REVIEW ARTICLE

Techniques to Enhance Solubility of Hydrophobic Drugs: An Overview

D. Christopher Vimalson[1]*, S. Parimalakrishnan[2], N. S. Jeganathan[1], S. Anbazhagan[1]

**Research Scholar, Department of Pharmacy, Annamalai University, Chidambaram, Tamil Nadu, India,*
[1]Department of Pharmaceutics, Surya School of Pharmacy, Vikravandi, Viluppuram, Tamil Nadu, India,
[2]Department of Pharmacy, Annamalai University, Chidambaram, Cuddalore, Tamil Nadu, India

Abstract

The solubility enhancement process of hydrophobic drugs plays a key role in the formulation development to achieve the bioavailability and therapeutic action of the drug at the target site. About 40% of the new chemical entities identified by pharmaceutical industry screening programs face numerous problems in the formulation and development stage because of poor water solubility and low bioavailability. Drug solubility and bioavailability enhancement are the important challenges in the field of formulation of pharmaceuticals. The Biopharmaceutics Classification System reflects that Class II and IV drugs have low water solubility, poor dissolution, and low bioavailability. This review article explores the various techniques to enhance solubility of hydrophobic drugs such as complexation of drugs, use of cosolvents, emulsion formation, microemulsions, micelles, polymeric micelles, pharmaceutical salts, pro-drugs, particle size reduction technologies, solid state alternation, soft gel technology, solid dispersion techniques, drug nanocrystals, nanomorph technology, and crystal engineering techniques.

Key words: Hydophobic-drugs, solubilization Techniques.

INTRODUCTION

Of the numerous challenges in pharmaceutical formulation, the most important is the drug solubility enhancement, bioavailability at the target site of therapeutic action of hydrophobic drugs. Poor water solubility tops the list of critical compound properties among the five key physicochemical parameters in early compound screening, *viz.,* dissociation constant, solubility, permeability, stability, and lipophilicity.[1] The progress in the treatment of diseases has been evident with the upsurge in development of new drugs. Approximately more than 40% new chemical entities (NCEs) developed in the pharmaceutical industry are practically insoluble in water.[2]

The present review gives an overall view about the development and the different approaches in enhancing the solubility and dissolution characteristics of hydrophobic drugs.

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

The BCS is the scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. It is a drug development tool that allows estimation of the contributions of three major factors, dissolution, solubility, and intestinal permeability that affect oral absorption of drugs. BCS Class II and IV drugs, which have low solubility, provide a number of challenges for formulation scientists working on the oral delivery of drugs.[3]

Solubility in quantitative terms is defined as the concentration of the solute in a saturated solution at a certain temperature.[4] The solubility of a solute in a solvent depends on the solvent used as well as on temperature and pressure.[5] Solubility varies over an extended range from infinitely soluble such as ethanol in water to poorly soluble such as silver chloride in water. The poorly or very poorly soluble compounds are often termed as insoluble.[6]

Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation

Address for correspondence:
D. Christopher Vimalson, Department of Pharmaceutics Surya School of Pharmacy, Vikravandi, Viluppuram, Tamil Nadu, India. Phone: +91-9843871165.
E-mail: crispharmacy@gmail.com

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for showing a pharmacological response. Hydrophobic drugs often require high doses to reach therapeutic plasma concentrations after oral administration. Most of the drugs are weakly acidic and weakly basic with poor aqueous solubility.[7] Drug release is an important and rate limiting step for oral bioavailability, particularly for drugs with low solubility and high permeability, i.e. BCS Class II drugs. By improving the drug release profile of BCS Class II drugs, it is possible to enhance their bioavailability and reduce side effects.[8]

The United States Pharmacopoeia and British Pharmacopoeia classify the solubility regardless of the solvent used, only in terms of quantification and have defined the criteria as given in Table 1.[9]

The BCS is a scientific framework for classifying a drug substance based on solubility, permeability, and dissolution criteria.[10,11]

According to the BCS, drug substances are classified as follows:

- Class I: High permeability and solubility
- Class II: High permeability and low solubility
- Class III: Low permeability and high solubility
- Class IV: Low permeability and low solubility.

Importance of solubility enhancement

1. Solubility is one of the important parameters to achieve preferred concentration of drug in systemic circulation for achieving required pharmacological response
2. Hydrophobic drugs frequently require high doses and need high dosage regimens to influence therapeutic plasma concentrations after administration
3. Low aqueous solubility is the main problem encountered with preparation and development of NCEs as well as for generic drugs
4. For orally administered drugs solubility is the one of the important rate limiting parameters to reach their desired concentration in complete circulation for pharmacological response
5. Water is the solvent of excellent for liquid pharmaceutical formulations
6. Most of the drugs like weakly acidic or weakly basic having poor aqueous solubility
7. Poorly water-soluble drugs having slow drug absorption leads to insufficient and gastrointestinal mucosal toxicity and variable bioavailability.[12]

Table 1: USP solubility description

Descriptive term	Parts of solvent required for 1 part of solute
Very soluble	<1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble or insoluble	10,000 and over

METHODS FOR SOLUBILITY ENHANCEMENT[7,13,14]

I. Physical modifications
II. Chemical modifications
III. Miscellaneous methods.

Physical modifications

Particle size reduction

Particle size reduction can be achieved by micronization and nanosuspension. Each technique utilizes different equipment for reduction of the particle size.

Micronization

The solubility of the drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Conventional methods of particle size reduction, such as comminution and spray drying, rely on mechanical stress to disaggregate the active compound. Micronization of drugs is done by milling techniques using the jet mill, rotor-stator colloid mills, etc.

A. Advantages
   - The micronization is used to increased surface area for dissolution
   - Micronization increases the dissolution rate of drugs through increased surface area.

B. Disadvantages
   - It does not increase equilibrium solubility
   - Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.[14]

Nanosuspension

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug which are stabilized by surfactants. Techniques for the production of nanosuspensions include homogenization and wet milling. Active drug in the presence of surfactant is defragmented by milling. Other techniques involve the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation produces drug precipitation in the presence of surfactants. The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel, and buparvaquone. All the formulations are in the

research stage. Drying of nanosuspensions can be done by lyophilization or spray drying.

A. Advantages: Increased dissolution rate is due to larger surface area exposed while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor
B. Disadvantages: The major concern related to particle size reduction is the eventual conversion of the high-energy polymorph to a low-energy crystalline form, which may not be therapeutically active one.[15]

Various particle technologies, from conventional size reduction methods to recent novel methods that can be used for formulating drugs with poor aqueous solubility as mentioned in Table 2.[16]

Modification of the crystal habit

Crystal engineering

The approach of crystal engineering offers a potentially fruitful method for improvement in solubility, dissolution rate, and finally bioavailability of hydrophobic drugs by polymorphs, Hydrates/solvates method. These techniques are developed for controlled crystallization of drugs to produce high purity powders with well-defined properties as particle size, shape, etc., leading to stable and robust pharmaceutical products.

Polymorphs

Most of the drugs reveal a phenomenon known as polymorphism, defined as the ability of drug moiety to exist in more than one crystalline form. Polymorphs are different crystalline forms of the drug that may have different physicochemical properties and biological activities such as shelf life, melting point, vapor pressure, solubility, morphology, density, bioavailability, and efficacy.

Metastable forms are associated with higher energy and increased surface area lead to increase solubility, bioavailability, and efficacy. Development of thermodynamically stable polymorph of the drug is assured the reproducible bioavailability of the product over its shelf life under real storage conditions. For example, stable α-polymorph of chloramphenicol palmitate produced low serum levels whereas metastable β-polymorph yielded much higher serum levels when the same dose was administered.

Hydrates/solvates

The stoichiometric type of molecular adducts, in which solvent molecules are incorporated in the crystal lattice of solid is called as solvates. The solvates can exist in different crystalline forms and called as pseudopolymorphs and this phenomenon is called as pseudopolymorphism. When solvent in association with the drug is water, the solvate is known as hydrate and thus have less energy for crystal breakup when compared to anhydrous forms. For example, the antidiabetic drug glibenclamide has been isolated as pentane and toluene solvates which exhibited higher solubility and dissolution rate than the non-solvated polymorphs.[17]

Drug dispersion in carriers

Eutectic mixtures

Eutectic mixture was first described as solid dispersions, in 1961, by Sekiguchi and Obi.[18] Eutectic mixtures are formed when the drug and polymer are miscible in their molten state, but on cooling, they crystallize as two distinct components with negligible miscibility. Both drug and carrier exist in the finely divided state, which results in the higher surface area and enhanced the dissolution rate of the drug, for example, sulfathiazole-urea mixture.[18]

Solid dispersion

Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or crystalline

Table 2: Particle technologies to improve the solubility of some drugs

Particle technology	Method	Example drugs
Mechanical micronization	Jet milling	Cilostazol, ibuprofen
	Ball milling	Danazol, carbamazepine, dipyridamole, indomethacin
	HPH	Prednisolone, carbamazepine, nifedipine
Particle size reduction by novel particle engineering	Cryogenic spraying process	Danazol, carbamazepine, glibenclamide, febantel, itraconazole
	Spray drying, *in situ* salt formation, solidification with polymers	Nimodipine, flurbiprofen, dexibuprofen, docetaxel, curcumin, meloxicam, fenofibrate, ibuprofen
Complexation with cyclodextrins	Freeze drying, vacuum evaporation, kneading	Celecoxib, clotrimazole, bifonazole, praziquantel
Polymeric micelles	Dialysis, freeze drying	Paclitaxel, etoposide, docetaxel, amphotericin-B
Solid lipid nanoparticles	HPH, solid emulsification-evaporation/ diffusion	All trans retinoic acid, tretinoin

HPH: High pressure homogenization

particles. Therefore, based on their molecular rearrangement, six different types of solid dispersions can be distinguished as a result fine particles formed have shown promising bioavailability of poorly water-soluble drugs [Table 3].[19,20]

Manufacturing techniques of solid dispersion

Solvent evaporation method

In solvent evaporation method, both the drug and the carrier dissolved in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. Tachibechi and Nakumara[21] first applied this technique to dissolve both the drug (β-carotene and the carrier polyvinylpyrrolidone [PVP]) in a common solvent such as ethanol, chloroform, or a mixture of ethanol and dichloromethane.

A. Advantages: The thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents
B. Disadvantages: They are expensive, ecological, and difficult to find common and removable solvents and difficulty of reproducing crystal form.[21]

Hot-melt extrusion method

This is a single step process was used since 1971 in the pharmaceutical industry, reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in the crystalline excipient.[22]

A. Advantages of solid dispersion
   - Preparation of solid dispersions results in particles with reduced particle size, and thus, the surface area is increased leads to increase dissolution rate results improved bioavailability
   - Wettability is improved during solid dispersion production leads to increase solubility. Here, the carriers play the major role to improve the wettability of the particles
   - Particles in solid dispersions have been found to have a higher degree of porosity as a result; solid dispersion particles accelerate the drug release profile which depends on the carrier properties
   - In solid dispersions, drugs are presented as supersaturated solutions which are considered to be metastable polymorphic form.
B. Disadvantages of solid dispersion: The major disadvantages of solid dispersion are related to their instability due to moisture and temperature. Several systems have shown changes in crystalline and a decrease in dissolution rate with aging. The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir, Abbott) from the market. Some solid dispersion may not lend them to easy handling because of tackiness.[23]

Solid solutions

This technique is applicable for either amorphous or crystalline type molecule. In amorphous solid solutions

Table 3: Solid dispersion types

Type	Matrix	Drug	Remarks	Number of phases
Eutectics	C	C	The first type of solid dispersion prepared	2
Amorphous precipitation in crystalline carrier	C	A	Rarely encountered	2
Solid solution				
Continues solid solution	C	M	Miscible at all composition, never prepared	1
Discontinuous solution	C	M	Partially miscible, two phases even though drug is molecularly dispersed	
Substitutional solid solution	C	M	Molecular diameter of drug differs less than 15% from the matrix diameter. In that case, the drug and matrix are substitutional	1or 2
Interstitial solid solution	C	M	Drug molecular diameter less than 59% of matrix diameter. Usually limited miscibility, discontinuous. Example: Drug in helical interstitial spaces of PEG	2
Glass suspension	A	C	The particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2
Glass suspension	A	A	The particle size of dispersed phase dependent on cooling/evaporation rate. Many solid dispersions are of this type	2
Glass solution	A	M	Requires miscibility or solid solubility, complex formation or upon fast cooling, many complexes especially with PVP	1

PVP: Polyvinylpyrrolidone, PEG: Polyethylene glycol

as the drug is molecularly dispersed in the carrier matrix, its effective surface area is significantly higher, and hence, the dissolution rate is increased. The physical stability of amorphous drugs increased due to inhibiting drug crystallization by minimizing molecular mobility. Crystalline solid solution may result when a crystalline drug is trapped within a crystalline polymeric carrier. According to the extent of miscibility of the two components, solid solutions are the continuous or discontinuous type. In continuous solid solutions, the two components are miscible in the solid state in all proportions. The components that are immiscible at intermediate composition, but miscible at extremes of the composition are referred to as discontinuous solid solutions. Examples include solid solutions of digitoxin, methyltestosterone, prednisolone acetate, and hydrocortisone acetate in the matrix of polyethylene glycol (PEG) 6000. They all exhibit faster rate of dissolution.

In 1965, Goldberg *et al*. discussed the theoretical and practical advantageous of solid solution over eutectic mixtures. The reason for the improvement in dissolution rate is that drug has no crystal structure in solid solution. Therefore, the energy normally required to break up the crystalline structure of the drug before it can dissolve is not a limitation to the release of the drug from a solid solution.[24]

Complexation

Complexation is the association between two or more molecules to form a non-bonded entity with a well-defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding, and hydrophobic interactions. There are many types of complexing agents, and a partial list can be given in Table 4.

Staching complexation

Staching complexes are formed by the overlap of the planar regions of aromatic molecules. Non-polar moieties tend to be squeezed out of the water by the strong hydrogen bonding interactions of water. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favored by large planar non-polar regions in the molecule. Stached complexes can be homogeneous or mixed. The former is known as self-association and latter as complexation. Examples of compounds to form staching complexes are nicotinamide, anthracene, pyrene, methylene blue, benzoic acid, salicylic acid, ferulic acid, gentisic acid, purine, theobromine, caffeine, and naphthalene, etc.

Table 4: List of complexing agents

Types	Examples
Inorganic	IB
Coordination	Hexamine cobalt (III) chloride
Chelates	EDTA, EGTA
Metal-olefin	Ferrocene
Inclusion	Cyclodextrins, choleic acid
Molecular complexes	Polymers

EGTA: Ethylene glycol tetraacetic acid,
EDTA: Ethylenediaminetetraacetic acid

Inclusion complexation

Inclusion complexes are formed by the insertion of the non-polar molecule or the non-polar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The cavity of the host must be large enough to accommodate the guest and small enough to eliminate water so that the total contact between the water and the non-polar regions of the host and the guest is reduced. The most commonly used host molecules are cyclodextrins. The complexation with cyclodextrins is used for enhancement of solubility. Cyclodextrin inclusion is a molecular phenomenon in which usually only one guest molecule interacts with the cavity of a cyclodextrin molecule to become entrapped and form a stable association. The internal surface of the cavity is hydrophobic and external is hydrophilic; this is due to the arrangement of hydroxyl group within the molecule. Molecules or functional groups of molecules, those are less hydrophilic than water, can be included in the cyclodextrin cavity in the presence of water. It was found that cyclodextrins increased the paclitaxel solubility by 950-fold. Complex formation of rofecoxib, celecoxib, clofibrate, melarsoprol, taxol, cyclosporine, etc., with cyclodextrins improves the solubility of particular drugs.[25]

Manufacturing techniques for complexation/inclusion complexation

Kneading method

An active drug with the suitable polymer in different ratios is added to the mortar and triturated with small quantity of ethanol to prepare slurry. Slowly, the drug is incorporated into the slurry with constant trituration. The prepared slurry is then air dried at 25°C for 24 h. The resultant product is pulverized and passed through sieve No. 80 and stored in desiccator over fused calcium chloride.

Co-precipitate method

Different molar ratios of active drug are dissolved in ethanol at room temperature, and suitable polymers are mixed, respectively. The mixture is stirred at room temperature for 1 h, and the solvent is evaporated. The resultant mass is pulverized and passed through sieve No. 80 and stored in desiccators.

Spray drying

The solvent evaporation of drug and polymer solution in the different ratio is carried out using spray dryer. The solutions are prepared by dissolving the drug in methanol and polymer in distilled water and mix both solutions, which produces a clear solution. The solvent evaporated using evaporator. The spray dried mixture of drug with polymer is obtained in 20-30 min.

Lyophilization/freeze-drying technique

This is a suitable method to get a porous, amorphous powder with a high degree of interaction between drug and CD. The solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and CD at reduced pressure. Thermolabile substances can be successfully made into complex form by this method. It is considered as an alternative to solvent evaporation method, which involves molecular mixing of drug and carrier in a common solvent.

Microwave irradiation method

This technique involves irradiation reaction between drug and complexing agent in a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a round bottom flask. The mixture is reacted for 1-2 min at 60°C in the oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate so obtained is separated using Whatman filter paper, and dried in vacuum oven at 40°C for 48 h.[26]

Solubilization by surfactants

Surface active agents enhance the solubility of poorly water-soluble drugs due to the formation of micelles. This phenomenon is known as micellar solubilization. For example, the solubility of procaine is enhanced by 25% in aqueous buffer, owing to the formation of surfactant micelles.[27]

Microemulsions

Microemulsions act as potential drug delivery vehicles largely due to stability and their abilities to incorporate a wide range of drugs of varying solubility. O/W microemulsion is expected to increase the solubility by dissolving hydrophobic drugs into its dispersed phase and to enhance the oral bioavailability the drug by increasing the rate of absorption and wettability.[28]

Self-micro emulsifying drug delivery systems (SMEDDS)

SMEDDS are isotropic mixtures of drug, lipids, and surfactants, usually with one or more hydrophilic cosolvents or coemulsifier with droplet size ranging from 10 to 100 nm.

A. Advantages
   - High drug solubilization capacity with stability
   - Protect the drug from enzymatic hydrolysis
   - Improvement in oral bioavailability and drug loading capacity
   - Reduce the intrasubject and intersubject variability and food effects which lead to specific absorption window.

B. Disadvantages
   - Lack of *in vitro* model for assessment of the formulations
   - Chemical instabilities of drugs with high surfactant
   - Moreover, volatile cosolvents are known to migrate into the shells of soft or hard gelatin capsule, resulting in the precipitation of the lipophilic drugs
   - These formulations should digest before releasing the drug.[29]

Chemical modifications

Salt formation

It is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs, which are converted into respective salt forms, e.g., aspirin, theophylline, and barbiturates. Alkali metal salts of acidic drugs such as penicillins and strong acid salts of basic drugs such as atropine are water soluble than parent drugs.

Co-crystallization

It is a molecular complexation process to form co-crystals. A co-crystal may be defined as crystalline material that consists of two or more molecular species held together by non-covalent forces. Only three of the co-crystallizing agents are classified and generally recognized as safe. It includes saccharin, nicotinamide, and acetic acid limiting the pharmaceutical application. It is an alternative to salt formation, particularly for neutral compounds.

pH adjustment

By this method, the hydrophobic molecule can be protonated (base) or deprotonated (acid) and be dissolved in water by applying a pH change. Ionizable compounds that are stable and soluble after pH adjustment are best suited.

Co-solvency

Cosolvents are mixtures of water and/or more water miscible solvent used to create a solution with enhanced solubility for poorly soluble compounds, e.g., of solvents used in the co-solvent mixture are PEG 300, propylene glycol, or ethanol. Dimethyl sulfoxide and dimethylacetamide have been widely used as cosolvent because of their large solubilization capacity of poorly soluble drugs and their relatively low toxicity.[30]

Hydrotrophy

Hydrotrophy was first coined by Neuberg[31] to describe the increase in the aqueous solubility of BCS Class 2 molecules by the addition of high concentrations of alkali metal salts of various organic acids**.** Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been observed to enhance the aqueous solubilities.

A. Advantages
   - Hydrotropy is suggested to be better than other solubilization methods such as miscibility, micellar

solubilization, cosolvency, and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification
- It only requires mixing the drug with the hydrotrope in water
- It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.[31]

Nanotechnology in pharmaceuticals

Nanotechnology or nanonization

Various nanonization techniques have been emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water and decrease systemic side-effects. Nanonization broadly refers to the study and use of materials and structures at the nanoscale level of approximately 100 nm or less. It is alternate to micronization because micronized product has the tendency to agglomerate, which leads to decrease effective surface area for dissolution. There are different techniques used for nanonization of drug including wet milling, homogenization, emulsification-solvent evaporation technique, pear milling, and spray drying.[32,33]

Drug nanocrystal

Drug nanocrystals are nanoscopic crystals of parent compounds with the dimension of <1 mm. They are composed of 100% drug without carriers and typically stabilized with surfactants or polymeric steric stabilizers. A dispersion of drug nanocrystals in an outer liquid medium and stabilized by surface active agents is so-called nanosuspensions. The dispersion medium can be water, aqueous, or non-aqueous media, e.g. liquid PEG and oils. The nanosuspensions can be used to formulate compounds that are insoluble in both water and oil and to reformulate existing drugs to remove toxicologically less favorable excipients [Table 5].[34]

Nanomorphs

Nanomorph technology converts drug substances with low water solubility from a coarse crystalline state into amorphous nanoparticles to enhance their dissolution. A suspension of drug substance in solvent is fed into a chamber, where it is rapidly mixed with another solvent. Immediately, the drug substance suspension is converted into a true molecular solution. The admixture of an aqueous solution of a polymer induces precipitation of the drug substance. The polymer keeps the drug substance particles in their nanoparticulate state and prevents them from aggregation or growth. Water-redispersible dry powders can be obtained from the nanosized dispersion rather than by conventional methods (e.g., spray drying) [Table 6].[35]

Miscellaneous methods

Super critical fluid technology

Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used either as a solvent for drug and matrix or as an antisolvent. When supercritical CO_2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. However, the application of this technique is very limited because the solubility in CO_2 of most pharmaceutical compounds is very low (<0.01 wt.%) and decreases with increasing polarity. Therefore, scaling up this process to kilogram-scale will be impractical.

Direct capsule filling

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystalline nature of the drug. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique.[37]

Table 5: Overview of drug nanocrystals for oral administration currently marketed and in various stages of research

Drug	Trade name/company	Indication	Applied technology	Dosage form	Status
Sirolimus	Rapamune/Wyeth	Immunosuppressant	Top-down, media mailing	Tablet	Marketed
Fenofibrate	Tricor/Abbott	Hypercholesterolemia	Top-down, media mailing	Tablet	Marketed
Griseofulvin	Gris-PEG/Novartis	Antifungal	Bottom up, co-precipitation	Tablet	Marketed
Nabilone	Cesamet/Lilly	Antiemetic	Bottom up, co-precipitation	Capsule	Marketed
Danazol		Estrogen antagonist	Top-down, media mailing	Nanosuspension	*In vivo* (dog)
Naproxen	-	Anti-inflammatory	Top-down, media mailing	Nanosuspension	*In vivo* (rat)
Cilostazol	-	Antiplatelet agent	Top-down, media mailing	Nanosuspension	*In vivo* (dog)

Table 6: Comparison of the advantages and disadvantages of different nanoformulations[36]

Nanoformulations	Advantages	Disadvantages
Nanocrystals	Established manufacturing techniques Good reproducibility with large scale production Good compatibility with drugs having different solubility profiles Fast dissolution rates Excellent for oral formulations	High-energy input Require stabilizers Not suitable for cytotoxic drugs with small therapeutic indices Lack of controlled release Not ideal for intravenous administration
Nanoemulsions	High drug loading content Suitable for various administration Approved pharmaceutical ingredients Low cost production	Potential flocculation and coalescence Lack of controlled release Poor blood stability
Polymeric micelles	Excellent blood stability Passive and active targeting to tumors Controlled release functions Multifunctional design Suitable for intravenous administration	Limited number polymers for clinical use Concern over nanotoxicity Concern over storage stability

Electrospinning method

In this procedure, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces prevail over the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are produced. This technique has tremendous potential for the preparation of nanofibers and controlling the release of biomedicine, as it is simplest and the cheapest technique can be utilized for the preparation of solid dispersions in future.

Dropping method solution

In 1997, Ulrich *et al*. developed this technique to facilitate the crystallization of different chemicals, producing round particles from melted solid dispersions gives a higher dissolution rate. It does not use organic solvents, and therefore, has none of the problems associated with solvent evaporation.[38] The drug solution has been dropped on tablet using microsyringe. Blank tablets were prepared by direct compression method using dicalcium phosphate dihydrate as diluents. Different types and concentration of super disintegrants were used. Drug solution dropping technique can be regarded as a novel technique to improve dissolution properties of potent drugs belonging to BCS Class II.[39]

CONCLUSION

Therapeutically effective concentration of a drug at the target site of action depends on the bioavailability, which ultimately depends on the solubility of drug molecules. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response. Solubility is also the basic requirement for the formulation and development of different dosage form of drugs. We conclude that the various techniques described above can be used alone or in combination to enhance the solubility of the drug. Numerous technological advancements have been introduced for solubility and dissolution enhancement of poorly water-soluble drugs. Selection of suitable method is the key process for the improvement of solubility of hydrophobic drugs. The selection of the techniques should be based on the nature of the drug, its compatibility, its interaction with other chemicals used, stability when the process is executed and yield of the final product.

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