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VARIOUS APPROACHES FOR PARTICLE SIZE REDUCTION FOR IMPROVEMENT OF ORAL BIOAVAILABILITY OF HYDROPHOBIC DRUGS

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ABSTRACT

Pharmaceutical particle technology is employed to improve poor aqueous solubility of drug compounds that limits in vivo bioavailability owing to their low dissolution rate in the gastrointestinal fluids following oral administration. The particle technology involves several approaches from the conventional size reduction processes to the newer. The conventional methods of size reduction involve mechanical micronization techniques that are simple and convenient methods to reduce the drug particle size and increase the surface area and thus enhance the solubility and dissolution of poorly soluble drugs. The conventional particle technologies are limited for some drugs due to their low efficiency hence novel particle technologies used to overcome the limitations of the conventional methods. Novel particle technologies modify the solubility properties of the drugs and produce solid, powdered form of the drugs that are readily soluble in water and can be easily formulated into various dosage forms. There are various techniques for improvement of oral bioavailability of hydrophobic drugs: 1) particle size reduction 2) mechanical micronization by jet milling, ball milling, and high pressure homogenization 3) engineered particle size control by cryogenic spray process, crystal engineering 4) some newer techniques are solid self emulsifying drug delivery system, complexation with cyclodextrin, polymeric micelles, freeze dried liposomes, solid liquid nanoparticles. Solid- SEDDS (S-SEDDS).

KEYWORDS: Particle technology, Drug solubility, poorly water soluble drug, Solubility enhancement, Dissolution.

INTRODUCTION

Drug solubility and bioavailability

Dissolution and gastrointestinal permeability are fundamental parameters that control rate and extent of drug absorption and its bioavailability. The water solubility of a drug plays an important role in the absorption of the drug after oral administration. It also gives information regarding the parenteral administration of a drug is possible or not and is useful in manipulating and testing of drug properties during the drug design and development process. The drug solubility is an important characteristic but also the dissolution rate at which the solid drug or drug from the dosage form passes into solution is critically important when the dissolution time is limited. Although the oral bioavailability of a drug depends on aqueous solubility, drug permeability, dissolution rate, first-pass metabolism and susceptibility to efflux mechanisms, aqueous solubility and drug permeability are also important parameters for oral bioavailability. In recent years, number of insoluble drug candidates increased, almost 70% of new drug candidates showing poor water solubility. For these drug candidates, poor aqueous solubility and poor dissolution in the GI fluids is a limiting factor to the in vivo bioavailability after oral administration. Therefore, in vitro dissolution has been consider as an important element in drug development and thus increasing the dissolution rate of poorly soluble drugs and enhancing their bioavailability is an important challenge to pharmaceutical scientists.

Table: 1 Biopharmaceutics Classification system

Table 1 – Biopharmaceutics Classification System (BCS) with characteristics of drugs.

BCS class	Solubility	Permeability	Absorption pattern	Examples
I	High	High	Well absorbed	*Metoprolol, Diltiazem, Propranolol*
II	Low	High	Well absorbed	*Phenytoin, Nifedipine, Danazol*
III	High	Low	Variable	*Cimetidine, Acyclovir, Captopril*
IV	Low	Low	Poorly absorbed	*Hydrochlorothiazide, Taxol, Furosemide*

Table-2 Conventional particle size reduction techniques

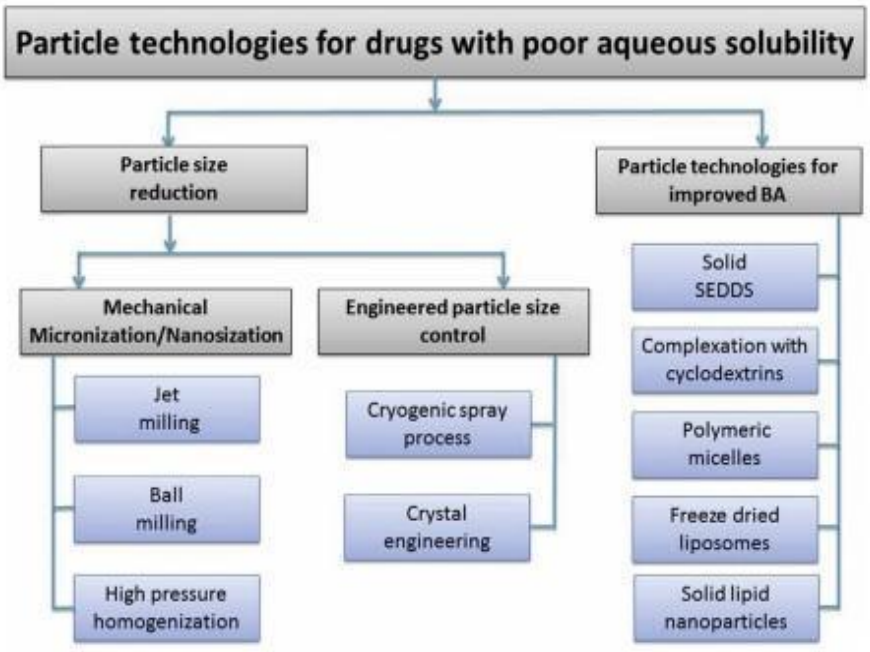

Table-3 Newer technologies for improvement of bioavailability

Particle Technology	Method	Example Drugs
Mechanical micronization	Jet milling	Cilostazol Ibuprofen
	Ball milling	Danazol Carbamazepine, Dypyridamole, Indomethacin
	High pressure homogenization (HPH)	Prednisolone, Carbamazepine Nifedipine
Particle size reduction by novel particle engineering	Cryogenic spraying process/spray freezing into liquid	Danazol Carbamazepine
	Crystal engineering	Glibenclamide Febantel, Itrazonazole
Solid SEDDS technology	Spray drying, in situ salt formation, solidification with polymers	Nimodipine Flurbiprofen Dexibuprofen Docetaxel Crucumin Meloxicam Fenofibrate Ibuprofen
Complexation with cyclodextrins	Freeze-drying, vacuum evaporation, kneading	Praziquantel Bifonazole, Clotrimazole Celecoxib
Polymeric micelles	Dialysis, freeze-drying	Paclitaxel Etoposide, Docetaxel, 17-AAG Amphotericin B
Freeze–dried liposomes	Freeze-drying	Sirolomus (Rapamycin) Paclitaxel
Solid lipid nanoparticles	HPH, solvent emulsification-evaporation/diffusion	All trans-retinoic acid Tretinoin

Newer particle technologies for improved bioavailability

1. Solid self-emulsifying drug delivery systems

- Solid self-emulsifying drug delivery systems (S-SEDDS) are novel particle technology to improve solubility of lipophilic drugs and drugs with poor aqueous solubility.
- S-SEDDS technologies provide an effective alternative approach to the conventional liquid SEDDS.
- S-SEDDS are formulated by incorporation of liquid or semisolid self-emulsifying (SE) ingredients into powders or nanoparticles by different solidification techniques. Solidification techniques are spray drying, adsorption to solid carriers, melt granulation and melt extrusion techniques, where the powders or nanoparticles refer to self-emulsifying nanoparticles, dry emulsions and solid dispersions that can be further processed into other solid self-emulsifying dosage forms or can be filled into capsules. S-SEDDS are solid at room temperature.
- There are various types of S-SEDDS like SE capsules, SE solid dispersions, dry emulsions, SE pellets and tablets, SE microsphere, SE nanoparticles, SE suppositories and SE implants, SE beads.
- SSEDDS are more desirable than conventional liquid SEDDS which are normally prepared either as liquids or encapsulated in soft gelatin capsules. Conventional liquid SEDDS has several limitations in manufacturing process that is its high production costs, difficult to use, have incompatibility problems with shells of soft gelatin and have problems in storage.
- Most common method of S-SEDDS preparation is spray drying technique plus the use of a solid carrier.
- From some studies confirm that a solid self emulsifying system can substantially improve the solubility or dissolution and bioavailability of drugs that have poor aqueous solubility. It can be a cost effective technique to prepare various solid oral dosage forms of a poorly soluble drug overcoming the disadvantages of conventional liquid SEDDS formulations concurrently. There are some limitations of S-SEDDS such as strong adsorption and physical interaction of the drug with the carriers that causes retarded or incomplete release of the drug from the S-SEDDS.

Table: 1.1 MARKETED FORMULATION

Brand name	Drug used	Dosage form	Company
Neoral	Cyclosporine	SGC	Novartis
Norvir	Ritonavir	SGC	Abbott laboraties
Fortovase	Saquinavir	SGC	Hoffmann roche
Convulex	Volporic acid	SGC	Pharmacia

Recent developments

Supersaturable SEDDS: Supersaturable SEDDS formulations are SEDDS formulation having reduced amount of surfactant and a crystal growth inhibitor such HPMC by using cellulosic polymers.

2. Complexation with cyclodextrins

- Cyclodextrins are a family of cyclic oligosaccharides derived from starch containing (α-1, 4)-linked a-D-glucopyranose units and having a hydrophilic outer surface and a lipophilic central cavity. There are different types of cyclodextrins based on the number of (α-1, 4)-linked a-D-glucopyranose units namely α, β, γ, δ, and ε cyclodextrins with six, seven, eight, nine and ten (or more) (α-1, 4)-linked a-D-glucopyranose units respectively.
- Cyclodextrins are large molecules with a number of hydrogen donors and acceptors and they do not penetrate lipophilic membranes.
- In pharmaceutical field, cyclodextrins are versatile, crystalline complexing agents that have ability to increase the solubility, bioavailability and stability of API, mask the color and taste of the drugs and also can prevent gastrointestinal and ocular irritation. Cyclodextrins are more widely used as a solubilizer for poorly soluble drugs.
- In pharmaceutical formulation processes, cyclodextrins are useful solubilizers, both liquid oral and parenteral dosage forms and can increase the apparent solubility of the compound leading so ultimate increase in dissolution and bioavailability.
- There are several methods of preparation of drug-cyclodextrin complex such as freeze drying, spray drying, co-precipitation of a cyclodextrin/drug solution, kneading, extrusion and grinding of slurry of drug and cyclodextrin in a mortar and pestle and each of these methods differ in outcomes such as resulting particle size, amount of complex formation and the degree of amorphous nature of the end product. Thus, the choice of preparation method is important when designing drug-cyclodextrin complexes.
- Based on mechanism of solubility two specific classes useful for the increasing solubility in aqueous media:

1) Inclusion complexes.
2) self association and stacking complexation.

Inclusion complexes

Inclusion of a nonpolar molecule or the nonpolar region of molecule (guest) into nonpolar cavity of another molecule or group of molecule (host).

When the guest molecule enters the host molecule the contact between water and the nonpolar regions of both is reduced.

Table-2.1 Self association and stacking complexation

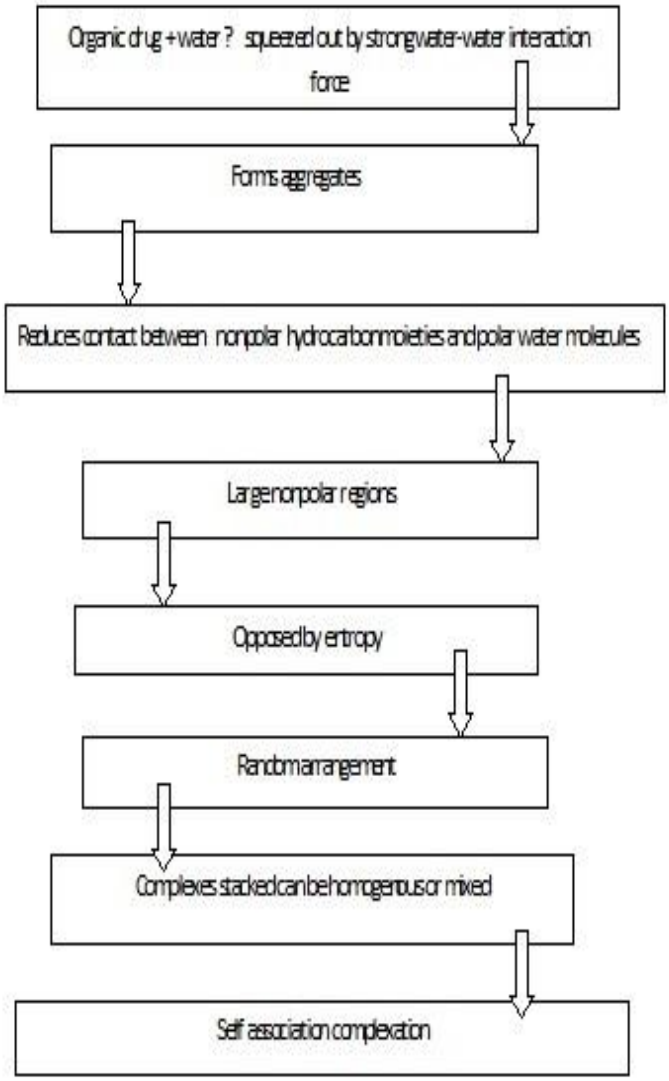

Table-2.2 MARKETED FORMULATION

Trade name	Drug/cyclodextrin	Dosage form	Company
Nitropen	Nitroglycerine/βCD	Sublingual tablet	Nippon kayaku
Nimedex	Nimesulid/βCD	Oral sachet	Novartis
Omebeta	Omeprazole/βCD	Tablet	Betapharm

3. Polymeric micelles

- **P**olymeric micelles are potential carriers for poorly soluble drugs by solubilizing them in their inner core and offering attractive characteristics such as a generally small size (100 nm) and a tendency to scavenge by the mononuclear phagocyte system.

Polymeric micelles are particles with diameter smaller than 100 nm formed by amphiphilic polymers dispersed in an aqueous media, and characterized by a core-shell structure which may have an A-B di-block structure (‘A’ being the hydrophilic polymer shell and B being the hydrophobic polymer core) or an A-B-A multi-block structure of co-polymers of different hydrophobicity or a graft co-polymer (hydrophilic backbone chain of a polymer grafted with hydrophobic blocks).

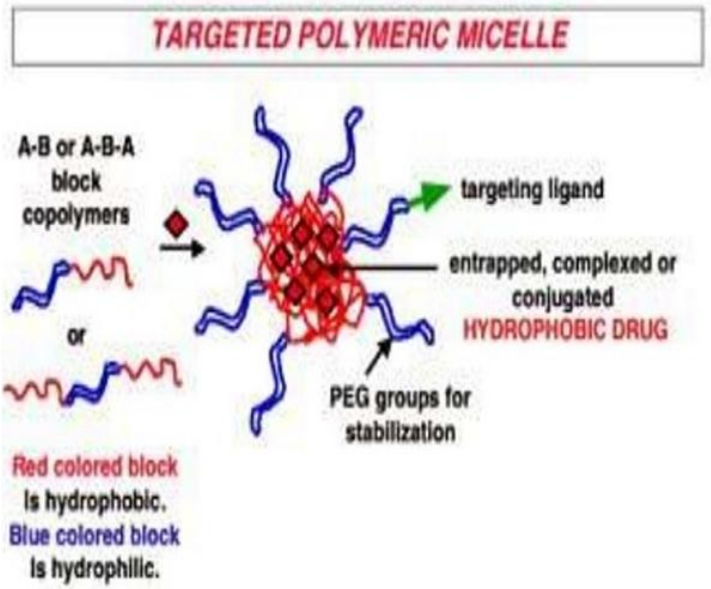

Fig. 3.1 Targeted Polymeric Micelle

Thus in a polymeric micelle, the hydrophobic fragments form the core of the micelle, while hydrophilic fragments form the micelle's corona. The nonpolar molecules are solubilized within the hydrophobic core while polar molecules will be adsorbed on the micelle surface and the substances with intermediate polarity will be distributed along surfactant molecules in intermediate positions.

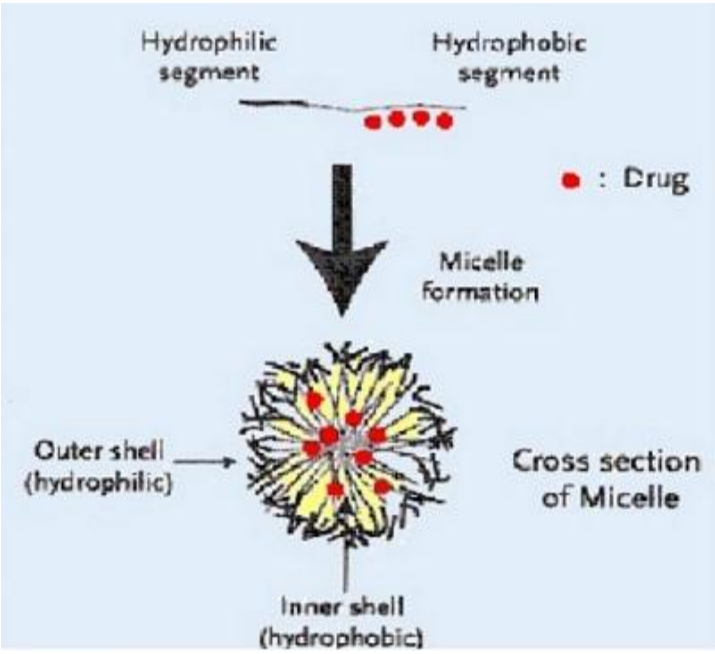

Fig. 3.2 Structure Of Polymeric micelle

Block copolymer micelles are further classified on the basis of intermolecular forces driving the segregation of the core segment from the aqueous environment such as amphiphilic micelles (formed by hydrophobic interactions), poly-ion complex micelles (resulting from electrostatic interactions) and micelles originating from metal complexation.

The shape of the micelles is also governed by the length of the hydrophobic core and the hydrophilic corona. The micelles are spherical when the hydrophilic segment is longer than the core block while an increase in length of the core segment beyond than that of the corona-forming chains may result in various spherical structures including rods and lamellae.

There are mainly two different processes for drug-loading into the polymeric micelles; the first method is the direct dissolution method and the second method is the preparation of drug-loaded micelles by solvent removal.

The direct dissolution method is a simple method, mostly employed for moderately hydrophobic copolymers. It involves dissolving the block copolymers along with the drug in an aqueous solvent, which may require heating to induce micellization.

The second category of drug-loading method is applied for amphiphilic co-polymers which are not readily soluble in water and require an organic solvent common to both the copolymer and the drug.

Micelle formation depends upon the solvent removal procedure which can be one among the several methods like dialysis, oil-in-water emulsion method, solution casting and freeze-drying. Dialysis can be used for water-miscible organic solvents whereby micellization occurs due to slow removal of organic phase. The solution-casting method involves evaporation of the organic phase to yield a polymeric film, which upon rehydration with a heated aqueous solvent produces drug loaded micelles. The oil-in-water emulsion process is useful for physical entrapment of a hydrophobic drug which involves the use of a non water-miscible organic solvent. All of these methods, after sterilization and freeze-drying steps, can be used to produce injectable formulations.

Polymeric micelles have several advantages as drug carriers and can incorporate several poorly soluble drugs and are considered inexpensive, safe and stable drug carriers.

Micelle-encapsulated drug can be targeted to organs or tissues of interest which can be achieved via the enhanced permeability and retention (EPR) effect. Site specific targeting of polymeric micelles is possible by preparing thermo- or pH-sensitive block co-polymers and additionally, a vector molecule such as antibody, peptide, lectin, saccharide, hormone and some low-molecular-weight compounds can be attached to the surface of micelles that helps in targeting against specific ligands at specific site of interest.

The polymeric micelles can spontaneously accumulate in tumors via the EPR effect thus they are exploited in tumor targeting by attachment of anticancer antibody to the micelle surface. Polymeric micelles have been the subject of interest for delivery of poorly soluble anticancer drugs.

Polymeric micelle systems are novel drug carrier systems that not only enhance water solubility of many hydrophobic drugs, but also are applicable in drug targeting, formulating unstable drugs and reducing the adverse effects. Due to their wide applicability to large group of therapeutic compounds, drug-loading into polymeric micelles is a promising particle technique for formulating other poorly soluble drugs in the future.

Table-3.1 MARKETED FORMULATION

Trade name	Drug used	Dosage form	Company
Genexol-PM	Paclitaxel	Intravenous injection	Lupin

4. Freeze-dried liposomes

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

- Because of their biphasic characteristics and diversity in design and composition, they offer a dynamic and adaptable technology for enhancing drug solubility.

- Drug encapsulation or entrapment into liposomes result in distinct changes in pharmacokinetic and pharmacodynamics properties of the free drugs, and also helps in decreasing toxicity and increases the therapeutic efficacy in some cases.

- However, one of the serious limitations with applicability of liposomes as drug delivery systems is associated with its poor stability during storage. The liposomal formulations can thus be stabilized by freeze drying process to obtain dry powders with enhanced stability while maintaining the potency of the incorporated drug.

- Freze-dried liposome system is a promising approach for formulating drugs with poor aqueous solubility as well as enhancing the stability of liposomal formulation. Liposomal incorporation of poorly soluble drugs followed by freezedrying approach can produce powdered form of the drug that can easily be solubilized in water. This particle technology can be further exploited for formulating wide range of therapeutic agents that are insoluble in water.

Table 4.1 MARKETED FORMULATIONS

Trade name	Drug used	Dosage form	Company
Doxil	Doxorubicin	Injectable solution	Sequus pharmaceuticals
DaunoXome	Daunorubicin	Injectable solution	NeXstar pharmaceuticals
Abelcet	Amphotericin B	Intravenous injection	Liposome company

5. Solid lipid nanoparticles

- Solid lipid nanoparticles (SLNs) are colloidal drug carrier systems which are like nanoemulsions, but differing in lipid nature in which the liquid lipid part of emulsions is replaced by a solid lipid at room temperature such as glycerides or waxes with high melting point.

- The interest towards SLN as a novel particle technology is increasing recently because of its potential as an alternative carrier system to traditional colloidal carriers, such as emulsions, liposomes and polymeric micro- and nanoparticles and also due to their possibility to be used in various routes of drug delivery.

- Among various methods of SLN preparation such as HPH (cold and hot homogenization), breaking of o/w microemulsion, solvent emulsification-evaporation or solvent emulsification-diffusion, solvent injection, water-in-oil-in-water double emulsion (w/o/w), high shear homogenization and/or ultrasound dispersion, the high pressure homogenization method is considered to be the most effective method of SLN preparation.

- SLNs prepared by high pressure homogenization have several advantages of narrow particle size distribution, high particle content in the dispersions, avoidance of organic solvents and scale-up feasibility. SLN technology is advantageous over other colloidal carrier systems due to its possibility of being formulated as controlled drug release delivery systems and also due to improved drug targeting, increased drug stability, no biotoxicity of the carrier and feasibility of incorporation of both lipophilic and hydrophilic drugs into the carrier.

- However, certain disadvantages of SLN like low drug-loading capacities and stability problems during storage or administration (gelation, particle size increase, drug expulsion from SLN) cannot be neglected.

- Several studies have been conducted to investigate the effectiveness of SLN on enhancement of the solubility of poorly water soluble drugs. In a study conducted to improve the oral bioavailability of a poorly soluble drug, all-trans-retinoic acid (ATRA) by incorporation into SLN, SLN formulations were found to significantly enhance ATRA absorption, suggesting that SLNs can offer an effective approach to improve the oral bioavailability of poorly soluble drugs. In another study aimed to prepare SLNs of a hydrophobic drug, tretinoin, by emulsification eultrasonication method, it was found that the drug release from SLN formulation demonstrated sustained/prolonged drug release from the SLN and the product was found to be stable for 3 months at 4 C. This proves the possibility of SLN technology in the formulation of sustained and prolonged drug dosage forms for hydrophobic drugs.

- SLN technology can be considered as a novel approach that can be utilized for various other drugs as well as new drug entities that are insoluble in water to formulate them into various dosage forms with enhanced bioavailability.

Table-5.1 MARKETED FORMULATION

Trade name	Drug used	Dosage form	Company
Apokyn	Apomorphin	Injectable solution	US WorldMeds, LLC

DISCUSSION

Compounds with poor solubility are increasingly posing challenges in the development of new drugs, since a large number of drugs coming directly from synthesis or from high throughput screening have a very poor solubility. It is well known that drug efficacy can be severely limited by poor aqueous solubility, leading to low dissolution rate and thus results in low absorption in the gastrointestinal tract after oral administration hence comprising oral bioavaibility.

The Biopharmaceutical Classification system divides drugs into four classes depending on *in vitro* and *in vivo* permeability data. For class II drugs dissolution /solubility and for Class III drug permeability limits the oral drug absorption. It is obvious that class II drugs the low ability to dissolve is a more important limitation to their overall rate and extent of absorption than their ability to permeate through the intestinal epithelia. There are several pharmaceutical strategies available to improve the aqueous solubility of poorly soluble drugs.

Self-emulsifying drug delivery systems (SEDDS) are usually used to improve the bioavailability of hydrophobic drugs. Conventional SEDDS, however, are mostly prepared in a liquid form, which can produce some disadvantages. Accordingly, solid SEDDS (S-SEDDS), prepared by solidification of liquid/semisolid self-emulsifying (SE) ingredients into powders, have gained popularity.

Cyclodextrins having a hydrophilic outer surface and a lipophilic central cavity. Cyclodextrins have ability to increase the solubility, bioavailability and stability of API, mask the color and taste of the drugs and also can prevent gastrointestinal and ocular irritation. The major mechanism associated with the solubilization potential of cyclodextrins is the inclusion complex formation while

non-inclusion complexation and supersaturation may also contribute to the solubilization process.

Polymeric micelle systems are novel drug carrier systems that not only enhance water solubility of many hydrophobic drugs, but also are applicable in drug targeting, formulating unstable drugs and reducing the adverse effects. Due to their wide applicability to large group of therapeutic compounds, drug-loading into polymeric micelles is a promising particle technique for formulating other poorly soluble drugs in the future. Polymeric micelles are particles with diameter smaller than 100 nm formed by amphiphilic polymers dispersed in an aqueous media. In a polymeric micelle, the hydrophobic fragments form the core of the micelle, while hydrophilic fragments form the micelle's corona. The nonpolar molecules are solubilized within the hydrophobic core while polar molecules will be adsorbed on the micelle surface and the substances with intermediate polarity will be distributed along surfactant molecules in intermediate positions.

Liposomes are phospholipid vesicles, comprising a phospholipid bilayer surrounding an aqueous compartment and can dissolve lipophilic drugs in their lipid domain. Because of their biphasic characteristics and diversity in design and composition, they offer a dynamic and adaptable technology for enhancing drug solubility. Drug encapsulation or entrapment into liposomes result in distinct changes in pharmacokinetic and pharmacodynamics properties of the free drugs, and also helps in decreasing toxicity and increases the therapeutic efficacy in some cases.

Solid lipid nanoparticles (SLNs) are colloidal drug carrier systems which are like nanoemulsions, but differing in lipid nature in which the liquid lipid part of emulsions is replaced by a solid lipid at room temperature

CONCLUSION

Poor aqueous solubility of a drug entity can be addressed with various pharmaceutical particle technologies. The particle technologies can be divided into two categories; the conventional methods and the newer, novel particle technologies. The conventional methods of size reduction involve mechanical micronization techniques that are simple and convenient methods to reduce the drug particle size and increase the surface area and thus enhance the solubility and dissolution of poorly soluble drugs. The conventional particle technologies are limited for some drugs due to their low efficiency, sometimes leading to thermal and chemical degradation of drugs, and resulting in non-uniform sized particles. The newer novel particle techniques can overcome the limitations of the conventional methods and are more efficient methods of formulating poorly soluble drugs. The novel methods are developed from conventional methods where the basic principle remains the size reduction for solubility improvement. The use of polymers, cyclodextrins and liposomes for formulating poorly soluble drugs has been discussed, providing wide applications in improving the solubility as well as stability of the drug formulations. Each particle technology has its own importance and applicability in enhancing water solubility of poorly aqueous soluble drugs. An appropriate method can be selected by considering the properties of drug to be formulated and the properties of desired dosage form. Other possible methods are yet to be explored in the field of pharmaceutical particle technology that can be used to formulate various drugs with poor aqueous solubility.

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