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Review

Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability

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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, novel particle technologies that 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. This review highlights the solid particle technologies available for improving solubility, dissolution and bioavailability of drugs with poor aqueous solubility.

1. Background

1.1. *Drug solubility and bioavailability*

It has been well explained that solubility, dissolution and gastrointestinal permeability are fundamental parameters that control rate and extent of drug absorption and its bioavailability [1]. The water solubility of a drug is a fundamental property that plays an important role in the absorption of the drug after oral administration. It also governs the possibility of parenteral administration of a drug and is useful in manipulating and testing of drug properties during the drug design and development process. The drug solubility is an equilibrium measure 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 [2]. Although the oral bioavailability of a drug depends

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on aqueous solubility, drug permeability, dissolution rate, first-pass metabolism and susceptibility to efflux mechanisms, aqueous solubility and drug permeability are also important parameters attributed to oral bioavailability [3]. In drug discovery, the number of insoluble drug candidates has increased in recent years, with almost 70% of new drug candidates showing poor water solubility [4]. 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 recognized 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 [5,6].

1.2. *Biopharmaceutics classification system*

Biopharmaceutics classification system (BCS) is a scientific classification of a drug substance based on its aqueous solubility and intestinal permeability that correlates *in vitro* dissolution and *in vivo* bioavailability of drug products (Table 1) [1,7]. When combined with *in vitro* dissolution characteristics of the drug product, BCS takes into account two major factors: solubility and intestinal permeability, which govern the rate and extent of oral drug absorption from solid dosage forms and ultimately, its bioavailability [8]. Due to this reason, BCS is the fundamental tool in the drug development especially in the development of oral drug products.

The food and drug administration (FDA) criterion for solubility classification of a drug in BCS is based on the highest dose strength in an immediate release (IR) oral product [8]. A drug is considered highly soluble when the highest strength is soluble in 250 ml (this volume is derived from typical bioequivalence study protocols) or less of aqueous media over the pH range of 1.0–7.5; otherwise the drug substance is considered poorly soluble. On the other hand, the permeability classification is based directly on the extent of intestinal absorption of a drug substance in humans or indirectly on the measurements of the rate of the mass transfer across the human intestinal membrane, or in animals, or *in vivo* models [7,8]. A drug substance is considered highly permeable when the extent of intestinal absorption is determined to be 90% or higher based on mass-balance or in comparison to an intravenous reference dose.

The bioavailability of BCS class II drugs is likely to be dissolution rate limited. But due to their high permeability, the BCS class II drugs have been on focus for solubility enhancement researches in the recent times and several formulation approaches for this class of compounds has been developed [9,10,11]. In case of class III drugs, the bioavailability is permeability-rate limited, but dissolution is likely to occur rapidly. Thus for class III drugs, formulating IR solid dosage forms with absorption enhancers can be a viable formulation option to improve their permeability [4]. But in case of BCS class IV compounds, the bioavailability is limited by both dissolution as well as intestinal permeability. Because of low membrane permeability, BCS class IV drugs are often poor candidates for drug development since solubility and dissolution enhancement alone might not help improve their bioavailability. However, these classes of compounds cannot be ignored just because of their permeability issues. Therefore the current approaches being used for BCS class II drugs, together with absorption enhancers, can be applied to formulate class IV compounds [4]. Another formulation development approach for class IV compounds is the selection of a better drug candidate with more appropriate physiochemical properties during the lead optimization phase [12,13].

1.3. *Science of pharmaceutical powders*

From one of the oldest professions of mankind, powder technology has now transformed itself from an art into a science with its principal applicability in food, chemical and pharmaceutical industries [14]. Not only the active drug substance, but also most of the pharmaceutical excipients are available in the powder form which makes the science of powder technology an inevitable discipline in pharmaceutical industry and pharmaceutics. Apart from the basic conventional processes like grinding, mixing and formulating, pharmaceutical manufacturing processes involve modification of powder and particle properties to create a novel drug formulation, with enhanced solubility and dissolution properties. Pharmaceutical powder technology deals with the examining of materials, formulations, additives and processes on achieving the desired properties or performance of the particles or composites [15]. Particle properties of active drug substances or excipients play an important role in the dosage form fabrication and performance. Pharmaceutical powder technology also deals with areas of surface engineering usually explored through the applications of surface chemistry and surface morphology. Overall, the properties like particle shape, size, adhesiveness, morphology, roughness, wettability, density, surface chemistry, plasticity, hardness, brittleness and hygroscopicity are important for successful dosage form design and development. Ultimately, these strategies are implemented to produce a drug product that is readily soluble in the GI tract because incomplete dissolution in the GI tract can severely restrict their oral bioavailability drug compounds [16].

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*

1.4. *Particle technologies: a tool for solubility enhancement*

Particle technology in pharmaceutics is a technique to modify physicochemical, micrometrics and biopharmaceutical properties of the poorly soluble drugs, thereby improving their solubility. Among various techniques for solubility enhancement, physical modifications of drug products such as reducing the particle size and modifying crystal habit are common approaches to increase drug solubility [17]. Apart from conventional micronizing techniques, particle technology now deals with various particle and nanoparticle engineering processes as promising methods of improving drug solubility [5]. This review focuses primarily on various particle technologies, from conventional size reduction methods to recent novel methods that can be used for formulating drugs with poor aqueous solubility as summarized in Fig. 1 and Table 2.

2. Conventional particle size reduction techniques

Particle size reduction is one of the oldest strategies for improving solubility of drugs since solubility of drugs is intrinsically related to drug particle size. When the particle size is decreased, the larger surface area of the drug allows the increase in the surface area to volume ratio thus increasing the surface area available for solvation. Particle size reduction technologies are therefore routinely used to increase the bioavailability of poorly soluble drugs [2]. Many strategies like polymorphism, salt formation, co–crystal formation and addition of excipients also marginally increase the solubility of the insoluble drugs but their use is mainly limited due to low success rates for increasing bioavailability and in some cases, being undesirable due to production of toxic side effects [18]. Because of this reason, particle size reduction remains to be a safe method to increase solubility of drug substances without altering the chemical nature of the drug. It is well known that decrease in particle size and corresponding increase in the surface area of the particles, increases the dissolution rate of that substance as described by the famous *Noyes–Whitney* equation back in the late nineteenth century [19]. However, as compared to the effect on dissolution properties, decrease in particle size has comparatively little effect on the solubility of the drug substances as it does not alter the solid-state properties of the particles. Williams et al. (2013) and Sun et al. (2012) have separately reported that particle size reduction indeed has effects on the kinetic solubility of the substance and according to *Ostwald-Freundlich* Equation (Equation (1)), the solubility increases significantly on reducing particle size below 1 μm (0.5 μm in radius) [2,20]. This is because the reduction of size below 1 μm increases solvation pressure, giving rise to an increase on solubility and also causes disruption of solute–solute interaction which eases the solubilization process [21].

$$\log\frac{C_S}{C_\infty} = \frac{2\sigma V}{2.303RT\rho r} \quad [1]$$

where, C_s is saturated solubility, C_∞ is solubility of solid consisting of large particles, V is molar volume of particles, R is gas constant, T is absolute temperature, ρ is density of solid, and r is particle radius.

Although reduction of particle size below 1 μm is suitable to improve the solubility, the particle technologies have now been developed to reduce the particle size to the nanometer-size range. The conventional particle size reduction still remains a basic size reduction procedure but particle size reduction techniques now involve nanotechnology and nanosization, which are being widely studied for the formulation approaches to drugs with poor aqueous solubility

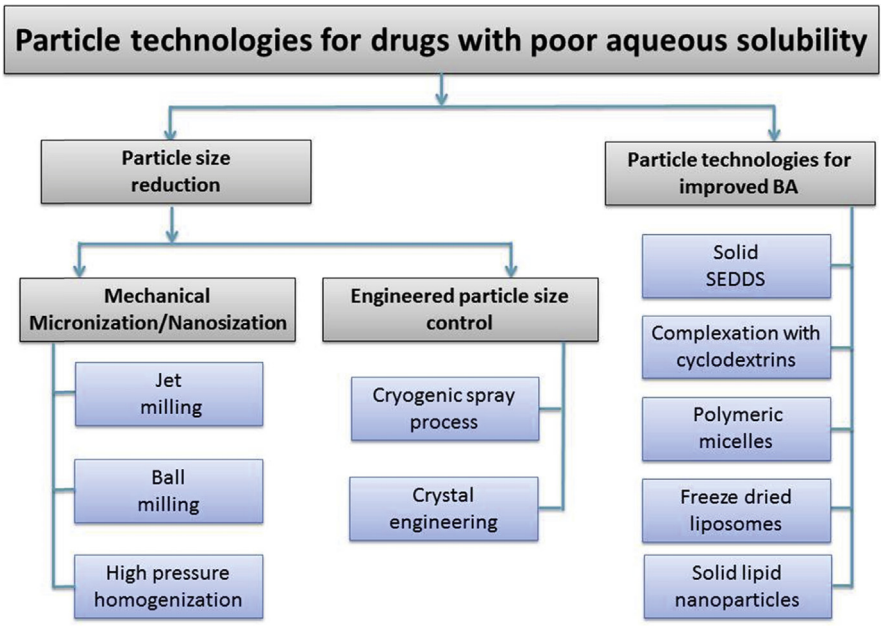

Fig. 1 – Pharmaceutical particle technologies for improved solubility, dissolution, and bioavailability of drugs.

Table 2 – Particle technologies, methods involved and examples.

Particle Technology	Method	Example Drugs	Reference
Mechanical micronization	Jet milling	*Cilostazol*	[26]
		Ibuprofen	[27]
	Ball milling	*Danazol*	[28]
		Carbamazepine, Dypyridamole, Indomethacin	[30]
	High pressure homogenization (HPH)	*Prednisolone, Carbamazepine*	[33]
		Nifedipine	[34]
Particle size reduction by novel particle engineering	Cryogenic spraying process/spray freezing into liquid	*Danazol*	[39,40]
		Carbamazepine	[41]
	Crystal engineering	*Glibenclamide*	[46]
		Febantel, Itrazonazole	[47]
Solid SEDDS technology	Spray drying, *in situ* salt formation, solidification with polymers	*Nimodipine*	[49]
		Flurbiprofen	[50]
		Dexibuprofen	[51]
		Docetaxel	[52]
		Crucumin	[53]
		Meloxicam	[54]
		Fenofibrate	[55]
		Ibuprofen	[56]
Complexation with cyclodextrins	Freeze-drying, vacuum evaporation, kneading	*Praziquantel*	[61]
		Bifonazole, Clotrimazole	[63]
		Celecoxib	[62]
Polymeric micelles	Dialysis, freeze-drying	*Paclitaxel*	[70]
		Etoposide, Docetaxel, 17-AAG	[71]
		Amphotericin B	[72]
Freeze–dried liposomes	Freeze-drying	*Sirolomus (Rapamycin)*	[76]
		Paclitaxel	[74,77]
Solid lipid nanoparticles	HPH, solvent emulsification-evaporation/diffusion	*All trans-retinoic acid*	[82]
		Tretinoin	[83]

[18,22]. According to Williams et al., particle size reduction to nanosize range involves two processes namely 'bottom-up' and 'top-down techniques'. The bottom-up technologies such as 'controlled crystallization' and 'precipitation after solvent evaporation' start from the molecules which are dissolved and then precipitated by adding a solvent to a non-solvent. Similarly, top–down technologies like 'pearl milling' and 'high-pressure homogenization' are disintegration methods involving wet milling that provide more efficient size reduction than the conventional size reduction techniques [2,23]. The particle size reduction techniques involving powder and particle technology are discussed in this review.

2.1. *Mechanical micronization*

Micronization is a conventional technique for the particle size reduction and is a commonly used method for increasing solubility of BCS class II drugs [18]. It is a simple technique that refers to transfer of coarse drug powder to an ultrafine powder with the mean particle size in the range of 2–5 μm and only a very little fraction of the particles lie below 1 μm size range [23]. Micronization does not increase the equilibrium solubility of the drug itself but it increases the dissolution rate by increasing the surface area to drug ratio by which the active ingredient can dissolve or diffuse from the drug particles. Conventional size reduction of pharmaceuticals is accomplished by mechanical comminution such as crushing, grinding and milling of previously formed larger particles. The size reduction in these processes takes place by pressure, friction, attrition, impact or shearing. Jet mills, ball mills and high-pressure homogenization are commonly used for mechanical micronization of drugs and dry milling in a fluid energy mill (jet mill) is the most preferred micronization technique [24]. All of these methods of size reduction have been reported in various studies to have increased the dissolution and bioavailability of poorly aqueous soluble drugs by decreasing their size and increasing the surface area of the drugs.

2.1.1. *Jet milling*

A fluid jet mill uses the energy of the fluid (high pressure air) to achieve ultra fine grinding of pharmaceutical powders (Fig. 2). It has several advantages of being a dry process, size reduction of micron-sized particles with narrow size distributions, absence of contamination and is suitable for heat sensitive drugs [25]. In a study conducted by Jinno et al., the *in vitro* dissolution rate of a poorly soluble drug cilostazol was improved by milling and a moderate enhancement of bioavailability was observed in absorption from cilostazol suspension produced by jet milling [26]. However in the same study, remarkably higher enhancements in bioavailability were observed for a nanocrystal suspension of cilostazol, suggesting that reduction of drug particle size to the nanometer-size range is more effective in enhancing the bioavailability of drugs with poor aqueous solubility. In another study, a BCS class II drug, ibuprofen was also subjected to simultaneous micronization through continuous fluid energy milling, resulting in the improvement of dissolution rate while avoiding disadvantages of conventional micronization such as agglomeration, poor flowability, loss of expected large

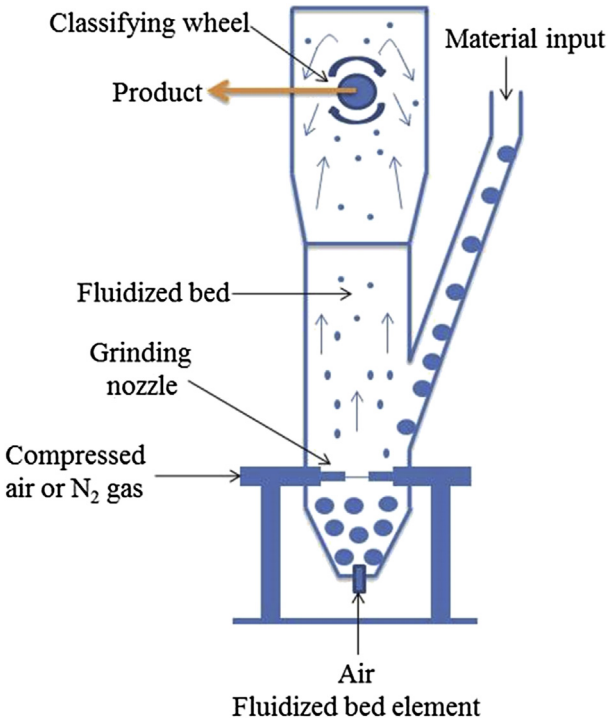

Fig. 2 – Schematic diagram of a pharmaceutical jet mill.

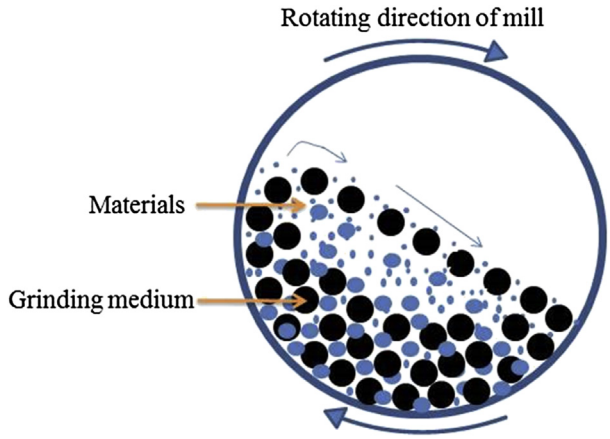

Fig. 3 – Schematic diagram of a ball mill.

surface area, low bulk density and insignificant or no dissolution improvement [27]. In this process, ibuprofen powders were micronized to the particle size range of 5–10 μm through the process of simultaneous micronization. The increase in dissolution behavior is attributed to the increased particle surface area, as per the *Noyes–Whitney* equation.

2.1.2. *Ball milling*

A pharmaceutical ball mill is usually a cylindrical crushing device that is used for grinding of pharmaceutical powders by rotation around a horizontal axis. The device is partially filled with the material to be ground plus the grinding medium usually ceramic balls, flint pebbles or stainless steel balls (Fig. 3). Back in 1995, Liversidge and Cundy reported that ball milling could be used for preparing nanoparticulate formulation of a poorly water soluble drug, danazol, which showed enhanced bioavailability in beagle dogs when compared to that of aqueous suspension of conventional danazol particles [28].

Ball milling technique for size reduction is also essential in preparing amorphous powders of drugs if milled together with polymeric compounds as suggested by Patterson et al. in 2006. Preparing amorphous form is an essential approach to improve dissolution of drugs since the amorphous state are more readily soluble than the crystalline form because of higher Gibbs free energy in the amorphous form [29]. In their work, Patterson et al. used three poorly water soluble drugs (carbamazepine, dipyridamole and indomethacin) with a polymer polyvinyl pyrrolidone K30 (PVP K30) at a 1:2 drug polymer ratio to prepare glass solutions of the drugs. The glass solution was referred to an amorphous solid in which the solute (drug) was dispersed in the solid solvent (polymer) on a molecular level [30]. Use of a ball mill to prepare the glass solutions was found to be effective in producing a single homogenous amorphous phase, and the dissolution rates were also found to be higher when compared to the glass solutions of the same drugs prepared by spray drying. This suggests the applicability of ball milling technique to produce homogenous amorphous preparations of poorly soluble drugs, and can be an important approach to improve the solubility of such drugs.

2.1.3. *High pressure homogenization*

High pressure homogenization (HPH), a top down technology, is a widely used technique for preparing nanosuspensions of drugs with poor water solubility. Its use has been reported to improve the dissolution rate and bioavailability of several poorly water soluble drugs such as spironolactone, budesonide and omeprazole by effective size reduction to the nanosize range [17]. HPH has also been known to overcome the drawbacks of conventional size reducing methods such as amorphization, polymorph transformation and metal contamination due to high mechanical energy associated with conventional milling processes [31]. Due to this reason, HPH is particularly advantageous for comminution of drug particles. In HPH, the solid to be comminuted is first dispersed in a suitable fluid and then forced under pressure through a nanosized aperture valve of a high pressure homogenizer, which is essentially a bottleneck through which the suspension passes with a high velocity, and then suddenly experiences a sudden pressure drop, turbulent flow conditions and cavitation phenomena (Fig. 4). Thus comminution of particles is achieved by collision of particles with each other, collision with the homogenizer and by cavitation and the two factors that influence homogenization in this process are the pressure drop and the number of passes across the homogenizer [17,31,32]. HPH is compatible for use in both aqueous as well as non-aqueous fluid media and attempts have been made to use different pressurized fluids like carbon dioxide and 1,1,1,2-tetrafluoroethane so that these fluids can undergo residue-free evaporation upon pressure release and the micronized products can be directly recovered in the form of a dry powder as suggested by Kluge et al. in their study [31].

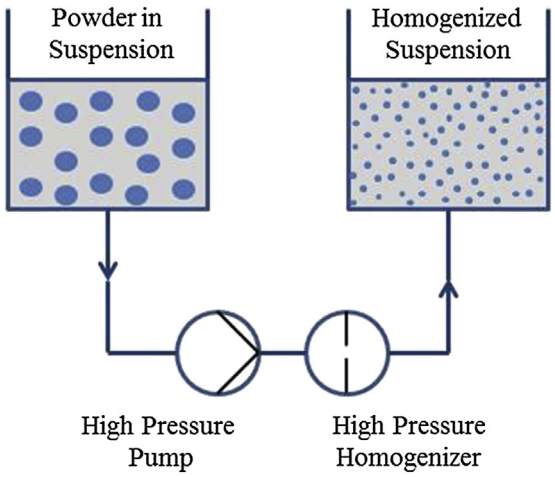

Fig. 4 – Scheme of high pressure homogenization process (adopted from Kluge et al. [31]).

Together with their applicability in oral dosage forms, HPH has also been widely used in formulating parenteral formulations of poorly water soluble drugs. This process is considered suitable for parenteral formulations since there is no risk of contamination from milling media and the high pressure environment is able to protect from microbial contamination by eliminating potential contaminants [2]. It was successfully demonstrated by Muller and Peters in 1998 that HPH can be used to formulate nanosuspensions of poorly soluble drugs like prednisolone and carbamazepine that could be considered acceptable for parenteral administration [33].

Hecq et al. have reported that HPH was successful in formulating nifedipine as nanoparticles, which showed enhanced dissolution as well as improved saturation solubility and have suggested HPH as a simple, adequate and easily scaled up technique that can have general applicability to many poorly water soluble drugs [34]. This technique is thus useful in oral as well as parenteral drug formulations and is remarkably efficient in enhancing saturation solubility, dissolution as well as bioavailability of poorly soluble drugs.

2.2. *Engineered particle size control*

Although conventional size reduction techniques are convenient and simple, they are sometimes undesired and unfavorable depending upon the types of drug substances and the particles to be micronized. Conventional methods of size reduction are usually known to have certain typical disadvantages of being less efficient due to high energy requirements, posing threats of thermal and chemical degradation of drugs and the end products being not uniform in the particle size distribution [35,36]. Conventional milling techniques, in particular, are considered to be uncontrolled processes that have limitations in controlling size, shape, morphology, surface properties and electrostatic charge and lead to heterogeneous particle shapes or even agglomerated particles as the end product [24]. To overcome these limitations and to specifically control the particle properties, several particle engineering techniques have been developed as an alternative and are utilized to produce the required particle size and carefully control the particle properties. These novel particle engineering technologies such as cryogenic spray processes and crystal engineering processes are novel methods of producing nanosized drug particles as an attempt to reduce particle size and enhance solubility, dissolution and hence the bioavailability of drugs with poor aqueous solubility.

2.2.1. *Cryogenic spray processes*

Cryogenic spray processes are novel size reduction techniques that can be used to enhance the dissolution rate of poorly soluble drugs by creating nanostructured amorphous drug particles with high degree of porosity at very low temperatures. These cryogenic processes can also be followed by various drying processes like spray freeze drying, atmospheric freeze drying, vacuum freeze drying and lyophilization to produce dry powders [17,37]. There are several types of cryogenic spray techniques like: spray freezing onto cryogenic fluids, spray freezing into cryogenic liquids (SFL), spray freezing into vapor over liquid and ultra-rapid freezing to produce smaller drug particles with improved wettability [17].

In conventional spray freezing into vapor process, halocarbons, chlorofluorocarbons and liquid nitrogen can be as cryogenic media and the feed solution is atomized through a nozzle positioned at a distance above the boiling refrigerant and the atomized droplets fall into the refrigerant and are immediately frozen on contact with the cryogen. The frozen powder is then collected and lyophilized to remove the solvent. However with this process, the limitations lie with the use of chlorofluorocarbons as they deplete the ozone layer, and even some alternatives to chlorofluorocarbons (such as hydrofluoroalkane) can solubilize the active pharmaceutical ingredient (API) and decrease the potency of the powder formulation [38]. With spray freezing into vapor process, a gradual agglomeration and solidification of droplets has been reported because the atomization occurs into the nitrogen vapor above the liquid gas which may sometimes result in broad particle size distributions and non-micronized dry powders [4].

SFL is a new cryogenic spray process that was developed to overcome problems associated with conventional cryogenic spray processes in 2001 at the University of Texas [23]. In SFL, an aqueous or organic solution, emulsion, or suspension containing a drug and excipients can be directly atomized into a compressed liquid (such as compressed fluid CO_2, helium, propane, ethane) or the cryogenic liquids (such as nitrogen, argon, or hydrofluoroethers) [4]. The atomization of the feed solution into a cryogenic liquid produces frozen nanostructured particles which, upon lyophilization, give dry, free flowing micronized powders. SFL is an efficient method to produce nanostructured particles with amorphous structure, high surface area and enhanced wettability that is considered advantageous to enhance the dissolution rate of a poorly soluble drug [37].

In a study conducted by Rogers et al. in 2002, SFL was found to be superior in enhancing the aqueous dissolution of danazol, a drug with poor aqueous solubility, when compared with conventional size reduction methods like co-grinding and slow freezing [39]. SFL was reported to be a novel particle technology for engineering pharmaceutical powders for

various routes of drug delivery by enhancing the dissolution properties of poorly water soluble drugs. It has also been reported that after the SFL of poorly soluble drugs like danazol, atmospheric drying process is more favorable than vacuum freeze drying as a commercial method for enhancing the aqueous dissolution in the pharmaceutical industry [40]. In a study conducted on comparative SFL of carbamazepine with two different liquid systems: organic solvent (acetonitrile) system and organic (tetrahydrofuran)/aqueous co-solvent system, SFL with acetonitrile was found to have several advantages over the organic/aqueous co-solvent system [41]. It suggests that SFL with organic solvent (such as acetonitrile) system can be an effective particle engineering process to improve dissolution rates of poorly water soluble drugs for oral delivery. SFL has also been proved to be successful in preparing oral and pulmonary formulations of drugs like danazol and itraconazole by enhancing the dissolution rates and thus increasing bioavailability of these drugs in animal experiments [42]. Thus, SFL is also one among the promising particle technologies to enhance the aqueous dissolution properties of drugs that are insoluble in water and cause difficulties in designing pharmaceutical formulation.

2.2.2. *Pharmaceutical crystal engineering*

Crystal engineering is a new and emerging method of controlled crystallization that can be described as the 'exploitation of noncovalent interactions between molecular or ionic components for the rational design of solid–state structures that might exhibit interesting electrical, magnetic, and optical properties' [43]. Crystal engineering technologies can be applied to pharmaceutical substances to improve drug solubility through controlled crystallization processes such as by forming co-crystals, metastable polymorphs, high energy amorphous forms and ultrafine particles [44].

Pharmaceutical co-crystals are an additional class of crystalline solids, which when incorporated into dosage forms, can provide options for improved properties. Formation of co-crystals can be an alternative to salt formation in case of neutral compounds or those having weakly ionizable groups [43]. In one of such cases, a crystalline molecular complex (glutaric acid) and an API was identified and used to demonstrate an improvement in the oral bioavailability of the API in dogs. The use of the co–crystal increased the aqueous dissolution rate by up to 18 times as compared to the homomeric crystalline form of the same drug [45].

Another application of crystal engineering in pharmaceutical technology is the preparation of pharmaceutical nanocrystals. Pharmaceutical nanocrystals are nanoparticles with a crystalline character which are gaining popularity because of their ability to increase the saturation solubility and the dissolution velocity by virtue of surface area enlargement. Nanocrystal technology has advantages of enhancing the solubility and dissolution which helps in fast absorption and fast onset of action of the drug and moreover allows the formulation to be developed without the use of surfactants, which is sometimes advantageous in reducing the undesired effects of some excipients [21]. Drug nanocrystals can also be stabilized by use of a lipid to prepare lipid nanocrystals while enhancing the solubility and drug delivery. In a recent work by Kumar et al., novel lipid nanocrystals were developed for glibenclamide, which showed enough promise for lipid nanocrystals as an approach to enhance the dissolution and maintain stability of the model drug [46].

Several solvent-free drug crystal engineering methods are suggested *viz* like wet milling, indirect sonication and ultrasonic melt precipitation [47]. In presence of a self-emulsifying excipient gelucire 44/14, all these three methods were able to reduce the drug crystal size and enhance the dissolution of model drug febantel. But in case of another model drug itraconazole, only ultrasonic melt precipitation was able to reduce the size but this method also produced a fraction of substances in the amorphous state which was desirable.

3. Other particle technologies for improved bioavailability

3.1. *Solid self-emulsifying drug delivery systems*

Solid self-emulsifying drug delivery systems (S-SEDDS) are gaining popularity as a novel particle technology to improve solubility behavior of lipophilic drugs and drugs with poor aqueous solubility. S-SEDDS technology is novel in a way that they provide an effective alternative approach to the conventional liquid SEDDS for formulating drugs with poor aqueous solubility. S-SEDDS are formulated by incorporation of liquid or semisolid self-emulsifying (SE) ingredients into powders or nanoparticles by different solidification techniques (e.g. 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 [48]. S-SEDDS are solid at room temperature and they can be exploited into various dosage forms that are solids with SE properties like SE capsules, SE solid dispersions, dry emulsions, SE pellets and tablets, SE microsphere, SE nanoparticles, SE suppositories and SE implants. S-SEDDS 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 leading to high production costs, are difficult to use, have incompatibility problems with shells of soft gelatin and have problems in storage [49,50].

S-SEDDS has been widely studied for the enhancement of solubility and dissolution of various poorly soluble drugs and the most common method of S-SEDDS preparation has been spray drying technique plus the use of a solid carrier. Spray drying technique, together with the use of solid carriers like dextran, gelatin, Aerosil® and lactose, has been successfully used to prepare S-SEDDS of drugs like nimodipine, flurbiprofen, dexibuprofen, docetaxel and curcumin with enhanced oral bioavailability [49,50,51,52,53]. An alternative method of S-SEDDS preparation was adopted by Agarwal et al. in their study where the powdered self-emulsified lipid formulation of meloxicam was obtained by simple trituration of liquid SEDDS with an adsorbent solid (1:1 mixture of silicon dioxide and magnesium aluminum silicate) in a mortar until a homogenous blend was formed [54]. The powdered SEDDS

formulation showed higher bioavailability in beagle dogs when compared with that of commercially available tablets. In another study, S-SEDDS of fenofibrate was formulated by solidification of the molten solution of the oily phase, surfactant and co-surfactant and drug mixture with a polymer (PEG 6000), where the S-SEDDS formulation with 10% w/w fenofibrate loading showed as much as 20-fold increase in the dissolution profile [55].

These numerous 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. However, certain aspects of S-SEDDS such as oxidation of vegetable oils, physical aging associated with glyceride and interaction between drugs and excipients must be considered while formulating future S-SEDDS [53]. In a study, the limitations of S-SEDDS were pointed out 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 [56]. In the same study, immediate release self-emulsifying tablets of ibuprofen were designed with the use of an acid-soluble powderizing carrier, Fujicalin® (granulated dibasic calcium phosphate) to facilitate the drug release process in the stomach, which suggested a novel approach to prepare immediate release S-SEDDS.

3.2. *Complexation with cyclodextrins*

Cyclodextrins are a family of cyclic oligosaccharides derived from starch containing (α-1,4)-linked α-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 α-D-glucopyranose units namely α, β, γ, δ and ε cyclodextrins with six, seven, eight, nine and ten (or more) (α-1,4)-linked α-D-glucopyranose units respectively [57]. 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 [58].

Cyclodextrins are extensively reviewed for their wide applications in the pharmaceutical formulation design including its major use as a solubilizer for poorly soluble drugs [57,59,60]. In pharmaceutical formulation processes, cyclodextrins are useful solubilizers, enabling both liquid oral and parenteral dosage forms and can increase the apparent solubility of the compound leading to the corresponding increase in dissolution and bioavailability. The major mechanism associated with the solubilization potential of cyclodextrins is the inclusion complex formation while non-inclusion complexation and super saturation may also contribute to the solubilization process [57]. 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 of the complex such as resulting particle size, amount of complex formation and the degree of amorphous nature of the end product [58,59]. Thus, the choice of preparation method is crucial when designing drug-cyclodextrin complexes. In terms of toxicology and kinetics of solubility enhancement, cyclodextrins are considered to have advantage over organic solvents as solubilizers, however, major limitations associated with drug formulation with cyclodextrins is the size of the dose and adjusting the appropriate amount of cyclodextrins for proper drug-loading [58].

Many studies have been conducted on cyclodextrin as a solubilizer for poorly soluble drugs. In a study conducted with the aim of improving aqueous solubility of praziquantel, the drug complexes with α, β and γ cyclodextrins were prepared by freeze drying method and then evaluated for the solubility improvement. Although the dissolution of praziquantel from all three complexes were greater than that of the pure drug, the drug complex with β-cyclodextrin had the optimum stability constant suggesting that β-cyclodextrin complex can be the preferred complex for other formulations as well [61]. β-cyclodextrin inclusion complex prepared by kneading method has also been shown to be effective in enhancing the dissolution rate of celecoxib, where the inclusion complexes showed higher dissolution rate and dissolution efficiency than the corresponding physical mixture and the pure drug [62].

An amphiphilic β-cyclodextrin has also been mentioned in literature for its use in preparation of highly loaded nanoparticulate systems to facilitate the parenteral administration of poorly soluble drugs like bifonazole and clotrimazole [63]. Inclusion complexes of drugs and the cyclodextrin were prepared by co-lyophilization technique, involving evaporation under vacuum of ethanolic phase and then lyophilization of aqueous phase. Nanospheres were successfully prepared from these inclusion complexes without use of surfactants and with high entrapment values. Thus use of a drug and amphiphilic β-cyclodextrin inclusion complexes can be a novel method of designing nanospheres for parenteral formulation of poorly soluble drugs.

The results of these studies show that cyclodextrins, especially β-cyclodextrin, can be a promising excipient in pharmaceutical particle technology to improve the solubility behavior of drugs with poor aqueous solubility.

3.3. *Polymeric micelles*

After being proposed as possible drug carriers for the first time by Bader et al. in 1984 [64], polymeric micelles have emerged as 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 evade scavenging by the mononuclear phagocyte system [65]. 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)

[65,66]. 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 [67]. 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 [68]. 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 non-spherical structures including rods and lamellae [68].

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 [66,68]. 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 co-polymer 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 [65,68,69]. 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 [68].

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 [66].

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. Along with its applications in the delivery of a large array of chemically diverse therapeutic compounds, polymeric micelles have been the subject of interest for delivery of poorly soluble anticancer drugs. High bioavailability, high solubilization and long-term stability of an anticancer drug, paclitaxel, were observed when the drug was solubilized into hydrotropic polymeric micelles by dialysis method [70]. The amphiphilic block copolymers consisted of a micellar *shell*-forming poly(ethylene glycol) (PEG) block and a *core*-forming poly(2-(4-vinylbenzyloxy)-*N*,*N*-diethylnicotinamide) block, suggested as a novel polymeric micelle system for solubilizing and enhancing the bioavailability of poorly soluble anticancer drugs. In another study, poly(ethylene glycol)-block–poly(D,L-lactic acid) (PEG-b–PLA) micelles were used to deliver multiple poorly water soluble anticancer drugs: paclitaxel, etoposide, docetaxel and 17-allylamino-17-demethyoxygeldanamycin (17-AAG) [71]. The PEG-b–PLA micelle system proved to be a novel, single carrier system for delivery of poorly soluble drugs that was able to solubilize all the chemotherapeutic agents alone or in combination with other drugs at clinically relevant levels. This polymeric system was suggested as a safer and less toxic alternative to common formulations that use vehicles like dimethyl sulfoxide, ethanol and tween 80 that are often undesired due to their toxicities. Therapeutic agents other than anticancer drugs can also be solubilized by using polymeric micelles. An antifungal drug, amphotericin B, has been solubilized successfully by the use of micelles of poly(ethylene oxide)-block-poly(β benzyl-L-aspartate) where the drug was loaded into the micelles using dialysis procedure [72]. The resulting drug-loaded micelle system was found to have reduced hemolytic activity of amphotericin B and the micelles could be kept in a freeze-dried state which was easily reconstituted with water to provide intact drug-loaded micelles that remained non-hemolytic.

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.

3.4. *Freeze-dried liposomes*

Liposomes are phospholipid vesicles, comprising a phospholipid bilayer surrounding an aqueous compartment and can dissolve lipophilic drugs in their lipid domain [12]. Because of their biphasic characteristics and diversity in design and composition, they offer a dynamic and adaptable technology for enhancing drug solubility [73]. 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 [74]. However, one of the serious limitations with applicability of liposomes as drug delivery systems is associated with its poor stability during storage [75,76]. 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. Freeze-dried liposomal formulation of

sirolimus (rapamycin) was found to have superior stability after reconstitution when compared to the conventional suspension product of the same drug and the stability of the formulation was even better when dextrose was used as lyoprotectant during freeze-drying [76]. It suggests that freeze-drying can be an effective approach to deal with the stability problems of liposomal formulations and variety of sugars such as dextrose, sucrose and trehalose can be used as lyoprotectants. This type of approach has been reported to be used for liposomal formulation of paclitaxel using sucrose as a lyoprotectant [74,77,78]. Freeze-dried liposome system was used to design a novel lyophilized liposome-based paclitaxel formulation that was sterile, stable and easy to use [74]. In another study, paclitaxel incorporated liposomes were prepared using polyethylene glycol 400 in the hydration medium of liposome which aided the solubilization as well as entrapment efficiency of paclitaxel [77]. The liposomal formulation was found to have enhanced solubility as well as enhanced physicochemical stability after freeze drying. Therefore, drugs can be formulated with liposomes, a polymer and a lyoprotectant and then freeze-dried to obtain a dry, lyophilized powder. Polymers like PEG are used in some cases for solubilizing the drug in the liposomal solution. A PEGylated liposomal formulation has been reported to enhance the aqueous solubility Paclitaxel and also improve the *in vivo* bioavailability in rats [78].

Freeze-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 freeze-drying 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.

3.5. *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 [79]. 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 [80].

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 ultra sound 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 [79,80].

Mehnert and Mader, in their review, have described several advantages as well as disadvantages of SLN technology [81]. 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 [82]. In another study aimed to prepare SLNs of a hydrophobic drug, tretinoin, by emulsification–ultrasonication 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 [83]. 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.

4. 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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