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Review Article

Strategies for improving hydrophobic drugs solubility and bioavailability

Krishna R. Gupta[1,*], Monali R Dakhole[1], Ketki S Jinnawar[1], Milind J Umekar[2]

[1]*Dept. of Pharmaceutical Chemistry, Smt. Kishoritai Bhoyar College of Pharmacy, Nagpur, Maharashtra, India*
[2]*Smt. Kishoritai Bhoyar College of Pharmacy, Nagpur, Maharashtra, India*

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ABSTRACT

Nowadays various drugs synthesized by various computational drug designs as well as various drugs have complex structure. Due to their complex structure, higher molecular weight which will increases solubility issues. Solubility is the most important and challenging task for researchers. Bioavailability and absorption of a drug depends on solubility of drug and thus we achieve pharmacological response. But poor aqueous solubility is a rate limiting step in bioavailability which made drug development more difficult. Drugs having low bioavailability require to be administered at a higher dose to achieve desired drug concentration in the systemic circulation and reach the target site. Thus, instead of getting desired effects drug produces side effects in the gastrointestinal tract. Hence, with the advancement of chemical science, the need of development of pharmaceutical technologies is also increasing. New techniques have been developed with a focus on enhancement of the solubility and oral bioavailability of poorly water-soluble drugs. The present review focuses on new technologies which are being used to resolve solubility issue of poorly soluble drugs which is the rate limiting step in bioavailability.

1. Introduction

Nowadays combinatorial chemistry, high throughput screening techniques, computer aided drug design adopted by various pharmaceutical industries for drug discovery of novel drugs and their development processes.[1] But such types of approaches have certain limitations such as water insolubility, stability, lipophilicity, molecular weight and H-bonding properties and hence they have poor aqueous solubility and poor bioavailability.[2] As per literature survey about 90% and 40% of drug molecules in the market have poor water solubility and less bioavailability respectively.[3]

The drugs having poor aqueous solubility is the major limiting factor but only because of their potential pharmacokinetic activity number of new drugs launch in market. Thus to get better bioavailability of such poorly water soluble drugs are required to administered higher dose than the actual dose to achieve drug plasma concentration and this will results in adverse reaction, increased in cost of therapy instead of getting potent pharmacological response and hence patient non-complains. In the view of pharmaceutical industries, the manufacturing cost would increases due to requirement of large amount of active pharmaceutical ingredient (API) for manufacturing and to fulfill demands of the drug product.[4]

Nowadays, Innovated drugs undergo various experimentation to improve solubility and dissolution of hydrophobic drug substances, but water solubility is the trickiest tasks in drug development. For better bioavailability drugs should be dissolve properly in aqueous medium like gastric fluid so it will radially available for better absorption and bioavailability for orally administered drug as well as parenteral formulation.[5] But bioavailability

* *Corresponding author*.
E-mail address: krg1903@gmail.com (K. R. Gupta).

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is depends on the drug absorption from the GI tract which is limited due to poor aqueous solubility and poor membrane permeability of the drug molecule. Membrane permeability of the drug molecule involves dissolution of active agent orally in gastric and intestinal fluids before it can permeate the membranes of the GIT to reach systemic circulation. Hence, pharmaceutical department focus on oral bioavailability of active agents by improving solubility and dissolution rate of poorly water soluble drugs.[6]

The Biopharmaceutics Classification System (BCS) was established and introduced by US food and Drug Administration (FDA) to assess oral drug product. The drug should have following ability to permeate biological membranes and aqueous solubility:

1. A drug is considered 'highly soluble' when the highest dose is soluble in 250 ml water or less in pH range 1 to 7.5.
2. A given drug substance is considered 'highly permeable' when extent of absorption human is determined to be ≥90% of an administered dose (in solution), based on mass balance or related to an intravenous reference dose.

For rapidly dissolving tablet, ≥85% of the labeled amount of drug substance must dissolve in 30 minutes.[7] According to BCS system, drug are classified into four groups are as fallows.[8]

Table 1: Biopharmaceutical Classification System

BCS Class	% Drugs	Criteria	Examples
BCS Class I	84%	High Solubility High Permeability	*B*-blockers propranolol, Metoprolol
BCS Class II	17%	Low Solubility High Permeability	NSAID's Ketoprofen, Antiepileptic Carbazepine
BCS Class III	39%	High Solubility Low Permeability	*B* blockers Atenolol,H2 antagonist Ranitidine
BCS Class IV	10%	Low Solubility Low Permeability	Diuretics Hydrochlorothiazide, frusemide

Thus number of methodologies and solubilisation technologies adopted to improve and to overcome this poor solubility issue. The methodology includes micronization, chemical modification, solid dispersion, pH adjustment, hydrotropy etc.

1.1. Solubility

Solubility is defined as the concentration of the solute in a saturated solution at a certain temperature .The solubility of a drug can be expressed as parts, percentage, molarity, molality, volume fraction, and mole fraction. Solubility of drug means the maximum concentration of the drug solute dissolved in the solvent under specific condition of temperature, pH and pressure that relates more closely to the bioavailability rate.[9]

Official pharmacopoeia classify the solubility with the solvent used for quantification and have defined the criteria as given in below table.[10]

Table 2: Definitions of solubility

Definition	Parts of solvent required for one part of solute
Very soluble	< 1
Freely soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100
Slightly soluble	100 – 1000
Very slightly soluble	1000 – 10,000
Insoluble	>10,000

1.2. Mechansm of solubilization[11]

The mechanism of solubilisation involves the breaking of weak wander wall forces of molecules such as intermolecular bonds in the solute the separation of the molecules of the solvent which provide space in the solvent for solute, interaction between the solvent and the solute molecule or ion.

1.3. Causes for poor oral absorption

Possible Causes for Poor Oral Absorption of Any drug is said to be when:

1. Aqueous solubility <100μg/ml
2. High crystal energy (melting point >2000 C)
3. Poor dissolution: Intrinsic dissolution rate <0.1 mg/cm2/min
4. High molecular weight: (>500), Self-association and aggregation.[12]

1.4. Factors affecting solubility

1.4.1. Temperature:[13–17]

As the temperature increases, the solution will absorbs energy and results in increased solubility. Whereas, as the temperature decreases the solution process releases energy which will decreased in the solubility of solution but in case of all gases, solubility decreases as the temperature of the solution increases.

1.4.2. Complex formation:[16]

Complexation may be by the addition of the third substance in system, that 3^{rd} substance will forms an intermolecular complex with the solute in solution results in either increased or decreased in apparent solubility of a solute in a particular liquid.

1.4.3. Solubilizing agent:[16]

These agents act as micelles in solution and forms large aggregates in the center of these aggregates resembles a separate organic phase and organic solutes may be taken up by aggregates, thus producing an increase water solubility. If polar solutes are taken up, their apparent solubility in the organic solvents are increased.

1.4.4. Pressure:[18]

In case of gaseous solutes, increase in pressure increases solubility and decrease in pressure decrease the solubility. For solids and liquid solutes, any change in pressure have practically no effect on solubility.

Nature of the solute and solvent:[19] 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature, while in case of zinc chloride 200 grams can be dissolved. The difference in the solubilities of these two substances is due to the different nature.

Particle Size:[19] As the size of the solid particles decreases/ smaller, the surface area to volume ratio increases so that larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be described by following equation 1.

$log\frac{S}{S0} = \frac{2YV}{2.3.3.RTr}$..... Equation 1

Where, S = solubility of infinitely large particles

S0 =solubility of fine particles

V = molar volume

γ = surface tension of the solid

r = radius of the fine particle

T = absolute temperature in degree Kelvin

R= universal gas constant.

1.4.5. Polarity:[19]

Generally like dissolves like phenomenon occurs as non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents because the polar solute molecules have a positive and a negative end to the molecule results in dipole-dipole interaction.

1.4.6. pH:[19]

The proportion of unionized acid molecules in the solution increases ss the pH of weakly acidic drug or a salt of such a drug is decreased. If there is a less unionized species than that of the ionized form precipitation may occur.

1.5. Molecular size:[20]

Larger molecule shows less solubility because they are more difficult to surround with solvent molecules in order to solvate the substance. In case of organic compounds as the carbon branching increases the solubility gets increased since more branching will reduce the size of the molecule and make it easier to solvate the molecules with solvent.

1.5.1. Polymorphs:[21]

A solid has a rigid form of shape or habit of a crystal which is made up of atoms, ions, or molecules in a regular geometric arrangement. Polymorphs can vary in melting point. It is because of differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy.

1.6. Need of solubility enhancement:[22]

About 40-50% of new drug applications of new chemical entities are rejected because of poor solubility and thus poor biopharmaceutical properties and pharmacological response such as membrane penetration, gastric fluid absorption and poor oral bioavailability.

1.7. Different approaches used to improve api solubility and thus bioavailability[23–25]

API having good solubility requires oral formulations as well as prerequisite for parenteral administration forms, as injectables or subcutaneous injection, hence the API should be in solubilized form. Different approaches to solubility enhancement are available which are as.

1.7.1. Liberation

1. Type of dosage form
2. Disintegration time

1.7.2. Absorption

Solubility

1.7.3. Chemical approach

1. pH adjustment
2. Salt formation
3. Use of buffer
4. Derivatisation
5. Use of precipitate inhibitor
6. Complexation
7. Cocrystallisation
8. Hydrotrophy

1.7.4. Physical approach

1. Particle size reduction
2. Modification of crystal habit
3. Drug dispersion in carriers

4. Solubilization by surfactant

1.7.5. Permeability

1. Administration route
2. Permeation enhancers
3. API lipophilicity, stability

1.7.6. Influence distribution

1. Tissue targeting
2. Protein binding

1.7.7. Reducemetabolism

• Avoid the first pass effect

2. Techniques for Solubility Enhancement

2.1. Co-solvency

The co-solvency is the process in which solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent which is known as co-solvent. Cosolvent acts by reducing the interfacial tension between the aqueous solution and hydrophobic solute of the system. Hydrophilic hydrogen-bonding groups confirms water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall intermolecular attraction of water.[26]

Table 3: Solubilization study of various poorly water-soluble drugs by co-solvency method[25–28]

Drug	Co-solvents
Etoricoxib	Water ,PEG 400 ,PG, Glycerin
Meloxicam and Rofecoxib	Glycerin, Methanol, Ethanol, Propanol , Butanol, Pentanol , Hexanol Heptanol, Octanol ,PG, PEG 400
Aceclofenac	Propylene Glycol, PEG 4000, Ethanol, Sucrose
Lamotrigine and piroxicam	Demineralised water,0.1N HCl acid,Phosphatebuffer,ethanol, PEG 400 +Solubilizers like Sodium caprylate, Sodium benzoate , Niacinamide

2.2. Complexation

Stacking and inclusion complex: Association between two or more molecules to form a non-bonded entity with a well-defined stoichiometry is called as Complexation, which involves relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions are involved. There are two types such as Stacking complexes, introducing non-polar part of drug and complexing agent which shows exclusion of the non-polar area from contact with water, reducing total energy of the system. This complex can be homogeneous or mixed, but results in clear solution. Second is Inclusion complexes, by inserting the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or group of molecules. Cyclodextrins (CD) are a group of cyclic oligosaccharides contains three major cyclodextrins α, ß and γ-CD are composed of six, seven, and eight D-(+) - glucopyranose units. Cyclodextrins have a hydrophilic exterior and ahydrophobic internal cavity which form complex with drug and improve the solubility and bioavailability of poorly soluble drug. R- cyclodextrin derivative with increased water solubility (e.g. hydroxypropyl-R-cyclodextrin HP-R-CD) are most commonly used in pharmaceutical formulation.[29–31]

2.3. Particle size reduction

The solubility is directly proportional to the drug particle size as a particle becomes smaller, the surface area increases and thus larger surface will available for direct contact and interaction with solvent.[32]

Table 4: Solubilization study of various poorly water-soluble drugs by particle technology[33]

Drugs	Method
Danazol	Cryogenic spraying process/spray
Carbamazepine	Freezing into liquid
Glibenclamide, Febantel, Itrazonazole	Crystal engineering

2.4. High-pressure homogenization

In this method water or alternatively in nonaqueous media or water-reduced media dispersion of the crystalline drug particles is passed under high pressure through a narrow homogenization gap with a very high velocity. The particles are disintegrated by stepwise in which, Boiling of a liquid due to static pressure exerted on the liquid results in formation of gas bubbles, gas bubbles collapse under normal air pressure which produces shock waves and crystals undergo collision, lastly disintegration of particle.[34]

Examples: Drugs such as Cefixime Trihydrate, Albendazole, Aphidicolin, Azithromycin, Fenofibrate and Valsartan solubility were improved by High Pressure Homogenization method and formulated in nanosuspension.[32,35–38]

2.5. Cryogenic method

In this method nanostructured amorphous drug particles are created with high degree of porosity at very low-temperature. The Type of injection device (capillary, rotary, pneumatic, and ultrasonic nozzle), location of nozzle (above or under the liquid level), and the composition of cryogenic liquid (hydrofluoroalkanes, N2, Ar, O2, and organic solvents) describes the Cryogenic inventions. After

cryogenic processing, the drugs are powdered by various drying processes like spray freeze drying, atmospheric freeze drying.[39]

Spray Freezing onto Cryogenic Fluids. Here drug and the carrier (mannitol, maltose, lactose, inositol) are dissolved in water and atomized above the surface of a boiling agitated fluorocarbon refrigerant. Sonication probe can be placed in the stirred refrigerant to enhance the dispersion of the aqueous solution.[40]

Spray Freezing into Cryogenic Liquids (SFL). This technology forms amorphous nanostructured aggregates of drug powder having good surface area and wettability. It incorporates direct liquid-liquid encroach between the automatized feed solution and cryogenic liquid to provide intense atomization into microdroplets and significantly faster freezing rates.[41]

Spray Freezing into Vapor over Liquid (SFV/L). Cryogenic fluid vapors freezes the drug solution with subsequent removal of frozen solvent and produces fine drug particles with high wettability. The drug becomes supersaturated as the solvent freezes and fine drug particles may nucleate and grow.[42]

Ultra-Rapid Freezing (URF). A novel cryogenic technology that creates nanostructured drug particles with large surface area and adequate surface morphology by using solid cryogenic substances. Utilizing drugs solution to the solid surface of cryogenic substrate results into rapid freezing and subsequent lyophilization which forms micronized drug powder with enhanced solubility.[43]

Lyophilisation monophase solution technique is also suitable alternative procedure that could overcome demerits of the conventional freeze-drying. In this technique, TBA, which is miscible with water in any proportion, was used as an organic cosolvent to solubilize the hydrophobic drug while the hydrophilic carrier was dissolved in water then the mixed isotropic solution was lyophilized. TBA possesses a high vapor pressure (41.25 mm Hg at 25^{O}C), a high melting point (24^{O}C) and has a low toxicity. All these factors contribute TBA as an ideal freeze-drying medium that could be removed rapidly and completely by freeze-drying. Lyophilization monophase solution technique was used to enhance the dissolution rate of the poorly soluble drugs; budesonide, salmeterol, ketoprofen and nitrendipine by complexation with βCD and HPβCD.[44]

2.6. Liquisolid compacts

The liquisolid technique is a novel concept where a liquid converted into free flowing, readily compressible and apparently dry powder by means of simple physical blending with selected carrier and coating material. The layer of a liquid will formed on the particle surface. This layer redially adsorbed by the fine coating particles. Thus, the liquid material converted to an apparently dry, free flowing, and compressible powder.[45]

Table 5: Solubilization study of various poorly water-soluble drugs by liquisolid compact technology[43,46–48]

Drug	Non-volatile solvent	Carrier material	Coating material
Ebastine	Tween 20	Avicel PH 102	Aerosil 200
Cinnarizine	Propylene glycol	Neusilin US2	Aerosil 200
Glibenclamide	PG,PEG200	Avicel, lactose	-
Nateglinide	Propylene glycol	Lactose	Syliod 244FP

2.7. pH adjustment

May potentially dissolve in water by applying a pH change approach can be applied for Poor water soluble drug, for this according to nature of a drug and the buffer capacity of the selected pH are important to consider. The excipients that increase environmental pH of drug within the dosage form which should have higher than pKa of weekly acidic drugs increase the solubility of that drug, whereas the excipients which are alkaline in nature (alkalyzing agents) may increase the solubility of weekly basic drugs.[49]

Examples: Flufenamic acid, Mefenamic acid, Niflumic acid, Diclofenac sodium and Meclofenamic sodium.[50]

2.8. Precipitation

In this method dilute solution is prepared by dissolving the drug substance in a solvent and this solution of drug is then poured with the help of injected into the water with stirring so that the substance will precipitate as nanocrystals. The obtained nanocrystals can be removed from the solution by membrane filtration and then dried in air.[51]

Example: JNJ-25894934 New molecule entity,[52] Pioglitazone.[53] ultrafine Rifampicin particles,[54] Fenofibrate-loaded nanoparticles by precipitation method,[55], Curcumin using HPMC K 15M by Solvent Change Precipitation Method[56] etc.

2.9. Manipulation of solid state/polymeric alteration

Drug that exhibits different crystalline forms and may have different properties is known as Polymorphs. They may have different physical and chemical stability, shelf-life, melting point, vapor pressure, intrinsic solubility, dissolution rate, morphology, density and biological activities as well as bioavailability. Therefore metastable form is the most stable crystalline polymorphs. Polymorphism showing drugs have different physicochemical properties such as melting point, density, stability and drug solubility because such as properties depend on the escaping tendency of the molecules from a particular crystalline structure. The metastable forms have many advantages of higher solubility but have poor

stability. Hence stabilizers added to stabilize and to prevent to crystal growth in the formulation. Eg: Withdrawal of ritonavir (Norvir®) capsules containing its polymorph from the market because a less soluble and less bioavailable.[57]

2.10. Hydrotrophy

In this method, large amount of second solute are added in excess which results in an increase in the aqueous solubility of another solute. Solute may be alkali metal salts of various organic acids, ionic organic salts. Sometimes addition of additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility in given solvent are said to "salt out" the solute. Various water soluble salts with large anions or cations are added in solvents result in "salting in" of non-electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism". Hydrotropic solutions involve a weak interaction between the hydrotropic agent and solute which are wander wall types in nature. Hydrotrophy increases solubility of API in water due to the presence of large amount of additives called hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs.[58]

Table 6: Solubilization study of various poorly water-soluble drugs by Hydrotropic agents[59]

Drug	Hydrotropic agent
Riboflavin	Procaine HCl, PABA HCl, Cinchocaine HCl, Resorcinol, Pyrogallol
Chartreusin	Sodium benzoate, Sodium p-hydroxybenzoate, Sodium m-hydroxybenzoate, Sodium o-hydroxybenzoate, Sodium 2,4-dihydroxybenzoate, Sodium 2,5-dihydroxybenzoate
Diazepam, Medazepam, Oxazepam, Nitrazepam, Clonazepam	Sodium salicylate
Theophylline, Hydrocortisone, Prednisolone, Phenacetin	Sodium benzoate, Sodium o-hydroxybenzoate, Sodium m-hydroxybenzoate, Sodium p-hydroxybenzoate, Sodium 2,4-dihydroxy benzoate, Sodium 2,5-dihydroxybenzoate, Sodium 2,6-dihydroxybenzoate, Sodium 3,4-dihydroxybenzoate, Sodium 3,5-dihydroxybenzoate
Progesterone, Testosterone 17- Estradiol, Diazepam and Griseofulvin	Nicotinamide, Isonicotinamide, Nipecotamide,N-methylnicotinamide, N, N-dimethylnicotinamide
Paracetamol	Sodium salicylate, Sodium glycinate, Sodium gentisate, Nicotinamide
Saquinavir	Nicotinamide, Ascorbic acid, Dimethyl urea, Resorcinol
Benzoic acid, Salicylic acid	Urea, Methyl Urea, 1-3-dimethyl urea
Rofecoxib, celecoxib, melocoxib	Nicotinamide, Sodium benzoate, Sodium salicylate
Riboflavin	Nicotinamide
Temazepam	Sodium salicylate, Nicotinamide
Ibuprofen	Sodium salt of Ibuprofen
Nifedipine	Urea, Methyl urea, Ehhyl urea, Butyl urea, icotinamide, N-methyl nicotinamide, N, N-dimethyl nicotinamide
Ketoprofen	Sodium benzoate, Sodium o-hydroxybenzoate, Nicotinamide, Sodium m-hydroxybenzoate, Sodium ascorbate
Carbamazepine	Sodium salicylate, Sodium benzoate

2.11. Solid dispersion

In solid dispersion method one or more active ingredients/API/Drugs (hydrophobic) are incorporated into in an inert carrier or matrix which are hydrophilic in nature are added at solid state and can be prepared in various ratios by various methods such as the melting (fusion), solvent, or melting-solvent method. Solid dispersion refers to a group of solid products consisting of atleast two different components such as hydrophilic matrix in crystalline or amorphous nature and a hydrophobic drug can be molecularly dispersed in amorphous particles or in crystalline particles. Commonly low cost green-eco-friendly solvents used for solid dispersions include water, methanol, ethanol, chloroform, DMSO, acetic acid etc.[60,61] Solid dispersion again classified into six categories; solid solution, eutectic mixtures, glass suspensions, amorphous precipitates, complex and above combinations.

2.12. Microemulsion and self-emulsifying system

A microemulsion is an optically clear pre-concentrate containing a mixture of oil, hydrophilic surfactant and hydrophilic solvent, which dissolves a poorly water-soluble drug. The formulation spontaneously self emulsifies upon contact with water to form a very clear emulsion having small and uniform oil droplets containing the solubilized poorly soluble drug. Microemulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a co-surfactant with a droplet size usually in the range of 20-200 nm. SMEDDS is an anhydrous system of microemulsions. It is composed of oil, surfactant and cosurfactant and has the ability to form o/w microemulsion when dispersed in aqueous phase under gentle agitation. The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and cosolvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS). Self-emulsifying drug delivery systems (SEDDS) and self micro-emulsifying drug delivery systems (SMEDDS) are

Table 7: Solubilization study of various poorly water-soluble drugs by solid dispersion technology [62–63]

Drug	Hydrophillic polymers	Method
Satranidazole	PVP K30 and PEG 4000	Solvent evaporation method.
Simvastatin	SSG	Kneeding method
Ritonavir	PVP	Melt extrusion
Itraconazole	HPMC/PVP	Melt extrusion
Teleprevir	HPMCAS-M	Spray drying
Vemurafenib	HPMCAS	Solvent/anti-solvent precipitation

isotropic solutions of oil and surfactant which form oil-in-water microemulsions on mild agitation in the presence of water. These novel colloidal formulations on oral administration behave like oil-in-water microemulsions. Compared with ready-to-use microemulsions, the SEDDS and SMEDDS have been shown to improve physical stability profile in long-term storage.[62] Various paper had reported the Microemulsion and self-emulsifying study on Drugs like resveratrol,[63] Fexofenadine Hydrochloride.[64] Olmesartan Medoxomil,[65] Loratadine etc.[66]

2.13. Solubilization using surfactants

Surfactants are molecules contain both polar and non-polar regions. Most of surfactants are of hydrocarbon nature containing hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic which accumulate small polar molecules into hydrophobic core of the micelles when they are mixed together and solublization of drug achieve. It is the natural process in pharmaceutical industry and widely used. The surfactants form micelle when the surfactants are added more than their critical micelle concentration (CMC, which is in the range of 0.05–0.10% for most surfactants); formed micelle will entrap the drugs within the micelles. Solubilizing materials used are includes superdisintegrants such as crospovidone, crosscarmellose sodium and sodium starch glycolate used as solubilizing agents in many formulations, which increase the solubility and dissolution rate of poorly water-soluble drugs. Example: Repaglinide solubilized by using surfactants such as SDS,CTAB, Tween-80, SDS+Tween- 80,CTAB+Tween-80[67]

2.14. Micronization

Micronization is another conventional technique for the particle size reduction and improves solubility by increased surface area by decreasing particle size. For micronization of drugs various mills can be used such as jet mill, rotor stator colloid mills and so forth butmicronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.[68] Domperidone was dissolved in appropriate solvent (acetone and methanol 1:1 v/v), and the stabilizing agents such as Soluplus® or PEG6000 was dissolved in water (as nonsolvent). The nonsolvent was poured rapidly into the drug solution under stirring by a homogenizer, and the resultant was freeze dried.[69]

2.15. Nanocrystallization

The drugs particle size reduces to 1-1000 nanometers by two distinct methods used for producing nanocrystals; 'bottom-up' and 'top-down' development. The top- down methods start milling down from macroscopic level, e.g. from a powder that is micron sized. In bottom-up methods nanoscale materials are chemically composed from atomic and molecular components.[70]

Examples: Griseofulvin,[71] Sirolimus, Aprepitant, Fenofibrate, Megestrol acetate, Nabilone, Ketoprofen, Cyclosporine, Spironolacton, Itraconazole. Etc[72]

2.16. Nanosuspension

This technology is applied for drugs which are insoluble in both water and oils. Hence nano sized drug particles produced by miles and are stabilized by surfactants in a system for either oral and topical use or parenteral and pulmonary administration. Nanosuspension particles have particle size distribution near about one micron with an average particle size ranging between 200 and 600 nm.[73]

2.17. Neutralization

Drug is added in alkaline solution like sodium hydroxide, ammonium hydroxide. To dissolve the joined drug solution of β-Cyclodextrin is then added. After few seconds the clear solution obtained under agitation is neutralized using HCl solution until reaching the equivalence point. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. The precipitate is then filtered and dried.[74]

Example: Rebamipide neutralization with microfluidization for rebamipide nanosuspensions formulation to improve solubility.[75]

2.18. Salt formation

This method is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Dissolution rates of salt forms of several weakly acidic compounds under gastrointestinal (GI) pH conditions were much higher than those of their respective free acid forms. Alkali metal salts of acidic drugs like penicillins and strong acid salts of basic drugs like atropine are more water soluble than the parent drug.[76]

Examples: Benexate in Benexate saccharinate monohydrate and Benexate cyclamate salt, Itraconazole in Itraconazole dihydrochloride salt, Diclofenac is available in five novel salts formation with the bases 2-amino-2-methyl-1, 3-propanediol, 2-amino-2-methylpropanol, tert-butylamine, benzylamine and deanol, Aceclofenac in Aceclofenac triethanolamine, Diphenhydramine in Diphenhydramine hydrochloride, Ketoconazole in Ketoconazole Dihydrochloride, Agomelatine in Agomelatine Sulfonate etc.[77–79]

2.19. Solvent deposition

This technique utilizes the solvent like methylene chloride to dissolve the drug and produce a clear solution. Then by stirring the carrier is dispersed in the solution and the solvent is removed by evaporation under temperature and pressure. The resultant mass is then dried, pulverized, and passed through a sieve. The increase in the dissolution rate by the reduced particle size of the drug deposited on the carrier and enhanced wettability of the particles brought about by the carrier.[80]

Table 8: Solubilization study of various poorly water-soluble drugs by Solvent deposition method[81–84]

Drug	Carrier	Solvent
Carvedilol	Lactose and MCC	Methanol
Indomethacin	Kaolin and microcrystalline cellulose	Alcohol solution
Piroxicam	Microcrystalline cellulose	Dichloromethane
Chlordiazepoxide	Starch-lactose granules	Dichloromethane

2.20. Sonocrystallization

Melt sonocrystallization is newer particle engineering technique. In this method by applying ultrasound energy in range of 20 to 100 kHz crystallization process is achieved. Ultra sound energy was tradionally introduced in pharmaceutical industry to increase the solubility of sparingly soluble drug. Ultrasound influences the initial nucleation stage of crystallisation. Cavitation is an important phenomenon of ultrasonication. In sonocrysatllization the energy of ultrasound causes repeated compression and expansion. After several cycles the bubble forms, grows and collapses. Due to bubble collapses, the energy is produced. Applying ultrasound to crystallization results in:

1. Nucleation at the lowest level of super saturation where the tendency of the compound to re-dissolve in the solution is overcome by crystallization.
2. Narrowing of the metastable zone width.
3. Narrow particle size distribution.
4. Low level of cooling necessary to achieve crystallization.
5. Highly repeatable and predictable crystallization.
6. Polymorph control.[85]

Examples: Rosiglitazone,[86] flurbiprofen[87]

2.21. Spherical agglomeration

It is a particle engineering technique, a process of crystallization, agglomeration and Spheronization, which convert fine crystal in spherical shape particle. This technique is important for improving the flow property, wettability and dissolution rate of poorly soluble drug. For production of spherical crystal , parameter like amount and mode of addition of spherical liquid, temperature and agitation speed must be optimize in this technique.[88] Examples: Simvastatin.[89]

2.22. Spray drying

Drug is dissolved in suitable solvent and the adequate amount of carrier material like β-cyclodextrin, Aerosol 200 is dissolved in water. Solutions are then mixed by the process of sonication or other suitable method to produce a clear solution, which is then spray dried. It gives the dried powder which is more soluble as well as more stable.[90]

Nowadays spray drying with solid dispersion technique widely used for drug solublization such as Atorvastatin Calcium, Griseofulvin.[91]

3. Conclusion

By this article we conclude that, Solubility is the most important physical characteristic which responsible API's / drugs ideal formulation characteristics like good oral bioavailability, reduce frequency of dosing and better patient compliance, production at low cost of production. Thus it will improve oral absorption and bioavailability drug. Hence Proper selection of solubility enhancement method will improve the therapeutic efficacy of the drug and ultimately helps to achieve goals of ideal dosage formulation of drugs. In this review we have described different techniques which can be used to enhance the solubility of the drug.

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None.

5. Conflict of Interest

None.

References

1. Liu R, Li X, Lam KS. Combinatorial chemistry in drug discovery. *Curr Opin Chem Biol*. 2017;38:117–43.

2. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. *J Pharmacol Toxicol Methods*. 2000;44(1):235–84.
3. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. *Acta Pharm Sinica B*. 2015;5(5):442–53.
4. Nikghalb A, Singh L, Singh G, Fazaelikahkeshan G. Solid dispersion: methods and polymers to increase the solubility of poorly soluble drugs. *J Appl Pharm Sci*. 2012;2(10):170–5.
5. Tekade AR, Yadav JN. A Review on Solid Dispersion and Carriers Used Therein for Solubility Enhancement of Poorly Water Soluble Drugs. *Adv Pharm Bull*. 2020;10(3):359–69.
6. Patil MS, Godse SG, Saudagar RB. Solubility Enhancement by Various Techniques: An Overview. *World J Pharm Pharm Sci*. 2013;2(6):4558–72.
7. Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. *Eur J Pharm Biopharmaceu*. 2004;58(2):265–78.
8. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. *Int J Pharm*. 2011;420(1):1–1.
9. Limbachiya MI. Solubility enhancement techniques for poorly soluble drugs: A review. . *IJPRD*. 2011;4:71–86.
10. Pharmacopoeia I. Ministry of Health and family welfare, Government of India. vol. 1. Delhi; 2007. p. 477.
11. Kannao SU. Solid dispersion-a technique for solubility enhancement of weakly water soluble drug-a review. *Indo Am J Pharm Res*. 2014;4(6):2839–87.
12. Bharti VP, Attal RV, Munde AV, Birajdar AS, Bais S. Strategies to Enhance Solubility and Dissolution of a poorly water soluble drug. *J Innov Pharm Biol Sci*. 2015;2:482–94.
13. Aulton ME. Pharmaceutics the science of dosage form design. 7th ed. New York: Churchill Livingstone: Churchill Livingstone; 1988. p. 744.
14. Singhal D, Curatolo W. Drug polymorphism and dosage form design: a practical perspective. *Adv Drug Deliv Rev*. 2004;56:335–82.
15. Blagden N, De Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Adv Drug Del Rev*. 2007;59(7):617–47.
16. Deshmukh AS, Tiwari KJ, Mahajan VR. Solubility Enhancement Techniques for Poorly Water-Soluble Drugs. *Int J Pharm Sci Nanotechnol*. 2017;10(3):3701–9.
17. Temperature Effects on Solubility; 2023. Available from: https://chem.libretexts.org/Bookshelves/Physical_and_Theoretical_Chemistry_Textbook_Maps/Supplemental_Modules_(Physical_and_Theoretical_Chemistry)/Equilibria/Solubilty/Temperature_Effects_on_Solubility.
18. 2023. Available from: http://chemistry.elmhurst.Edu/vchembook/174temppres.html.
19. 2023. Available from: https://www.sisd.net/cms/lib/TX01001452/Centricity/Domain/466.
20. Available from: https://chem.libretexts.org/Bookshelves/General_Chemistry/Book.
21. 2023. Available from: https://pharmascope.org/ijrps/article/view/2044/3564#.
22. 2023. Available from: http://www.expresspharmapulse.com/.
23. Deshmukh AS, Mahale VG, Mahajan VR. Liquisolid compact techniques: A Review. *Res J Pharm Dosage Forms Technol*. 2014;6(3):161–7.
24. Ghule PN, Deshmukh AS, Mahajan VR. Floating Drug Delivery System (FDDS): An Overview. *Res J Pharma Dosage Forms Technol*. 2014;6(3):174–82.
25. Sharma N, Bharkatia M. Solubility enhancement techniques: A review. *Int J Pharm Erudition*. 2011;1(3):40–53.
26. Kasselkus A, Schornick E, Zheng M, Bauer F, Lubda D. Improving solubility-a close look at available approaches. *Int J Pharm Investig*. 2012;2(1):1–16.
27. Babu P, Subrahmanyam C, Thimmasetty J, Manavalan R, Valliappan K, Kedarnath SA. Solubility Enhancement of Cox-Ii Inhibitors by Co-solvency Approach. *Dhaka Univ J Pharm Sci*. 2008;7(2):119–45.
28. Nayak AK, Panigrahi PP. Solubility Enhancement of Etoricoxib by Co-solvency. *Int Scho Res Network ISRN Physical Chem*. 2012;820653:1–5.
29. Prasad SG, Gupta RM, Devanna N, Rama DM, Rao G, Harish N. Mixed Co-Solvency Concept: A Promising Tool To Enhance Solubility of Poor Soluble Drug Aceclofenac. *Int Pharm Chem Biol Sci*. 2012;2(3):338–80.
30. Jain S, Maheshwari RK.
31. De Miranda JC, Martins, Veiga F, Ferraz HG. Cyclodextrins and ternary complexes: technology to improve solubility of poorly soluble drugs. *Braz J Pharm Sci*. 2011;47(4):665–81.
32. Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, et al. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. *Asian J Pharm Sci*. 2014;9(6):304–20.
33. Dhillon B, Goyal NK, Malviya R, Sharma PK. Poorly water-soluble drugs: Change in solubility for improved dissolution characteristics a review. *Glob J Pharmacol*. 2014;8(1):26–35.
34. Chaudhary A, Nagaich U, Gulati N, Sharma VK, Khosa RL, Partapur MU, et al. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. *J Adv Pharm Educ Res*. 2012;2(1):32–67.
35. Anjana M, Joseph J, Nair SC. Solubility enhancement methods-A promising technology for poorly water-soluble drugs. *Int J Pharm Sci Rev Res*. 2013;20(2):127–61.
36. Gora S, Mustafa G, Sahni JK, Ali J, Baboota S. Nanosizing of valsartan by high pressure homogenization to produce dissolution enhanced nanosuspension: pharmacokinetics and pharmacodyanamic study. *Drug Del*. 2016;23(3):930–70.
37. Langguth P, Hanafy A, Frenzel D, Grenier P, Nhamias A, Ohlig T, et al. Nanosuspension formulations for low-soluble drugs: pharmacokinetic evaluation using spironolactone as model compound. *Drug Dev Ind Pharmmm*. 2005;31:319–48.
38. Jacobs C, Müller RH. Production and characterization of a budesonide nanosuspension for pulmonary administration. *Pharm Res*. 2002;19(2):189–94.
39. Möschwitzer J, Achleitner G, Pomper H, Müller RH, et al. Development of an intravenously injectable chemically stable aqueous omeprazole formulation using nanosuspension technology. *Eur J Pharm Biopharma*. 2004;58(3):615–24.
40. Patil MS, Godse SZ, Saudagar RB. Solubility enhancement by various techniques: an Overview. *World J Pharm Pharma Sci*. 2013;2:4558–72.
41. Rogers TL, Hu J, Yu Z, Johnston KP, Williams I. A novel particle engineering technology: spray-freezing into liquid. *Int J Pharm*. 2002;242(1-2):93–100.
42. Buxton IR, Peach JM, Wyeth J. Process for production of nanoparticles and microparticles by spray freezing into liquid. 1984;Available from: https://patents.google.com/patent/US6862890B2/en.
43. Purvis T, Mattucci ME, Crisp MT, Johnston KP, Williams RO. Rapidly dissolving repaglinide powders produced by the ultra-rapid freezing process. *AAPS Pharm Sci Tech*. 2007;8(3):52–60.
44. Elgindy N, Elkhodairy K, Molokhia A, Elzoghby A. Lyophilization monophase solution technique for improvement of the physicochemical properties of an anticancer drug, flutamide. *Eur J Pharma Biopharma*. 2010;74:397–405.
45. Sisinthy SP, Selladurai S. Cinnarizine liquid solid compacts: preparation evaluation. *Int J Appl Pharm*. 2019;11:150–7.
46. Chandel P, Kapoor RK. Liquisolid Technique: An Approach for Enhancement of Solubility. *J Drug Del Thera*. 2013;3(4):131–68.
47. Harmalkar D, Godinho S, Bhide PJ, Kumar L, Shirodkar RK. New Formulation Technique for Solubility and Dissolution Rate Enhancement of Poorly Soluble Drugs. *Pharma Chem J*. 2019;53(8):720–9.
48. Azharshekoufeh L, Shokri J, Jalali MB, Javadzadeh Y. Liquigroud technique: a new concept for enhancing dissolution rate of

glibenclamide by combination of liquisolid and co-grinding technologies. *BioImpacts*. 2017;7(1):1–5.
49. Patil MS, Godse SZ, Saudagar RB. Solubility enhancement by various techniques: An overview. *World J Pharm Pharma Sci*. 2013;2(6):4558–72.
50. Pobudkowska A, Domańska U. Study of pH-dependent drugs solubility in water. *Chem Ind Chem Eng Quarter*. 2014;20(1):115–41.
51. Wadher SJ, Gattani SG, Jadhav YA, Kalyankar TM. Recent Approaches in Solubility Enhancement of Poorly Water-Soluble Drug Simvastatin: A Review. *World J Pharm Pharm Sci*. 2014;3(4):366–84.
52. Dai WG, Dong LC, Shi X, Nguyen J, Evans J, Xu Y, et al. Evaluation of drug precipitation of solubility-enhancing liquid formulations using milligram quantities of a new molecular entity (NME). *J Pharm Sci*. 2007;96(11):2957–69.
53. Varshosaz J, Ahmadipour S, Tabbakhian M, Ahmadipour S. Nanocrystalization of pioglitazone by precipitation method. *Drug Res*. 2018;68(10):576–83.
54. Viçosa A, Letourneau JJ, Espitalier F, Re MI. An innovative antisolvent precipitation process as a promising technique to prepare ultrafine rifampicin particles. *J Crystal Growth*. 2012;342(1):80–7.
55. Shelake SS, Patil SV, Patil SS. Formulation and evaluation of fenofibrate-loaded nanoparticles by precipitation method. *Indian J Pharm Sci*. 2018;80(3):420–7.
56. Waghmare P, Kadu P. Solubility enhancement of curcumin using HPMC K 15M by solvent change precipitation method. *Int J Adv Res Pharma Bio Sci*. 2014;4(2):1–7.
57. Ojha N, Prabhakar B. Advances in Solubility Enhancement Techniques. *Int J Pharm Sciences Rev Res*. 2013;21(2):351–8.
58. Kapadiya N, Singhvi I, Mehta K, Karwani G, Hydrotropy DJ. A Promising Tool for Solubility Enhancement: A Review. *Int J Drug Dev Res*. 2011;3(2):26–33.
59. Jain P, Goel A, Sharma S, Parmar M. Solubility enhancement techniques with special emphasis on hydrotrophy. *Int J Pharma Professional's Res*. 2010;1(1):34–45.
60. Mankar SD, Rach PR. solubility enhancement of poor water soluble drugs by solid dispersion: A review. *J Drug Deliv Therapeutics*. 2018;8(5):44–53.
61. Sriamornsak P, Limmatvapirat S, Piriyaprasarth S, Mansukmanee P, Huang Z. A New Self-Emulsifying Formulation of Mefenamic Acid with Enhanced Drug Dissolution. *Asian J Pharma Sci*. 2015;10(2):121–48.
62. Sriamornsak P, Limmatvapirat S, Piriyaprasarth S, Mansukmanee P, Huang Z. A New Self-Emulsifying Formulation of Mefenamic Acid with Enhanced Drug Dissolution. *Asian J Pharm Sci*. 2015;10(2):121–48.
63. Mandawgade SD, Sharma S, Pathak S, Patravale VB. Development of SMEDDS using natural lipophile: application to β-artemether delivery. *Int J Pharm*. 2008;362(1-2):179–83.
64. Aloisio C, Bueno MS, Ponte MP, Paredes A, Palma SD, Longhi M, et al. Development of solid self-emulsifying drug delivery systems (SEDDS) to improve the solubility of resveratrol. *Therapeutic Deliv*. 2019;10(10):626–67.
65. Patel AM, Patel JB, Patel TB, Suhagia BN, Patel TR. Preparation and evaluation of self microemulsifying drug delivery system for fexofenadine hydrochloride. *J Drug Deliv Therap*. 2013;3(4):26–32.
66. Prajapati ST, Joshi HA, Patel CN. Preparation and characterization of self-microemulsifying drug delivery system of Olmesartan medoxomil for bioavailability improvement. *J Pharma*. 2013;doi:10.1155/2013/728425.
67. Vlaia L, Coneac G, Olariu I, Am M, Anghel DF, Maxim ME, et al. Loratadine-loaded microemulsions for topical application. Formulation, physicochemical characterization and in vitro drug release evaluation. *Farmacia*. 2017;65(6):851–61.
68. Vandana KR, Raju YP, Chowdary VH, Sushma M, Kumar NV. An overview on in situ micronization technique- An emerging novel concept in advanced drug delivery. *Saudi Pharm J*. 2014;22(4):283–9.
69. Blagden N, De Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Adv Drug Deliv Rev*. 2007;59(7):617–47.
70. Hashimoto N, Yuminoki K, Takeuchi H, Okada C. Development of nanocrystal formulation of mebendazole with improved dissolution and pharmacokinetic behaviors. *Asian J Pharm Sci*. 2016;11(1):122–5.
71. Lua Y, Wu LY. Injected nanocrystals for targeted drug delivery. *Acta Pharma*. 2016;6(2):106–19.
72. Telsang S. Enhancement of solubility and dissolution properties of griseofulvin by nanocrystallization technique (Doctoral dissertation, RGUHS). Available from: https://www.proquest.com/openview/891c99413c9cca94427b256028a78524/1?pq-origsite=gscholar&cbl=2026366&diss=y.
73. Attari Z, Bhandari A, Jagadish PC, Lewis S. Enhanced ex vivo intestinal absorption of Olmesartan medoxomil nanosuspension: Preparation by combinative technology. *Saudi Pharm J*. 2016;24(1):57–63.
74. Patel M, Shah A, Patel NM, Patel MR, Patel KR. Nanosuspension: A novel approach for drug delivery system. *Jpsbr*. 2011;1(1):1–10.
75. Thorat YS, Gonjari ID, Hosmani AH. Solubility enhancement techniques: a review on conventional and novel approaches. *Int J Pharma Sci Res*. 2011;2(10):2501.
76. Shi Y, Zou M, An Y, Gao JZ, Cheng P. A potent preparation method combining neutralization with microfluidization for rebamipide nanosuspensions and its in vivo evaluation. *Drug Dev Ind Pharma*. 2013;39:996–1004.
77. Kumar K, Bhandari A. Solubility and dissolution enhancement: Technologies and research emerged. *J Biol Sci Opin*. 2013;1(2):105–21.
78. Putra D, Umeda O, Fujita D, Haraguchi E, Uchida T, Yonemochi T, et al. Solubility improvement of benexate through salt formation using artificial sweetener. *Pharmaceutics*. 2018;10(2):64. doi:10.3390/pharmaceutics10020064.
79. Available from: https://shodhganga.inflibnet.ac.in/bitstream/10603/15605/9/09_chapter%203.pdf.
80. Thorat YS, Gonjari ID, Hosmani AH. Solubility enhancement techniques: a review on conventional and novel approaches. *Int J Pharma Sci Res*. 2011;2(10):2501–13.
81. Kumar K, Bhandari A. Solubility and dissolution enhancement: Technologies and research emerged. *J Biol Sci Opin*. 2013;1(2):105–16.
82. Arun RR, Harindran J. Enhancement of bioavailability of carvedilol using solvent deposition techniques. *Int J Pharma Sci Res*. 2017;8(8):3391–401.
83. Alsaidan SM, Alsughayer AA, Eshra AG. Improved dissolution rate of indomethacin by adsorbents. *Drug Dev Ind Pharm*. 1998;24(4):389–94.
84. Barzegar-Jalali M, Maleki N, Garjani A, Khandar AA, Hajihosseinloo M, Jabbari R, et al. Dastmalchi S. Enhancement of dissolution rate and anti-infammatory effects of piroxicam using solvent deposition technique. *Drug Dev Ind Pharm*. 2002;28(6):681–6.
85. Kakkar AP, Gulati R, Bansal A. Solvent deposition of chlordiazepoxide on starch-lactose granules. *Indian J Pharm Sci*. 1993;55(6):212–29.
86. Shinde PR, Parve BS, Rawat S, Rathod SS. Different Approaches towards the Solubility Enhancement of Drug: A Review. *World J Pharma Pharma Sci*. 2014;3(4):625–71.
87. El-Kamel AH. Improvement of physicochemical and biopharmaceutical properties of flurbiprofen using melt sono crystallization technique. . *Drug Dev Res*. 2008;69(1):34–41.
88. Chaudhari PD, Uttekar PS. Melt-sono crystallization: a novel particle engineering technique for solubility enhancement. *Int J Pharm Tech Res*. 2009;1(1):111–31.
89. Deshkar SS, Borde GR, Kale RN, Waghmare BA, Thomas AB. Formulation of cilostazol spherical agglomerates by crystallo-co-agglomeration technique and optimization using design of experimentation. *Int J Pharma Invest*. 2017;7(4):164–73.
90. Fouad EA, El-Badry M, Mahrous GM, Alanazi FK, Neau SH, Alsarra IA, et al. The use of spray-drying to enhance celecoxib solubility. *Drug Dev Ind Pharma*. 2011;37:1463–72.

91. Kwon J, Giri BR, Song ES, Bae J, Lee J, Kim DW, et al. Spray-dried amorphous solid dispersions of atorvastatin calcium for improved supersaturation and oral bioavailability. *Pharmaceutics*. 2019;11(9):461. doi:10.3390/pharmaceutics11090461.

Author biography

Krishna R. Gupta, Professor and HOD

Monali R Dakhole, Assistant Professor

Ketki S Jinnawar, Research Scholar

Milind J Umekar, Professor and Principal

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