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STRATEGIES FOR SOLUBILITY ENHANCEMENT

Amrutha O.* and Shijith K. V.

College of Pharmaceutical Sciences, Govt. Medical College, Pariyaram, Kannur, Kerala University of Health Sciences, Kerala-670503.

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***Corresponding Author**
Amrutha O.
College of Pharmaceutical Sciences, Govt. Medical College, Pariyaram, Kannur, Kerala, University of Health Sciences, Kerala-670503.

ABSTRACT

The solubility of drug in the biological milieus and its permeability across biological barriers are the two main central attributes that contributes to therapeutic effectiveness of any drugs. The low solubility is related to a lower drug dissolution rate, which in turn directs poor bioavailability. Approximately 40% of the marketed drugs have low solubility and almost 80-90% drug candidates in the R& D product development pipeline fails due to the solubility concerns. Solubility may be defined as the concentration of the solute in concentrated solution at a certain temperature. The process of solubilization involves the breakage of intermolecular or interionic bonds in the solute molecule, the split-up of the solvent component to provide space in the solvent for the solute, and interaction between the solvent and the solute molecule or ion. When the drug is administered orally, it has to first dissolve in the gastrointestinal fluids before it can be absorbed in to the blood and reach its site of action. The objective of this article is to briefly outline the key aspects of the techniques used to improve the solubility, dissolution, and bioavailability of poorly soluble drugs. The techniques used are micronization, solid dispersion, lipid-based delivery system, inclusion complexes, prodrug approach etc. A number of poorly soluble drugs have been successfully introduced to the market by using new technologies. This review focus on the solubilization techniques explored in pharmaceutical product development to enhance aqueous solubility.

KEYWORDS: Solubility, cyclodextrins, solid lipid nanoparticles, biopharmaceutical classification system, self -microemulsifying drug delivery system, self-nanoemulsifying drug delivery system, solid dispersion.

INTRODUCTION

Oral route is the most preferred and convenient route of drug administration due to its ease of administration, high patient compliance, reduced sterility constraints, cost adequacy and adaptability. Poor aqueous solubility of drugs is the major limiting factor for the successful launch of many drugs into market. About 40-90 % of all compounds in the actual drug delivery pipelines are reported to be poorly soluble in water and most of the drugs are either weakly acidic or weakly basic, which contributes to the poor aqueous solubility. As a general rule, a compound having a solubility of at least 0.1 g/L is considered as adequately soluble and a compound having a solubility of ≤ 0.01 g/L is considered as poorly soluble.[1] For a drug to get absorbed when administered via oral route, it should be first soluble in the fluid of gastrointestinal tract and be present in the form at the absorption site. For an intravenous drug it should be in a soluble form in the blood stream. The poor water solubility can severely affect the dissolution rate and presystemic metabolism events.

The amount of drug absorbed into the systemic circulation is lower than the concentration found in the GIT which leads to poor water solubility which in turn affects the dissolution rate and presystemic metabolism events. Thus, a much higher dose is needed in the dosage form in order to attain the necessary plasma drug levels. The use of higher dose of drug can cause increased adverse reactions, erratic pharmacological responses, and hence poor patient complaints. It can increase the manufacturing cost and also the cost of therapy. The impairment of solubility and drug bioavailability depends upon the physicochemical properties of the active compound. The low aqueous solubility <100 µg/mL is expected for active compounds with 5 or more carbon atoms, a log P of 2 or greater, high molecular weight (>500 Da), and high crystal energy (melting point >20000 C). Amidon et al. proposed Biopharmaceutical classification system (BCS) as a useful decision-making tool in the development of pharmaceutical formulation which categorizes the drugs based on the aqueous solubility and intestinal permeability.[2]

This classification defines the drug in four categories from BCS class I to BCS class IV.

Table 1: Biopharmaceutical classification of drugs.

Class	Solubility	Permeability	Absorption pattern	Limiting step for drug absorption	Examples of drugs
I	High	High	Well absorbed	Gastric emptying	Propranolol hydrochloride, diltiazem, Warfarin sodium, verapamil hydrochloride
II	Low	High	Variable	Dissolution	Nifedipine, Phenytoin, Albendazole, Carbamazepine, Ibuprofen
III	High	Low	Variable	Permeability	Insulin, methyldopa,
IV	Low	Low	Poorly absorbed	Case by case	Taxol, Azathioprine, sulfasalazine

There are several technologies that have been successfully adopted to enhance the solubility, dissolution, and bioavailability of poorly soluble drugs.

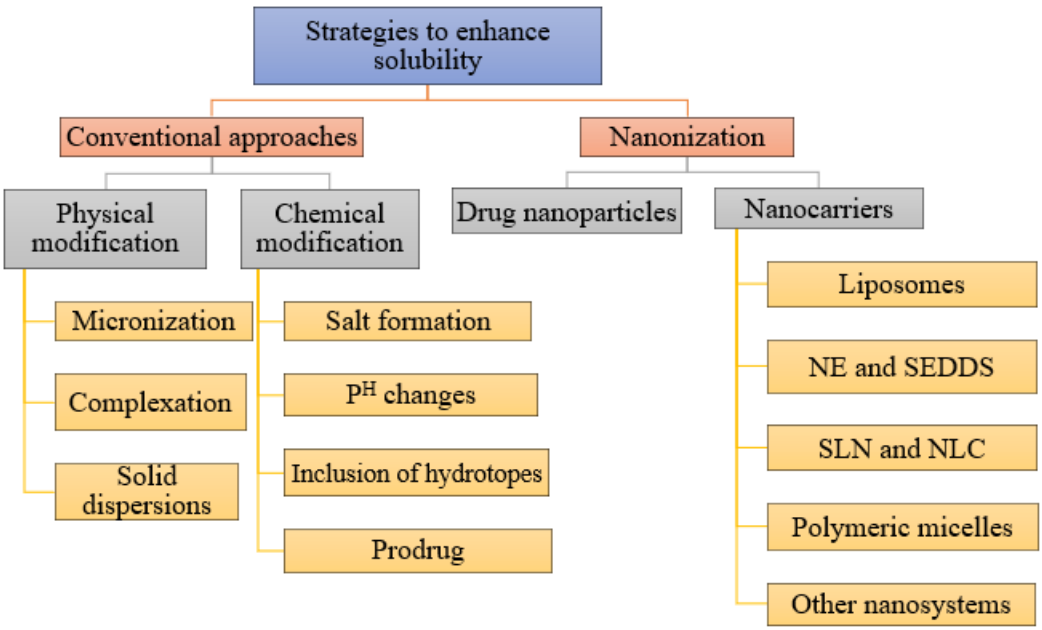

Figure 1: Diffferent strategies to enhance solubility.

Conventional strategies for solubility enhancement

Physical and/or chemical modification techniques are used for improving the solubility and many of them are utilized as precursor techniques for nanonisation of BCS class II or IV drugs. The major physical modifications include particle size reduction by micronization or

super critical fluid process, modification of crystal polymorphic or pseudopolymorphic form, utilization of complexing agents, dispersion in carriers or by surfactants including eutectic mixtures, solid dispersion, solid solutions, cryogenic techniques and solubilization in ionic liquids or in liquid crystals.[2]

Table 2: Conventional strategies for solubility enhancement with examples.

Strategies	Representative drugs	References
Micronization	Griseofulvin, Progesterone, Spironolactone Diosmin, and Fenofibrate. Gliclazide Microcrystals, Betamethasone, Budesonide and Prednisolone	[3]
Changes in pH and/or use of buffers	Diltiazem hydrochloride; Sibutramine; Verapamil hydrochloride; Naproxen; Celecoxib; Quinolone antibiotic	[4]
Modification of crystal polymorphic or pseudo-polymorphic form	Ritonavir; Chloramphenicol Palmitate; Oxytetracycline; Carbamazepine; Atorvastatin Calcium; Axitinib; Phenylbutazone; Rifaximin	[5]
Cocrystallization techniques	Adefovir Dipivoxil-Saccharin Co-Crystal; Piroxicam, Norfloxacin, fluoxetine, caffeine; Insulin; Itraconazole; Paracetamol; Fluoxetine Hydrochloride; Acyclovir; Carbamazepin; Indomethacin	[6]
Complexation with Cyclodextrins	Acetazolamide, Carbamazepine Hydrocortisone, Naproxen, Pregnenolone, Tropicamide, Alprostadil (PGE1); Cephalosporin; Chlordiazepoxide; Dexamethasone; Nimesulide; Omeprazole; Piroxicam	[7]
Eutectic mixtures	Lovastatin Posaconazole, Benznidazole	[8,9]
Solid dispersion	Celecoxib, Halofantrine, and Ritonavir; Meloxicam, Naproxen, Nimesulide; Nabilone; Itraconazole; Tacrolimus; Lopinavir/Ritonavir; Etravirine; Everolimus; Ritonavir; Itraconazole; Telaprevir; Vemurafenib; Ivacaftor	[3,10]
Solid solutions	Itraconazole, Griseofulvin	[11]
Micellar solubilization	Gliclazide, Glyburide, Glimepiride, Glipizide, Repaglinide, Pioglitazone, Rosiglitazone	[3,12,13]
Pro-drug or derivation	Fosamprenavir (Phosphate ester of Amprenavir); Valganciclovir (l-Valyl ester of ganciclovir); Valacyclovir (l-Valyl ester of acyclovir); Estramustine phosphate (phosphate ester of estramustine); Oseltamivir (prodrug of oseltamivir carboxylate); Fosphenytoin (phosphate ester of phenytoin)	[6,14]

Micronization

Micronization is a conventional technique for particle size reduction. Micronization increases the surfacea area, thereby increasing the dissolution rate,it does not increase the equilibrium solubility. Micronization of drugs is done by milling techniques using Jet mill, Ball mill,Rotor-stator colloid mills. These techniques were applied to drugs like griseofuvin, progesterone, spironolactone and fenofibrate. Micronization can improve the digestive absorption, consequently their bioavailability and clinical efficacy.[15]

Micronized fenofibrate exhibited more than 10 fold increase in dissolution in 30 minutes. After micronization, the resulting particle size is less than 10 microns. Micronization size reduction involves acceleration of particles thereby the grinding occurs by particle-particle impact or impact against a solid surface.[3]

According to Noyes-Whitney equation, reducing the particle size of a drug can significantly enhance the bioavailability of poorly soluble compounds by increasing their dissolution rate. Smaller particles, especially those smaller than 5 micrometers have thinner diffusion layer around them, which accelerates the distribution of dissolved molecules and improves the drug's effectiveness.[16]

Advantages

- Simple size reduction process.
- It increases the dissolution rate of drugs through increased surface area.

Disadvantages

- It is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.
- It has limited applicability to range of compounds.[15]

Technique

To micronize the large drug particles, various types of mills can be used depending on the nature of the drug and the desired particle size. The size reduction is achieved through methods such as pressure, friction, attrition, impact, or shearing. Milling can be performed either as dry grinding or wet grinding.[16]

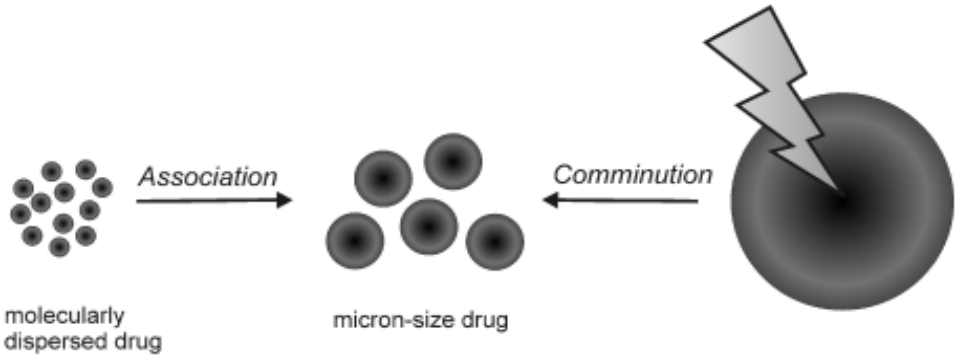

Figure 2: Illustration of the two principle methods for the production of a micron-size drug powder.

Milling a substance dispersed in a nonsolvent helps to prevent the formation of dust and the agglomeration of particles. Commonly, jet mills, high-pressure homogenizers, or pearl-ball mills are employed for a mechanical micronization of a drug. Dry milling using a fluid energy mill is the most frequently used method for micronization. At a milling pressure between 3 and 10 bar, the drug particles collide with each other in the milling chamber as the air jet reaches a high speed due to the rapid expansion.[16]

High-pressure homogenization is another micronization method used in pharmacy. During this process, a suspension is homogenized at pressures around 1000 bar and subjected to up to 10 cycles, causing a high shear strain of the drug.

Another method of communition is milling with a ball mill, which involves a rotating vessel that is partly filled with balls. The process of comminution is caused by attrition and impact. For micronization by wet milling, pearlball mills can be employed. A pearl-ball mill consists of a vessel that is filled to 74.4% with pearl balls that are moved using a stirrer.[16]

Complexation

Cyclodextrins(CDs) are cyclic oligosaccharides composed of glucose units linked by α-1,4 bonds. They consist of a hydrophilic outer surface and a lipophilic central cavity. The natural cyclodextrins include α,β and γ cyclodextrins. Cyclodextrins have the ability to form inclusion complexes with the drugs by noncovalent intermolecular forces. This will change the physiochemical properties of the included drug. The formation of a drug/cyclodextrin inclusion complex can enhance the drugs aqueous solubility, improve its chemical and physical stability and enhance drug delivery through biological membranes. This process does not involve the formation or breaking of covalent bonds. In aqueous solutions, drug

molecules within the CD inclusion complex are in dynamic equilibrium with free drug molecules. Drug molecules are easily released from the complex upon media dilution or by competative complexation. One or more drug molecule can form complex with one CD molecule and one or more CD molecule can form a complex with one drug molecule. Usually one drug molecule(D) forms a complex with one CD molecule. CDs can enhance the oral bioavilability of BCS Class Ⅱ drugs and also for BCS class Ⅳdrugs.[7]

Figure 2: Drug-Cyclodextrin Inclusion Complex[15]

The surface of cyclodextrin molecules make them water soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized non-polar molecules. On the basis of the structure and properties of the drug molecule it can form 1:1 or 1:2 drug cyclodextrin complex.

Table 3: List of selected Marketed Cyclodextrin (CD) based products.[15]

Drug	Cyclodextrin	Dosage form	Company/Country
Nimesulide	Beta- CD	Tablet	Novartis, Europe
Nicotine	Beta- CD	Sublingual tablet	Pharmacia,Sweden
Omeprazole	Beta- CD	Tablet	Betafarm, Germany
Aripiprazole	Sulfo butyl ether beta-CD	i.m. solution	BMS, USA
Vericonazole	Sulfobutylether Beta-CD	i.v. solution	Pfizer, USA
Diclofenac Na	Hydroxypropyl Gamma-CD	Eye drop solution	Chauvin, France
Benexate	Beta-CD	Capsules	Teikoku/Japan
Piroxicam	Beta-CD	Tablet	Chiesi/Italy
Nitroglycerin	Beta-CD	Sublingual tablet	Nippon Kayaku/Japan
Cefotiam hexatil hydrochloride	Alpha-CD	Tablet	Takeda/Japan
Itraconazole	2-hydroxypropyl-Beta-CD	Oral solution and intramuscular injection	Janssen/Europe/USA

Solid dispersion

Solid dispersion is an established solubilization technology which basically consist of two-component system, where the drug and the polymer act as solute and solvent. Solid dispersion converts a crystalline drug into an amorphous form. The amorphous form of a

compound is more soluble in water, more hygroscopic and thermodynamically less stable compared to its crystalline counterparts. These system can form multiple structures depending on their composition and sample processing history.[10,15]

Solid dispersion referred to as molecular dispersion where a drug is incorportaed into a carrier at molecular level. This incorporation typically transforms the drug from crystalline form to an amorphous form. The amorphous form generally offers higher solubility when compared to the crystalline form. This is because in amorphous state no energy is required to break the crystal lattice. But in crystalline state, the molecules occupies in definite positions and these ordered arrangements is repeated several times in all three dimensions. So more enrgy is required to break the crystal lattice as compared to amorphous form. Most of the drug candidate exist in crystalline state and by using various technique the drug can be converted fully or partly into amorphous state.[17]

Spray drying and hot melt extrusion are two commonly employed methods to make solid dispersions of poorly soluble drugs.

Spray drying

A spray dried dispersion(SDD) is an amorphous molecular dispersion of a drug in a polymer matrix achieved by dissolving both the drug and the polymer in an organic solvent and then spray drying the resulting solution. For effective spray drying, the solubility of the active pharmaceutical ingredient in the solvent is crucial. SDDs improves the oral absorption of poorly water-soluble drug by maintaining a supersaturated concentration of the drug in gastrointestinal fluids. These dispersions can be incorporated into various dosage forms including capsules, tablets and sachets.[15]

Commonly used polymers for spray dried dispersions are hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methylcellulose, polyvinylpyrrolidone, copovidone and methacrylate polymers. In the spray drying process, a poorly soluble drug is mixed with a suitable polymer in a solvent like acetone, ethyl alcohol, or isopropyl alcohol. This drug polymer solution is pumped to an atomizer inside the drying chamber of a spray dryer. The atomizer coverts the solution into small droplets. These small droplets are rapidly converted to fine particles by the hot drying gas like nitrogen. By using a cyclone or filter system, the dried powder is collected from the gas stream. The spray dried intermediates are blended with

a few other ingredients like diluent/glidant/lubricant and can be compressed into a tablet or encapsulted into a capsule.

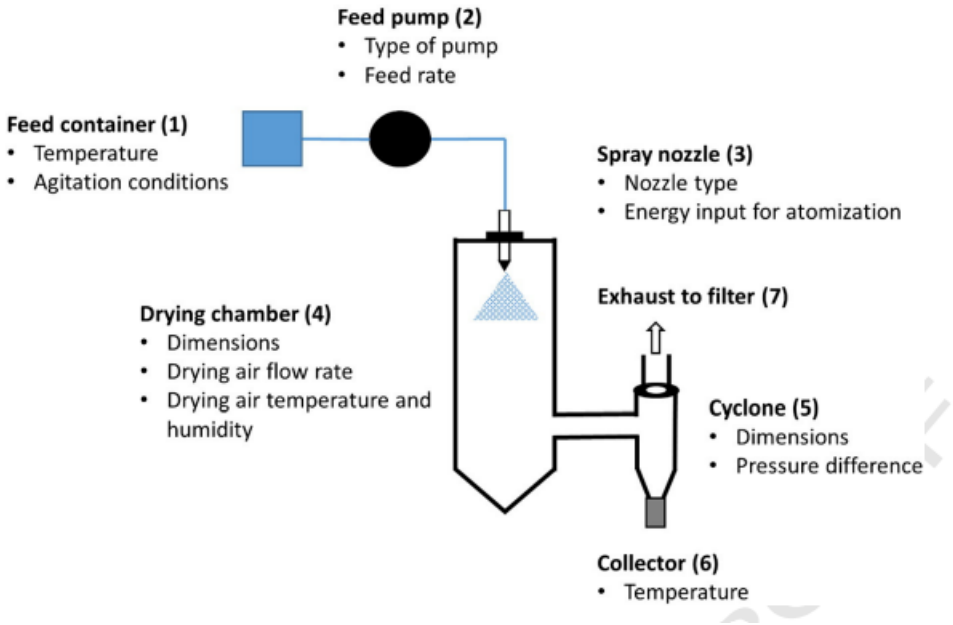

Figure 3: Spray drying set-up.[18]

Hot melt extrusion

It is a direct melting method proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage form. The main advantages of this method is its simplicity and economy. The physical mixture of drug and carrier are heated directly until the two melts. This molten mixture is then rapidly cooled and soldified in an icebath with rigorous stirring. The resulting solid mass is then crushed, pulverized and sieved which can be compressed into tablets with the help of tableting agents. The melting point of the binary system in this method depends on its composition, that is the choice of the carrier and the weight fraction of the drug in the system.

An important factor that must be considered for the formulation of solid dispersion by the hot-melt method is the miscibility of the drug and the carrier in the molten form. Another important factor is the thermostability of both the drug and the carrier.[3]

Table 4: Examples of FDA- approved medicines that use solid dispersion technologies.[10]

Product name	API	Polymer	Solid dispersion preparation method
Sporanox	Itraconazole	HPMC	Spray drying on sugar beads
Prograf	Tacrolimos	HPMC	Spray drying
Kaletra	Lopinavir/ritonavir	PVP/VA	Melt extrusion
Intelence	Etravirine	HPMC	Spray drying
Zotress	Everolimus	HPMC	Spray drying
Novir	Ritonavir	PVP/VA	Melt extrusion
Onmel	Itraconazole	HPMC	Melt extrusion

Chemical modification

pH adjustment

For organic solutes that are ionizable, changing the pH of the system is the simplest and most effective means of enhancing the aqueous solubility. By adjusting the pH of the solution under suitable conditions, the solubility of an ionizable drug can increase exponentially. A drug that can be efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with high pKa. For example, Furosemide (pKa of 3.9) is unstable at an acid pH, but is very stable under alkaline conditions.[19]

Salt formation

Salt formation is one of the most common and effective method for increasing the solubility and dissolution rates of acidic and basic drugs. Converting a drug into its salt form can alter both its solubility and permeability, there by enhancing the bioavailability. It is well known technique to enhnace the dissolution rates. Alkaloid bases are slighlty soluble in water, but if the pH of the medium is reduced by the addition of acid, the solubility of the base is increased as the pH continues to be reduced.

Hydrotopes

Hydrotropy is an organic solvent- free solubilizing approach. This process involves the additon of a large amount of second solute, the hydrotropic agent results in an increase in the aqueous solubility of first solute. This approach occurs due to the weak interactions between the poorly soluble solutes and hydrotopic agents such as sodium benzoate, sodium alginate, urea etc. Another hypothesis suggests that the hydrotopic agents distort the tertrahedral water structure or form micelles at concentrations above the minimum hydrotope concentration (MHC). In a study investigating the solubilization of sparingly soluble riboflavin using nicotinamide as a hydrotrope, researchers found that hydrotropic molecules self-associate

through stacking of pyridine rings, and formed sandwich complexes with riboflavin molecules. The self aggregation and the formation of complexes between riboflavin and the hydrotrope affect the hydrogen bonds between solute - water, hydrotrope - water, solute-solute, solute - hydrotrope, and hydrotrope - hydrotrope.[20]

Prodrug

Prodrug approach is defined as the chemical modification of the pharmacologically active agent which upon invivo enzymatic or chemical action gets converted into the active drug. The prodrugs are classified as carrier-linked prodrugs and bioprecursors. The carrier linked prodrugs comprise of drug and carrier joined by an ester linkage which are generally activated by enzymatic hydrolysis. Where as bioprecursors lack promoiety and are activated by mechanisms involving hydration or oxidation or reduction.[20]

Nanonization

In recent times, nanonization techniques have gained greater importance in increasing the dissolution rate and bioavailability of numerous drugs that are poorly soluble in water. Nanonization is regarded as nonspecific size reduction techniques. These strategies include increasing the surface area to volume ratios of drug powders, designing novel nanomaterials that can act as carriers for controlled release and changing the crystalline form. Particles with large specific surface area and high energy are obtained by this method which results in higher dissolution rate. This technique improves drug solubility and pharmacokinetics and it might also decrease systemic side effects. Numerous researchers have investigated nanoscale delivery systems such as liposomes, polymeric nanoparticles, and occular nanosystems.[20,21]

Drug nanoparticles

Nanocrystals are nanometer-scale drug crystals made up of the drug itself without the presence of a carrier material; such is the case of lipid and polymeric nanoparticles. When these nanocrystals are dispersed in liquid, they form nano-suspensions, which are stabilized by surfactants or polymeric stabilizers. The dispersing medium may be water, aqueous solutions or non aqueous media such as polyethylene glycols or oils. There are three categories of nanocrystal preparation methods namely bottom-up, top-down, and combined methods. One of the main bottom-up technique is the nanoprecipitation, which involves solubilization of the drug in a suitable solvent followed by precipitation of the dissolved drug through the addition of a non solvent, resulting in the production of nanocrystals. When carefully managed this process leads to the formation of small and uniform nanocrystals.

Top-down production techniques are high energy process applied for size reduction of drug particles such as media miling or high pressure homogenization. Inorder to further reduce the crystal size, the both techniques can be combined. The combined method includes a pretreatement step in which drug crystals are precipitated into suspensions, followed by a high energy process is applied in the sequence. The resulting nanocrystals and nanosuspensions enhance the bioavailability of drugs that are poorly soluble in water and reduces the administered dose with consequent low adversee effects and increased patient compliance. The improvement in bioavailability occurs due to the higher surface area and saturation solubility. Additionally the low amount of excipients used also reduces the potential toxicity associated with these materials.[2]

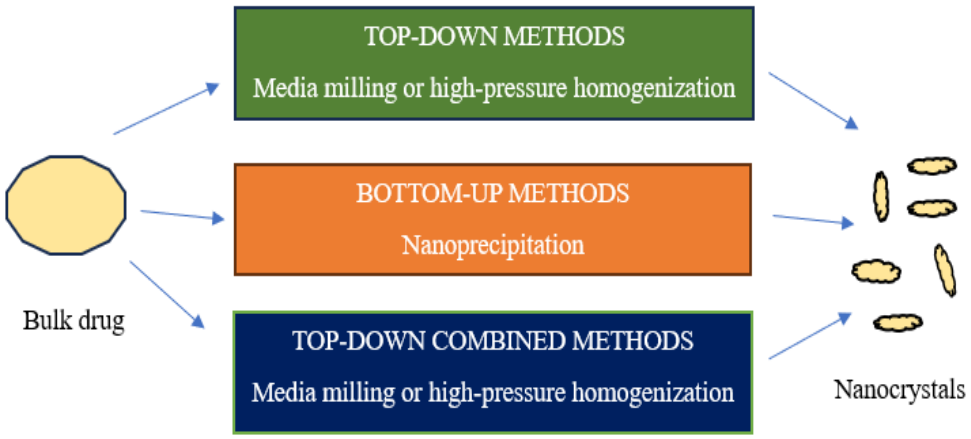

Figure 4: Nanoparticle preparation techniques.

Nanocarriers

Liposomes

liposomes are spherical vescicles consisting of one or more bilayers of phopholipids and cholesterol. They can solubilize water insoluble drugs into their lipid domain of the liposomal membrane. Liposomes have both aqueous cavity and hydrophobic bilayer, so they can encapsulate both hydrophilic and hydrophobic molecules in their structure. Because of the good biocompatibility and flexibility, liposomes have become a talented drug delivery system. The most widely used method of prepartaion of liposome is the film hydration method.[22,23]

Table 5: Clinically available liposome- based products.

Clinical products	Administration	Active agent	Indication
Doxil®	i.v.	Doxorubicin	Ovarian, breast cancer, Kaposi's sarcoma
DaunoXome®	i.v	Daunorubicin	AIDS-related Kaposi's sarcoma
Depocyt®	Spinal	Cytarabine/Ara-C	Neoplastic meningitis
Myocet®	i.v.	Doxorubicin	Metastatic breast cancer
Mepact®	i.v.	Mifamurtide	Non-metastatic osteosarcoma
Abelcet®	i.v.	Amphotericin B	Invasive severe fungal infections
Ambisome®	i.v	Amphotericin B	Fungal infections
Amphotec®	i.v.	Amphotericin B	Fungal infections
Exparel®	i.v.	Bupivacaine	Pain management
Epaxal®	i.m.	Inactivated hepatitis A virus	Hepatitis A
Inflexal®	i.m.	Inactivated hemaglutinine of Influenza virus	Influenza
Marqibo®	i.v.	Vincristine	Acute lymphoblastic leukaemia
DepoDur™	Epidural	Morphine sulfate	Pain management

Nanoemulsion and SEDDS

Nanoemulsions are generally O/W emulsions in the nanometer scale madeup of oil phase, water phase, emulsifier and a selected co-emulsifier. The oil used in the nanoemulsions formulation is a liquid lipid, which offers a great practicality for high load of poorly soluble drugs. Nanoemulsion can spontaneously form when there is a high concentration of surfactants.[22] The self-dispersing formulations such as self-emulsifying, self-micro/nano-emulsifying drug delivery system (SMEDDS/SNEDDS) are of a special interest as a promising approach for the delivery of poorly water-soluble lipophilic drugs. This is due to their self-dispersion behaviour and small droplet sizes upon dispersion that improves drug absorption from the large intestinal area. These self- dispersing formulations are complex mixture of oil, surfactant, co-surfactant and co-solvent that self emulsify and form thermodynamically stable oil-in-water (O/W) emulsion or microemulsion in the GI tract upon the mild agitation provided by GI motility.[24]

Table 6: Self emusifying drug delivery systems and their marketed products.[25]

Product name/ drug	Use	BCS class	Dosage form	Manufcatured by/for
Sandimmune®(cyclosporine A/I)	Organ rejection prophylaxis in allogenic transplants of kidney, liver, and heart.	IV	Soft gelatin capsule	Novartis pharmaceuticals corporation
Neora® (cyclosporine)	Systemic immunosuppressant	IV	Soft gelatin capsule	Novartis pharmaceuticals corporation
Gengraf® (Cyclosporine A/III)	Systemic immunosuppressant	IV	Hard gelatin capsule	AbbVie Inc.
Fortovase® (Saquinavir)	Inhibitor of the human immunodeficiency virus (HIV) protease	IV	Soft gelatin capsule	Roche Laboratories Inc.
Depakene®(Valproic acid)	Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures	II	Soft gelatin capsule	AbbVie Inc.
Rocaltrol® (Calcitriol)	Management of secondary hyperparathyroidism and management of hypocalcemia	II	Soft gelatin capsule	Roche Products Limited
Vesanoid® (Tretinoin)	Retinoid that induces maturation of acute promyelocytic leukemia	II	Soft gelatin capsule	Roche Laboratories Inc.

Lipid nanocarriers and Solid lipid nanoparticles

Lipid based formulations in the form of nanosuspensions offers a sufficiently large surface for drug absorption in the gastrointestinal tract. Even after digestion, they will reconstitute into miscelles that results in supersaturated drug concentration. These characteristics offers favorable conditions for drug absorption. The oral bioavailability of lipophilic drug (eg: Itraconazole) can be enhnaced when administered with a fat-rich meal or vegetable oil. These lipid nanocarriers creates a positive impact on drug absorption, preventing drug precipitation, improving membrane permeability, reducing CYP enzymes, inhibiting efflux transporters, providing bioadhesion to the absorptive epithelia and improving lymphatic transport. This lipid dispersion augments the rate and extent of absorption of lipophilic drugs.[22]

Solid lipid nanoparticles(SLNs) represent the first generation of lipid nanoparticles composed of a high melting point solid lipid and a small number of surfactant, which are developed on the base of from O/W emulsions. They possess high physical stability and show multiple advantages as drug delivery system, such as high drug loading, sustaining drug release, facilitating drug absorption, and ease of scale up production. Wang et al. used soild lipid nanoparticles for oral delivery of sorafenib, an anticancer agent for hepatocarcinoma, inorder to achieve a desrable liver targeting.[22]

CONCLUSION

There are variety of methods that have been explored for enhancing the solubility of poorly water soluble drugs, especially BCS class Ⅱ drugs. The conventional approaches includes salt formation, pH modification, prodrug approaches, solid dispersion, and complexation. Nanonization techniques are of great importance in recent times as they are efficient in increasing the solubility. While selecting a technology, consideration should be given to the physicochemical characteristics of the drug and advantages and disadvantages of different technologies.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

ABBREVIATIONS

GIT - Gastrointestinal tract
BCS - Biopharmaceutical classification system
CD - Cyclodextrin
SDD - Spray dried dispersion
SLN - Solid lipid nanoparticle
SMEDDS - Self microemulsifying drug delivery system
SNEDDS - Self nanoemulsifying drug delivery system

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