dispersion of a poorly soluble drugs in solid matrix of water-soluble carrier would increase the dissolution rate and absorption of the drug. Since then, modifications of the technique have been suggested under a variety of names, including solid solutions, eutectics, co-precipitates, and fast release solid dispersions.

Advantages:

- Many polymers with high melting temperatures that cannot be utilized in melt solid dispersions processes could be carriers for solvent deposited drug formulations.
- Tacky and sticky materials associated with melt or fusion method can be avoided.
- .

preparation: Fine powders of the drug and different water-soluble adsorbents or carriers are accurately weighed in certain ratios. Drug is added to organic solvent in a beaker sufficient enough to dissolve the drug. Then required quantity of adsorbent is added to above drug solution. This slurry or gel are stirred by a magnetic stirrer and evaporated by a stream of filtered air or water bath. Temperature maintained for evaporation is generally a little higher than the boiling point of solvent to allow organic solvent to evaporate. The samples are then placed in a heated vacuum desiccator or vacuum oven to facilitate the drying process. The solid masses are then remixed by tumbling end over end for few minutes. Then solvent deposited systems is stored in desiccators for future use[15].

Investigators	Water insoluble drugs	Solvents used	Carrier used
Monkhouse	Indomethacin, griseofulvin, chloramphenicol, hydrochlorothiazide, aspirin, reserpine	Acetone, chloroform, dichloromethane	Fumed silicon dioxide, silicic acid
Johansen	Phenylbutazone, norethindrone, digoxin	Acetone, chloroform,	Lactose, starch, silicon dioxide

Lia	Corticoids (prednisolone, prednisone, hydrocortisone)	N,N-dimethylacetamide polyethylene glycol 400	Non porous and porous amorphous silicas
Alsaidan	indomethacin	Alcohol solution	Kaolin and microcrystalline cellulose
Dastmalchi	glibenclamide	chloroform	Microcrystalline cellulose
Cui	Nitrendipine	Ethanol and dichloromethane	Microcrystalline cellulose, light anhydrous silicic acid, lactose and low substituted hydroxypropyl cellulose
Kakkar	chlordiazepoxide	dichloromethane	Starch-lactose granules

Table 2: Literature on Solubility enhancement techniques

Characterization of solvent deposition system:

- Differential scanning calorimetry
- Fourier transform infrared spectroscopy
- X-ray diffraction studies
- Dissolution rate studies
- Scanning electron microscopy
- In vivo evaluation

Applications:

- Solubility enhancement for drugs in capsule and tablet dosage form.
- To increase flow property.
- Sustained release microspheres containing solid dispersion structure.

Applications

- Micronization reduces the size of particles so that it enhances the solubility. It gives uniform particle size and nano particle size distribution.
- In nanosuspension reduction of size increases the surface area which in turn increases solubility.
- Solid dispersion stabilizes the unstable drug.
- In supercritical fluid process drug particle are solubilized and recrystallized at greater reduced particle size to create a nanosuspension.
- In Co solvency PH is adjusted to further increase solubility of poorly soluble drugs.Salt formation technique was used so that they are easily dispersed in aqueous solution further increases the solubility[16].

Conclusions

Pharmaceutical nanotechnology provides opportunities to improve materials and technology where existing technologies reaching their limits. It raises new hope to pharmaceutical industries by providing new patentable technologies in view of revenue loss caused due to off patent drugs. This provides profound tools for understanding the cells between normal and abnormal or any insights of molecular basis.

References

1. Leon Lachman, Herbert A Lieberman's Roop K khar, S P Vyas, Farhan J Ahmad, Gaurav K Jain, Industrial pharmacy, Solubility studies, 4th Edition, CBS Publishers and distributors pg:271-278
2. CVS Subrahmanyam, Biopharmaceutics and pharmacokinetics concepts and application, physicochemical factors influencing drug absorption, 2nd Edition, Delhi Vallabh Prakashan, pg:101-112
3. D.M. Brahmankar, Sunil B Jaiswal, Biopharmaceutics and pharmacokinetics atreatise, physicochemical properties of drug, Vallabh prakashan, Nagpur, may 15th 1995 pg:77
4. CVS Subrahmanyam, J.Thimma Shetty, Sarasija Suresh, V Kusum Devi, Pharmaceutical Engineering, volume-II, Classification of size reduction equipment, 2nd Edition, Delhi Vallabh prakashan, pg:6-16
5. K Sambamurthy, Pharmaceutical Engineering, Crystallizers, New Age International Publishers, pg: 235-240
6. Aman Shrivastava, Jeetendra K Gupta, Manoj K Goyal, Therapeutic approaches of Nanotechnology, Indian journal of pharmaceutical education and research, The official publication of association of pharmaceutical teachers of India pg:628-635
7. ShincyMariya Francis, Elizabeth N Xavier, Therapeutic approaches of nanotechnology, Solubility Enhancement of Lawsone by Complexation with beta Cyclodextrin, The official publication of association of pharmaceutical teachers of India pg:706-715
8. Amol Deshmukh, Pratik Ugale, Vaibhav Toche,(2008).Asian journal of research in biological and pharmaceutical sciences, Solid dispersion: A technique to enhance solubility of poorly soluble drugs,pg:85-90.
9. Ahmed Mustafa Khidir, M Aksayid, Ali Awadallah Saeed,(2020).World Journal of Pharmacy and Pharmaceutical sciences, Pharmaceutical Nanotechnology and Application,pg:202-210.
10. Yellela S.R. Krishnaiah,(2020). Journal of Bioequivalence and Bioavailability volume II, Pharmaceutical Technologies for Enhancing Oral Bioavailability of poorly soluble drugs,pg:28-33.
11. Kim JS, Kim MS, Park HJ, Jin SJ, Lee S,(2008).Journal of Bioequivalence and Bioavailability, Physicochemical properties and Oral Bioavailability of Amorphous atorvastatin hemi-calcium using spray drying and SAS process,pg:211-219
12. Keck CM, Muller RH,(2006).European journal of pharmacy and Biopharmaceutical, Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation,pg:3-16.
13. M. Kalani, R. Yunus,(2011).International Journal of Nanomedicine, A Review on Application of supercritical antisolvent method in drug Encapsulation,pg:1429-1442.
14. R.H. Muller, C. Jacobs, O. Kayer,(2000).Nanosuspensions for the Formulation of Poorly Soluble drugs, in Pharmaceutical Emulsion and Suspension,pg:383-407.
15. R.H Muller, B.H.L. Bohm, J. Grau,(2000).Handbook of Pharmaceutical Controlled release Technology, Nanosuspensions: A Formulation approach for poorly soluble and poorly bioavailable drugs,pg:345-357.
16. Prakash Rao B, Sarasija S, Narendra C,(2007).Indian Journal of Pharmaceutical Education and Research,

Recent Advances in Cyclodextrin Complexes; Mechanistic Analysis of permeation Enhancers,pg:102-113.

DOI: 10.31579/ 2693-7247/126