Biomaterials Connect
2025, Vol. 1, Cite as: doi:10.x/journal.x.x.x

SCIFINITI PUBLISHING

OPEN ACCESS

Review Article

Novel Nano-Technologies to Enhance Drug Solubility, Dissolution and Bioavailability of Poorly Water-Soluble Drugs

Komal Parmar[1]✉, Rajendra Patel[2]

[1]ROFEL Shri G.M. Bilakhia College of Pharmacy, Rajju Shroff ROFEL University, Vapi, India
[2]Department of Pharmaceutical Sciences, Gujarat Technological University, Ahmedabad, India

Abstract

For any drug to be therapeutically efficacious it must enter the systemic circulation and in order to do so, the administered drug must be dissolved in the GIT. Approximately 40 % of drugs developed in the past and about 70-90 % of drugs in development were found to be poorly water soluble. Various pharmaceutical particle technologies are applied to enhance the aqueous solubility of poorly soluble drugs that restrict *in vivo* bioavailability upon oral administration due to their low dissolution rate in gastrointestinal fluids. The approach involves from traditional to modern particle technologies such as micronization, complexation, nano-suspension, and others. The employed technologies modify the drug's solubility properties, produce drug forms that are readily soluble in water and can be easily formulated into different dosage forms. The aim of this review paper is to summarize the key aspects of currently used particle technologies to enhance the solubility, dissolution and bioavailability of poorly water-soluble drugs.

Keywords

particle technology; drug solubility; poorly water-soluble drug; dissolution of drugs; bioavailability of drugs

Introduction

Drug solubility is the maximum concentration of the drug solute dissolved in the solvent under specific condition of temperature, pH and pressure. The solubility of a drug in saturated solution is a static feature, whereas the rate at which it dissolves is a dynamic property that is more directly related to bioavailability. The pace and degree of medication absorption, as well as its bioavailability, are governed by solubility, dissolution, and gastrointestinal permeability [1].

Oral treatment of medications is still the preferred method of delivery due to its numerous benefits, including ease of administration, high patient concordance, and economic viability. A medication first dissolves into gastrointestinal fluids in order to absorb in the systemic circulation and reach its site of action when delivered orally. The number of poorly soluble drugs has been greatly increased by combinatorial chemistry, computational molecular modelling, and high-throughput screening in drug discovery. Around 40% of the existing pharmaceutical drugs and about 70-90% of the drugs in the research pipeline are found to be poorly water soluble [2].

The absorption of the drugs from the gastrointestinal tract (GI) after oral administration is governed by the aqueous solubility which is an essential property for any drugs [3, 4]. The most significant challenges currently faced by many pharmaceutical industries is to improve solubility and bioavailability of poorly soluble drugs. Novel particle approaches adopted to enhance the solubility, dissolution and bioavailability properties of poorly soluble drugs are different from available conventional pharmaceutical techniques [5].

* Corresponding Author: Dr. Komal Parmar
ROFEL Shri G.M. Bilakhia College of Pharmacy, Vapi, India
komal.parmar2385@gmail.com; Orcid ID: 0000-0001-8564-163X
Tel.: +91 9714037405

Biopharmaceutics classification system (BCS)

The Biopharmaceutics classification system is a scientific framework for classifying drugs on the basis of their solubility and permeability. A drug compound is considered to be highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media within the pH range of 1 - 6.8 at a temperature of 37 ± 1°C. The 250 mL volume estimate is derived from standard bioequivalence study protocols that recommend drug product administration to fasting human volunteers with an 8 fluid ounce glass of water. Permeability limit of any drug is determined by measuring rate of mass transfer of a drug through human intestinal membrane or non-human systems such as animal or *in-vitro* culture methods. A drug agent is found to be highly permeable when the degree of absorption in humans is measured to be >/= 90% of the given dose in comparison to an intravenous dose [6]. BCS is considered as an important tool in the development of oral drug products. Two major attributes of drugs are taken into consideration by BCS classification, i.e. solubility and intestinal permeability which control the extent of absorption after oral administration of solid oral dosage form and finally its bioavailability [7].

BCS Class I drugs have high solubility and high permeability so they are well absorbed from the gastrointestinal tract and have high bioavailability after oral administration. When dissolved, BCS class II medicines show poor water solubility, but are well absorbed from the GIT. Because the rate of *in-vivo* dissolution is often the rate limiting step in the absorption of class II drugs, improving the solubility and dissolution properties might prove useful to improve their bioavailability. BCS class III medicines show high solubility and low permeability, making them difficult to pass through bio membranes. Bioavailability is restricted by permeability rate; however, dissolution is likely to happen quickly. Addition of absorption enhancers in immediate release solid dosage formulation for class III drug is viable option to improve their permeability. Drugs in BCS class IV category show low water solubility and membrane permeability, making them poor candidates for formulation development because improving solubility and dissolution alone may not be enough to increase the bioavailability. Unfortunately, most new developed drugs are poor water soluble, hydrophobic molecules or in other terms; Class II or Class IV drug compounds [8].

Science of pharmaceutical powders

Powder technology has evolved from an art form to a science with applications in the culinary, chemical, and pharmaceutical industries [9]. Powder technology is an important practice in the pharmaceutical sector because most pharmaceutical active components and excipients are found in powder form. Pharmaceutical manufacturing processes involves alteration in powder particles characteristics for improvement in their solubility and dissolution properties of formulated drug products. Pharmaceutical powder engineering is concerned with analyses of formulations, additives, raw materials, and processes in order to obtain desired particle characteristics [10, 11]. Pharmaceutical powder technology deals with surface engineering areas explored through surface chemistry and surface morphology. For efficient dosage form design and development; physical and chemical properties of powder are important. Ultimately these properties need to be optimized in order to develop a formulation that is readily soluble in the GIT and bioavailable [12].

Particle technologies for solubility improvement of drugs

The application of pharmaceutical particle technologies serves to improve the poor aqueous solubility of drug compounds, which hinders *in vivo* bioavailability as a result of their low dissolution rate in the gastrointestinal fluids post oral administration [13]. Physical changes to drug materials such as micronization and crystal habit modification, are common methods for increasing drug solubility [14]. In conjunction with traditional micronizing techniques, particle engineering deals with novel processes involving nanotechnology in order to improve drug solubility [5].

This review focuses on several particle technologies, including traditional size reduction approaches as well as recent innovative methods that can be employed for the production of oral formulations for drugs with low water solubility. A brief account of various pharmaceutical technologies is demonstrated in Figure 1 and Table 1 [14-41].

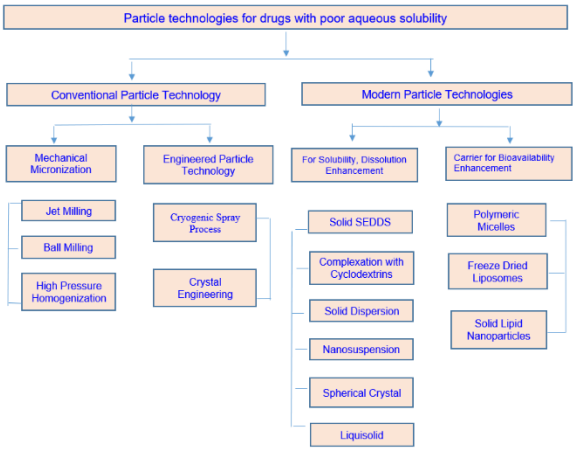

Figure 1: Pharmaceutical Particle Technologies used for solubility enhancement of poorly soluble drugs

Table 1: Particle Technologies employed for improving solubility properties of poorly soluble drugs

Particle Technology	Method	Drugs	Reference
Mechanical Micronization	Jet milling	Cilostazol	[15]
		Dienogest	[16]
		Itraconazole	[17]
		Bosentan Hydrate	[18]
	Ball milling	Danazol	[19]
	High pressure homogenization (HPH)	spironolactone, budesonide and omeprazole	[14]
		Prednisolone, Carbamazepine	[20]
		Curcumin	[21]
Engineered Particle Technology	Cryogenic spray process	Tacrolimus	[22]
		Carbamazepine	[5]
		Itraconazole	[23]
	Crystal engineering	Temozolomide	[24]
Modern Particle Technologies For solubility & Dissolution Enhancement	Solid SEDDS	Paclitaxel	[25]
		Gliclazide	[26]
		Bambuterol hydrochloride	[27]
	Complexation with cyclodextrins	Flavonoids	[28]
		Temozolomide	[29]
	Solid dispersion	Ticagrelor	[30]
	Nano Suspension	Loratidine	[31]
		Naringenin	[32]
	Spherical crystal	Naproxen	[33]
	Liquisolid	Carbamazepine	[34]
Particle Technology for Bioavailability Enhancement	Polymeric micelles	Paclitaxel	[35]
		Etoposide, Docetaxel, 17-AAG	[36]
		Epirubicin	[37]
	Freeze dried liposomes	Sirolomus (Rapamycin)	[38]
		Prednisolone	[39]
	Solid lipid nanoparticles	Irbesartan	[40]
		Norfloxacin, Miconazole	[41]

Conventional particle technologies

The reduction of particle size is considered as one of the easiest approaches to improve the solubility properties of poorly soluble drugs. When the particle size is reduced, the larger surface area enables an increase in the surface area to volume ratio, consequently augmenting the surface area of the drug that is exposed to the solution. Thus, technology for reducing particle size is commonly used to improve the bioavailability of such drugs [3]. Many approaches, such as polymorphism, salt formation, cocrystallization, and excipient addition, can marginally increase the solubility of insoluble drugs, but they are not commonly successful in enhancing bioavailability [42]. As specified in the popular Noyes Whitney equation from the late 1800s, the decrease in particle size and consequent increase in particle surface area improves the material's dissolving rate [16]. When the particle size is in nanoscale, the solubility increases rapidly, as per the Ostwald-Freundlich Equation (Equation (1)) [3, 43]. This is because shrinking the particle size boosts the solvation pressure, increasing solubility while simultaneously disrupting the solute-solute association that facilitates the solubilization mechanism [44].

$$log\ \frac{Cs}{C\infty} = \frac{2\,\sigma\,V}{2.303RT\rho r} \qquad \text{eq 1}$$

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, p is density of solid, and r is particle radius.

Conventional particle size reduction is considered as a basic size reduction method. Now, there are several particle technologies like nanotechnology and nanosizing for particle size reduction which are broadly considered for development of drug formulation with poor water solubility [42, 45, 46].

Mechanical micronization

Micronization is conventional particle size reduction method and is a conventionally used method for ameliorating the solubility of drugs [42]. In mechanical micronization technique, coarse drug powder is converted into ultrafine powder with a mean particle size of 2 to 5 µm and a very small proportion of particles have a size below 1 µm. Although micronization does not affect the drug's equilibrium solubility, it does accelerate the amount of dissolution by increasing surface area of the drug, which allows the dissolution/diffusion process into the aqueous phase [47]. Mechanical size reduction methods, such as crushing, grinding, and milling of bigger particles, is used to reduce the size of drug particles. Pressure, friction, attrition, abrasion, or shearing, are the mechanism involved in the above-mentioned methods of size reduction. The mechanical micronization of drug substances commonly employs jet mills, ball mills, and high-pressure homogenization, with jet mills being the most favored technique

for micronization [48]. These size reduction methods are previously documented in various research works in order to increase the dissolution rate as well as bioavailability of poorly aqueous soluble drugs, by reducing the particle size and thereby increasing their surface area.

Jet milling

Drug particle size can be reduced from a range of 20-100 µm to less than 10 µm by jet milling. A fluid jet mill uses the energy of the fluid to achieve ultrafine grinding of medicinal powders (high pressure air) (Fig. 2). It has various advantages, including being a dry process, size reduction with narrow size distributions of micron-sized particles, and the absence of contamination, making it excellent for heat-sensitive pharmaceuticals [49]. In a study conducted by Jinno et al, milling enhanced the *in vitro* dissolution rate of a poorly soluble drug, Cilostazol. A moderate increase in bioavailability was reported in cilostazol suspension produced by jet milling. However, in the same study, cilostazol nanocrystal suspension had much higher bioavailability, demonstrating that lowering the particle size of the medication to the nm size range is more beneficial in boosting the bioavailability of drugs with limited water solubility [15]. Dienogest is a synthetic progesterone which is orally active and indicated in endometriosis, hysteromyoma and uterine leiomyoma therapy. In the study conducted by Pankaj and co-researchers, Dienogest Oral Tablet is being developed by micronization process that typically involves size reduction of solid drug particles to 1 to 10 microns by using attrition (Fluid Energy or Air Jet Mill) methods. Dienogest's micronization improved its multimedia dissolution rate compared to non-micronized content [16].

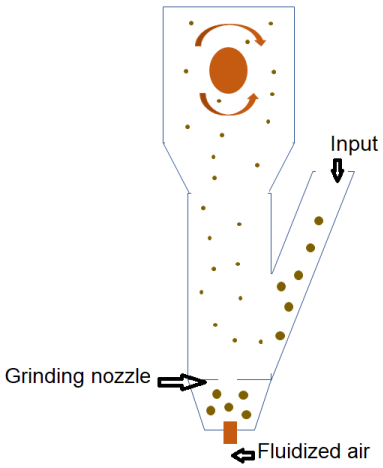

Figure. 2 Jet Mill Functioning in Size Reduction Process

Ball milling

A pharmaceutically employed ball mill is typically a cylinder-based grinding system that is utilized to grind and blend the bulk coarse material into nanosized particles using different sized balls, rotate around a horizontal axis to grind pharmaceutical powders. Grinding media, such as ceramic balls, flint pebbles, or stainless-steel balls, is partially put into the apparatus with the material to be pulverized (Fig. 3). The quantity of balls and beginning material determines the volume of the vessel filling and the speed of the milling operation. Although there are differences in the literature, the balls and starting material typically take up 50% and 25% of the overall volume of the vessel, respectively [47].

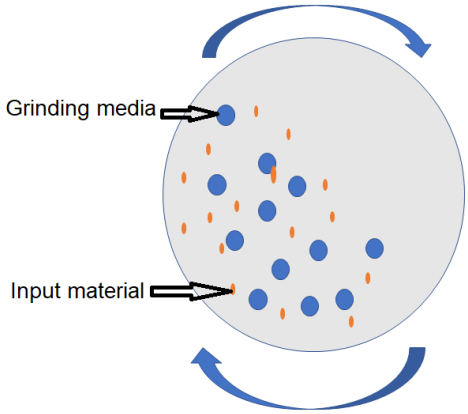

Figure. 3 Ball Mill Functioning in Size Reduction Process

Ball mill is classified in two groups depending on their mechanism mode: direct and indirect milling. In the first case direct milling, the particles are directly influenced by rollers or mechanical shafts and transmit kinetic energy. In the second case indirect milling, the kinetic energy is transmitted first to the body of the mill and then to the grinding medium. In the field of cellulose ball mills are the most frequently used and they can be further divided into three groups based on design: Tumbler ball mills, Vibratory mills and planetary mills. A Tumbler mill consists of a cylinder revolving around its longitudinal axis, partially filled with steel balls. The efficiency of the method primarily depends on the diameter of the mill in this type of instrument. Larger diameters allow greater fall height and higher energy to be transferred to the balls as a result. The jar carrying the sample and the grinding medium is agitated back and forth at high vibrational frequencies in

vibratory mills. The vibratory frequency, amplitude of vibration, and mass of the milling medium are all important parameters in this scenario. Finally, the vessels in a planetary mill are mounted on a revolving support disc and rotate around their own axes. Again, the size of the vessels is an important factor in the process' efficiency because a longer distance allows for more kinetic energy and thus larger collisions [50]. A modernized variant of the ball mill can be called media milling. It is a typical wet milling technique where drug particles are subjected to a conventional ball milling process in an aqueous or non-aqueous liquid medium in a sufficiently dispersed medium. Grinding balls, also known as milling media, cause mechanical attrition and impaction of dispersed drug particles in media milling. They are made of a range of materials including glass (yttrium-stabilized), zirconium oxide, ceramics, or strongly cross-linked polystyrene resins. Unlike ball milling, where the entire vessel rotates during operation, media milling keeps the vessel fixed [47]. Liversidge and Cundy reported back in 1995 that nanoparticulate formulation of poorly water-soluble medicine can be prepared by using ball milling. When compared to an aqueous suspension of standard Danazol particles, Danazol, a poorly soluble medication, showed better bioavailability in beagle dogs [19]. When milled together with polymeric compounds, the size reduction by ball milling process is also important in the preparation of amorphous drug powders, as suggested by Graeser et al. in 2006. As the amorphous state is more readily soluble than the crystalline form due to higher Gibbs free energy, the preparation of amorphous form is an important approach to enhance drug dissolution [51].

High pressure homogenization

High Pressure Homogenization (HPH) is a top-down technology and this technique commonly used for preparation of nanosuspensions of drugs having low water solubility. High pressure homogenization technique is used for many poorly water-soluble drugs such as spironolactone, budesonide and omeprazole to improve the dissolution rate and bioavailability through successful size reduction to the nanosized range [14]. Various disadvantages have been seen in traditional size reduction methods such as amorphous transformation, polymorphic transformation and metal contamination due to high mechanical energy associated. So, to overcome these problems high pressure homogenization (HPH) technique is established [21]. Due to this cause HPH is especially beneficial for the reduction of drug particles. A sufficient amount of fluids is required to disperse the solid material, which is then put under pressure by a nanosized high-pressure homogenizer, which is essentially a bottleneck through which the suspension moves at a high velocity and then suddenly encounters a rapid decrease in pressure, turbulent flow conditions, and cavitation (Fig. 4). The collision of the particles with each other accomplishes particle comminution. The drop in pressure and the number of passes through the homogenizer are two elements that affect homogenization in this process [14, 52].

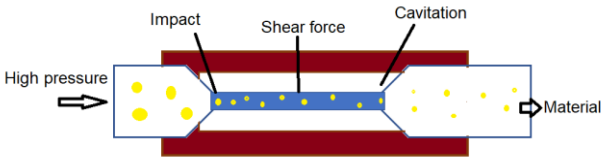

Figure. 4 High Pressure Homogenization Functioning in Size Reduction Process

Engineered particle technology

Even though traditional size reduction methods are simple and convenient, they are not always appropriate depending on the drug or the features of the particle to be micronized. Traditional size reduction procedures are thought to have certain limitations, such as being less successful due to their high energy requirements, the likelihood of drug's thermal and chemical degradation, and a lack of precision in particle size distribution [53]. Traditional milling procedures have limitations in terms of managing form, size, morphology, surface characteristics, and electrostatic charge, and they can result in agglomerates or different particle shapes [54]. Many particle engineering approaches have been formed and are utilised to acquire the appropriate particle size and characteristics in order to solve these limitations.

Cryogenic spray processes

The term "cryogenics" comes from a Greek word that means "cold creation" or "cold manufacturing." Cryogenic spray processes are new methods for improving the dissolution rate of poorly soluble drugs by forming nanosized amorphous drug particles with high porosity at extremely low temperatures, which are then dried using spray freeze drying, atmospheric freeze drying, vacuum freeze drying, and lyophilization to produce dry powder. Spray freezing on cryogenic fluids, spray freezing into vapour over liquid (SFV/L), and ultra-rapid freezing are all cryogenic spray techniques used to create smaller drug

particles with better wettability [14].

Briefly, the drug and the carrier (mannitol, maltose, lactose, inositol, or dextran) are dissolved in water and atomized above the surface of a boiling agitated cryogenic fluid. Further, the solution/dispersion is subjected to spray freezing in cryogenic gas, followed by precipitation of particles with supercritical or compressed fluid CO_2, resulting into frozen solid particles [55]. In spray freezing into vapor over liquid (SFV/L); Fine drug particles with high wettability are formed by the freezing of drug solutions in cryogenic fluid vapours and subsequent removal of the frozen solvent. The atomized droplets normally begin to freeze in the vapor phase during SFV/L before they enter the cryogenic liquid. In the unfrozen regions of the atomized droplet, the drug is supersaturated as the solvent freezes, so fine drug particles can nucleate and develop. The feed solution is atomized by a nozzle placed above the boiling refrigerant, and the atomized feed solution droplets freeze instantly when they come into touch with the cryogen. The solvent is removed from the frozen powder by lyophilization. Liquid nitrogen, chlorofluorocarbons, and halocarbons are the cryogenic media utilised in the traditional spray freezing into vapour technique. However, downside of this method is use of chlorofluorocarbons as they deplete the ozone layer and when alternatives of chlorofluorocarbons (such as hydrofluoroalkane) is used it can reduce potency of powder formulation as they can solubilize the active pharmaceutical ingredient (API) [55]. Use of nitrogen vapors may lead to wide distributions of particle size and non-micronized dry powders due to gradual agglomeration and solidification of droplets since atomization occurs into the nitrogen vapour above the liquid gas [8].

Ultra rapid freezing: Ultra-rapid freezing is a novel cryogenic technology that involves use of solid cryogenic substances to produce nano-sized drug particles with high surface area and improved surface morphology. When drug solution is sprayed on the surface of solid cryogenic substance, it results in instantaneous freezing followed by subsequent lyophilization (for solvent removal) to form drug powder with increased solubility. The phase separation and crystallization of the pharmaceutical ingredients are prevented by ultra-fast freezing [23]. Solid dispersions of Tacrolimus using poloxamer 407 prepared by an Ultra-rapid Freezing (URF) process shows 1.5-fold increase in AUC. This might be due to enhanced supersaturation characteristics offered by URF process that leads to increased oral absorption of tacrolimus [22].

Pharmaceutical crystal engineering

Crystal Engineering can be defined as 'understanding of intermolecular interactions with respect to crystal packing and the use of such understanding in the design of particles with the desired physical and chemical properties'. Crystal engineering technology can be applied to enhance drug solubility by controlled crystallization processes like formation of nanocrystals, co-crystals, metastable polymorphs, high energy amorphous forms, ultrafine particles, etc [56]. Co-crystal formation can be a better option than salt formation of neutral compounds or weakly ionizable groups [57]. The key problem for Temozolomide, an antitumor drug is discoloration due to hydrolytic degradation at room temperature within a few weeks. In laboratory conditions the Temozolomide co-crystals with oxalic acid, salicylic acid and succinic acid demonstrated outstanding stability for up to one year and in addition to that the succinic acid cocrystal also remains stable in long term stability studies without sign of discoloration [24]. Drug nanocrystals are crystals of drugs smaller than 1μm without any matrix content [58].

The application of crystal engineering in pharmaceutical science is nano co-crystallization that can also be applied to improve the dissolution rate and bioavailability of drugs. In a study, baicalein-nicotinamide (BE-NCT) nanococrystals were produced using a high-pressure homogenization process and tested *in vitro* and *in vivo*. BE-NCT nanococrystals outperform Baicalein (BE) coarse powder in an *in vitro* dissolving test by more than 2-fold. BE-NCT nanococrystals (6.02-fold) had a considerably larger integrated AUC_{0-t} than BE coarse powder (1-fold), BE-NCT cocrystals (2.87-fold), and BE nanocrystals (2.87-fold) after oral administration (3.32-fold) [59]. Wet milling, indirect sonication, and ultrasonic melt precipitation are some of the solvent-free drug crystal engineering techniques that can be applied. Using the self-emulsifying excipient gelucire 44/14, all three approaches were examined for Febantel, and all were able to reduce the size of the drug crystal and improve the drug's dissolution [60].

Solid self-emulsifying drug delivery systems

Solid self-emulsifying drug delivery systems (S-SEDDS) are gaining popularity as a new particle technology for improving the solubility of lipophilic drugs. S-SEDDS technology is groundbreaking in that it provides a cost-effective alternative to classic liquid SEDDS for the formulation of pharmaceuticals with low aqueous solubility. The SEDDS is an isotropic mixture of oils and surfactants, with or without cosolvents, that creates an oil-in-water emulsion spontaneously when gently agitated with water. Because the free energy required to create an emulsion is less than the entropy, it forms fine oil-in-water emulsions with only modest agitation, such as GI motility, when it enters GI media. S-SEDDS are made by employing various solidification processes to combine liquid or semisolid self-emulsifying (SE) materials with powders or nanoparticles (e.g. spray drying, melt granulation, adsorption to solid carriers or melt extrusion) [61]. S-

SEDDS are solid at room temperature and can be utilised in SE capsules, SE solid dispersions, dry emulsions, SE pellets and tablets, SE microspheres, SE nanoparticles, SE suppositories, and SE implants, among other dosage forms. S-SEDDS are commonly made as liquids or as soft gelatin capsules, which are more convenient than regular liquid SEDDs. By producing solid SEDDS, the advantages of SEDDS (i.e. higher solubility and bioavailability) are combined with the advantages of solid dosage types such as lower processing costs, simplicity of process management, high stability, reproducibility, and greater patient compliance [62]. Gliclazide solid-SEDDS morphology from scanning electron microscopy studies showed the presence of spherical granular particles suggesting strong flow capability. X-ray diffraction studies have confirmed the solubilization of the drug in lipid excipients and/or the conversion of the crystalline form of the drug into an amorphous form. *In vitro* dissolution tests have demonstrated increased release of the drug from solid-SEDDS as compare to plain drug and marketed formulations [26]. Some important aspects of S-SEDDS, such as vegetable oils degradation, glyceride-associated physical ageing and drug and excipient reactions, must be addressed when formulating future S-SEDDS formulations [63]. Studies has demonstrated the limits of S-SEDDS, such as heavy adsorption and physical connection of the drug with the carriers, which cause delayed or partial drug release from S-SEDDS [64].

Complexation with cyclodextrins

Cyclodextrins are a type of starch made up of (-1,4)-linked a-D-glucopyranose units with a centre lipophilic chamber and an outside hydrophilic surface. There are six, seven, eight, nine, and ten (or more) (-1,4)-linked -D-glucopyranose units in cyclodextrins with six, seven, eight, nine, and ten (or more) (-1,4)-linked -D-glucopyranose units in cyclodextrins with six, seven, eight, nine, and ten (or more) (-1,4)-linked -D-glucopyra [65]. Cyclodextrins do not penetrate lipophilic membranes with a range of hydrogen donors and acceptors because they are big molecules [66]. Cyclodextrin molecules have shaped like truncated cones with a central hydrophobic cavity and a hydrophilic surface, so cyclodextrin can integrate a wide range of compounds to form host-guest complexes [67]. The apparent solubility of many lipophilic drugs is reported to be increased by preparation of non-covalent inclusion complexation with cyclodextrins. Cyclodextrins are crystalline complexing compounds that are used in pharmaceutical formulations to boost API solubility, bioavailability, stability, mask drug colour and taste, and prevent gastro-intestinal discomfort.

Inclusion complexes are created when the "guest" molecule normally contains a drug that partially or entirely goes inside the "host's cavity." As a host, cyclodextrins give the suitable space for contact due to the hydrophobic cavity. The outer sphere of cyclodextrins is water compatible, allowing coherent interactions with hydrogen bonding. Cyclodextrins form inclusion complexes with a wide range of hydrophobic compounds due to that they modify the physicochemical and biological properties of drug molecules [68-70].

Various methods are used for 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, and each of these methods have different outcomes in terms of particle size, amount of complex formation, and the degree of amorphous nature of the final product [68].

Flavonoid compounds have limited aqueous solubility which hinder its oral administration, also decreases the bioavailability and pharmacological activities. dos Santos Lima et al, developed formulation which improve the solubility and bioavailability of the flavonoids by using the cyclodextrin inclusion complexation method. Pharmacokinetic study results shows that the bioavailability of flavonoid compounds, complexed with cyclodextrins were extensively improved when compared to uncomplexed flavonoids [29]. Cyclodextrins have been shown to be effective as complexing agents for poorly soluble anti-cancer medicines, improving their solubility, dissolution, and hence drug bioavailability [71]. The use of amphiphilic-cyclodextrin in the production of heavily loaded nanostructured systems to improve parenteral administration of poorly soluble medicines like Bifonazole and clotrimazole has also been documented. An innovative way of creating nanospheres for intravenous formulation of poorly soluble pharmaceuticals is to combine amphiphilic -cyclodextrin with drug inclusion complexes [72].

Solid dispersion

Solid dispersions can be defined as ‘the dispersion of one or more drugs in an inert carrier at solid state prepared by the melting method, solvent method, and/or melting solvent method’. First generation solid dispersion or Eutectic mixtures: The eutectic mixture can be prepared by rapid solidification of melted physical mixture of the drug and the carrier [73]. Crystalline carriers like urea and sugars are used to prepare this type of dispersion. First generation dispersion is more thermodynamically stable and hence retard the release of drug [74]. Second generation solid dispersion or amorphous precipitation: Drugs with low carrier solubility or high melting point can be forced solubilize into amorphous carriers such as PVP, PEG, Cellulose derivatives, etc. to prepare second generation dispersion. Based on physical state of drug in dispersion this can be classified as amorphous solid suspensions or

amorphous solid solutions [glass solutions]. As drug is forced solubilize to form dispersion, the major disadvantage of the method is drug precipitation and recrystallization which affect the *in vitro* or *in vivo* drug release. Third generation solid dispersion or Solid solution: Third generation dispersion contains carriers having surface activity and self-emulsifying properties such as Poloxamer 408, Tween 80, and Gelucire 44/14 [74].

Advantage of solid dispersion techniques are: Reduced particle size which results in increased dissolution by increasing surface area, improved wettability that increases solubility and hence bioavailability, Amorphous state of drug helps to improve solubility, and improved porosity. Drawbacks of this technique are instability of formulation due to moisture content, difficulty in incorporation it in to dosage forms, and difficulty in handling. Ticagrelor, a BCS class IV drug when formulated into solid dispersion using solvent evaporation method shows 34-fold increase in drug release as compared to commercial product in distilled water. Peak plasma concentration (Cmax) and relative bioavailability of solid dispersion formulation and pure drug was found to be 238.09 ± 25.96% and 219.78 ± 36.33%, respectively [75].

Nanosuspension

Nanosuspensions are defined as a nanosized aqueous dispersion of poorly soluble drug in aqueous or nonaqueous liquid media such as liquid PEG or oils with an average particle size ranging between 200 and 600 nm, and stabilized by surfactant, polymer, or both [76, 77].

Two types of methods are used in formulation of nanosuspensions:

1) Top-down methods like Wet milling, Dry milling, High Pressure Homogenization and co-grinding

2) Bottom-up methods like Antisolvent precipitation method, Liquid emulsion technique and Sono-precipitation method. These methods are followed by various solidification techniques like Freeze drying, Spray drying and Spray freezing. Nanosuspensions demonstrate number of advantages such as improved aqueous solubility and bio-availability, simple method for production, can be incorporated in various dosage forms like tablets, capsules, pellets, etc., lowers fasted/fed variability in drug absorption and distribution.

Spherical crystals

Spherical crystallization is a process which is having an ability for transformation of a crystalline drug directly into compacted spherical form for improving the flow ability, solubility and compactability. This technique is used for particle size enlargement that applies crystallization and agglomeration using bridging liquid. Particle orientation is influenced by crystal habit; therefore, it can modify physical stability, solubility and dissolution profile of a drug molecule. It would be reasonable to expect that spherical crystallization would be able to improve manufacturability and dissolution performance of drugs. The precipitated crystals can be agglomerated into more or less spherical particles with sizes between 300 and 500 um using this approach, which eliminates the need for binders during the final synthesis phase. Spherical crystallisation has been shown to improve the solubility profile of some drugs that are poorly water soluble. Briefly, a saturated drug solution in a good solvent is poured into a poor solvent according. Small amounts of a third solvent, known as the bridging liquid, is then added to moisten the crystal surface and facilitate the creation of liquid bridges between the drug crystals, resulting in spherical agglomerates. The affinity between the drug and the good solvent should be high. In addition, the bridging liquid should not be miscible with the bad solvent. Agglomeration growth can be divided into four stages: Zones of flocculation, zero growth, rapid growth, and constant size (Fig 5) [78, 79].

Maghsoodi and colleagues produced Naproxen agglomerates using a simple spherical crystallisation process, which showed better micromeritics and dissolving rate properties. Because of their enhanced solubility, the agglomerates were found to have enhanced anti-inflammatory action in rats than the pure drug [33].

Figure. 5 Step of agglomeration growth in spherical crystallization technique

Liquisolid compacts

Liquisolid technique refers to the process of converting liquid pharmaceuticals into seemingly dry, non-adherent, free-flowing, and compressible powder mixtures by combining them with suitable excipients, also known as carriers and coating ingredients. The liquid medicine is first absorbed into the carrier's internal architecture. When the inside of the carrier is saturated with liquid medication, a liquid layer forms on the carrier particles' surface, which the tiny coating materials quickly adsorb [80].

This method can create liquisolid tablets or capsules with drug release patterns that are pH-independent. Furthermore, the high flowability and squeezability of liquisolid

powder make large-scale production viable. This approach works well for water-insoluble low-dose medications, but its fundamental drawback is the inability to incorporate water-insoluble high-dose drugs into liquisolid systems. Because these medications require a substantial volume of liquid vehicle, large amounts of carrier and coating material are necessary to produce a liquidsolid powder with good flow and compressible qualities. This may cause the weight of the tablet to exceed the limit, making it difficult for patients to swallow. Several approaches to overcoming the aforementioned barrier have been documented. For example, increasing the viscosity of liquid pharmaceuticals with additives (such as PVP and PEG 35000) can reduce the amount of carrier and coating material needed. Organic solvents employed in the liquisolid technique should be orally safe, with water-miscible organic solvents with a high boiling point, such as PEG 400, being preferred. To absorb liquid medication, carriers should be porous materials with a large specific surface area and a high liquid absorption capacity. As a carrier, various grades of cellulose, starch, and lactose can be employed. As coating materials, however, only excipients with very tiny particle size and high adsorptive properties, such as silica powder, can be employed. Remeth and co-workers developed the liquisolid compacts of Carbamazepine, which can be prepared using the novel carriers like Neusilin and Fujicalin and PEG [34].

Polymeric micelles

The ability of a copolymer to self-assemble into nanoscale aggregates with a hydrophilic shell and a hydrophobic centre characterises polymeric micelles. The hydrophobic polymeric micelle's core provides a home for water-insoluble pharmaceuticals, while the hydrophilic shell effectively isolates the drugs from the outside environment and prevent their rapid degradation [81-83]. Block copolymer micelles are further classified based on the intermolecular forces that drive the separation of the core segment from the aqueous environment, such as amphiphilic micelles (formed by hydrophobic interactions), poly-ion complex micelles (formed by electrostatic interactions), and metal complexation micelles. The shape of the micelle is determined by the length of the hydrophobic centre and the hydrophilic corona. Micelles are spherical when the hydrophilic segment is longer than the core block, but when the core segment is longer than the corona forming chains, different non-spherical structures, such as rods and lamellae, arise. [84].

Polymeric micelles have some advantages as drug carriers for poorly soluble medicines, such as being stable, safe, and affordable. Through the enhanced permeability and retention (EPR) effect of the micelle encapsulated drug, it is feasible to target organs or tissues of interest. For site-specific targeting of polymer micelles, thermosensitive or pH sensitive block co-polymers can be prepared, as well as a vector molecule such as an antibody, peptide, lectin, saccharide, hormone, or some low molecular weight compounds that can be attached to the surface of micelles to help target specific ligands at specific sites of interest can be employed [85].

Polymeric micelles can spontaneously collect in tumours due to the EPR effect; hence they are used in tumour targeting by integrating an anticancer antibody onto the micelle's surface. High solubility, increased bioavailability, and long-term stability of anticancer drugs such as Paclitaxel can be achieved by dialysis of the molecule into hydrotropic polymer micelles [35]. A new polymeric micelle framework for solubilizing and improving the bioavailability of anticancer medicines that are poorly soluble: 17-allylamino-17-demethyoxygeldanamycin, paclitaxel, etoposide, docetaxel, and 17-allylamino-17-demethyoxygeldanamycin are investigated by researchers [36]. By introducing the hydrophobic polymer into the micellar core for interlacing the monomers and stabilising the micelle structure, Wen and colleagues created polymer stabilised micelles. Medicines loaded in polymer stabilised micelles exhibit lower clearance, higher plasma concentration, and poor volume distribution than drugs loaded in non-polymer stabilised micelles, according to *in vivo* pharmacokinetic studies. Micelles stabilised by polymers can limit rapid drug clearance by strengthening the micellar structure and increasing the amount of accessible drug in plasma, expanding the range of medicinal applications for micelles [86]. Quader et al. formulated cyclic-Arg-Gly-Asp (cRGD) micellar nanomedicines that loaded Epirubicin, a strong anti-glioblastoma drug, through a pH-sensitive hydrazine bond for effective treatment of glioblastoma multiforme. These cRGD-installed epirubicin-loaded polymeric micelles (cRGD-Epi/m) penetrated U87MG cell-derived 3D-spheroids faster and deeper than the non-cRGD-installed micelles, possibly via a cRGD-integrin mediated pathway. By distributing high amounts of Epirubicin throughout the tumour tissue *in vivo*, the cRGD-installed micelles significantly reduced the growth of an orthotropic glioblastoma multiforme [37].

Freeze dried liposomes

Liposomes are phospholipid vesicles that consist of a phospholipid bilayer surrounding an aqueous compartment and can dissolve lipophilic drug in their lipid domain. As a drug carrier for drug delivery systems, since both hydrophilic and lipophilic compounds can carry them, liposomes have attracted higher interest [87]. Liposomes consist of vesicles around an aqueous compartment consisting of bilayers or multilayers that contain or have phospholipids and cholesterol.

Liposome are having amphiphilic phospholipid bilayer which closely resembles the mammalian cell membrane, allowing efficient liposome-cell membrane interactions and subsequently efficient cellular uptake. Phospholipid is important component that give liposomes their distinct features, such as how they encapsulate substances and how they are functionalized in the body [88]. Liposome qualities are influenced by size, surface charge, number of lamellae, bilayer rigidity, surface modification, and preparation process, among other factors [89]. They deliver a versatile and adaptable technology for improving drug solubility due to their biphasic characteristics and variety in nature and composition [90]. Drug encapsulation or liposome trapping contributes to distinct changes in the properties of free drugs in pharmacokinetics and pharmacodynamics and also helps to reduce toxicity and, in certain cases, boost therapeutic efficacy [91]. However, one of the major drawbacks of using liposomes as drug delivery vehicles is their inability to maintain stability during storage [38]. The freeze-drying approach is used to stabilise the liposomal formulations, resulting in dry powders with greater stability while keeping the drug's efficacy.

The stability of freeze-dried Prednisolone sodium phosphate loaded long circulating liposomes was examined in relation to cryoprotectant type and concentration. Trehalose was found to be superior in maintaining the structural integrity and permeability properties of the liposome bilayers at a 5:1, carbohydrate to lipid molar ratio, ensuring the desired characteristics of the final product: a porous cake that is easy to reconstitute, a similar size to the liposomes before freeze-drying, a high % of encapsulated drug, and a low residual moisture content [39]. After freeze drying, the liposomal formulation was shown to have improved solubility and physicochemical stability. As a result, pharmaceuticals can be made with liposomes, a polymer, and a cryoprotectant, then freeze-dried to produce a dry, lyophilized powder. In some circumstances, polymers such as PEG are utilised to solubilize the drug in the liposomal solution. The aqueous solubility of a PEGylated liposomal formulation has been reported to be improved [92].

Solid lipid nanoparticles

Solid Lipid nanoparticles (SLNs) are made of solid lipid matrix consisting drug covered by a monolayer of surfactant. Solid lipids used for SLNs formation are mono/di/tri-triglycerides, fatty acids, steroids and waxes. Poloxamer, polysorbate 20 or 80, phosphatidyl choline, soy or egg lecithin, poloxamine, sodium dodecyl sulphate, sodium oleate, sodium taurocholate, sodium glycocholate, sorbitan monolaurate or monooleate, and butanol are all surfactants employed to stabilise the lipid dispersion. High-pressure homogenization (hot/cold homogenization), Ultrasonic/high-speed homogenization (probe/bath ultra-sonication), Solvent evaporation method, Solvent emulsification-diffusion method, Supercritical fluid method, Microemulsion based method, Double emulsion method, Precipitation Technique, Film-ultrasound dispersion using a membrane contractor and using a solvent injection technique are employed in the preparation of SLNs [41]. The interest in SLN as a novel particle technology has recently increased due to its potential as an alternative carrier system to conventional colloidal carriers such as emulsions, liposomes, and polymeric micro and nanoparticles, as well as its ability to be used in a variety of drug delivery applications [20]. SLN technology has various benefits and downsides, according to Mehnert and Mader, including improved drug targeting, higher drug stability, no carrier biotoxicity, and the capacity to include both lipophilic and hydrophilic drugs into the carrier. However, some disadvantages of SLN, such as limited drug-loading capacity and stability issues during storage or administration (gelation, particle size increase, SLN drug ejection), cannot be overlooked [93]. Soma and colleagues used glyceryl monostearate to make Irbesartan solid lipid Nanoparticles utilising a solvent emulsification process followed by probe sonication. The formulation was then tested in Wistar rats for pharmacokinetic investigations. In Wistar rats, irbesartan loaded SLN with a particle size of 523.7nm and a 73.8 % entrapment efficiency demonstrated good bioavailability and optimum stability. The SLN produced via solvent emulsification with glyceryl monostearate improves the drug's bioavailability [40]. Miconazole SLNs formulation shows increase in oral bioavailability 2.5-fold and antifungal activity miconazole against candidiasis as compare to capsule formulation [41].

Future perspectives

The future perspective of solubility enhancement techniques in pharmaceuticals emphasizes a shift toward advanced, eco-friendly, and highly efficient approaches, including nanotechnology, supercritical fluid technology, and interdisciplinary strategies. Future advancements will emphasize nanotechnology, particularly nanocrystals and lipid-based nanocarriers, supercritical fluid technologies, and solid dispersion systems to tackle the issues associated with poorly soluble medications. The shift towards sustainable practices, including the adoption of supercritical CO_2 rather than organic solvents, is projected to rise, influenced by regulatory standards and sustainability aspirations. Moreover, a growing trend is evident in the integration of computational methods alongside machine learning (ML) to predict and optimize strategies for enhancing solubility. Models based on ML, such as support

vector machines and deep learning algorithms, can effectively predict solubility and bioavailability, which facilitates drug development and decreases the number of experimental trials required. Thus, advancements in this domain will be driven by collaborative efforts among pharmaceutical scientists, computational chemists, engineers, and regulatory specialists. The integration of experimental and computational techniques is anticipated to result in more efficient, safe, and targeted strategies for improving solubility.

Conclusions

To improve drug water solubility, many pharmaceutical particle technologies have been used. There are two types of particle technologies: traditional techniques and current particle technologies. Mechanical micronization and Engineered particle methods are two common approaches. Mechanical micronization methods are simple and convenient for reducing particle size and increasing surface area, thereby improving the solubility and dissolution of poorly soluble drugs. However, they have some drawbacks, such as high energy requirements, the possibility of drug thermal and chemical degradation, and poor control over particle size distribution. Mechanical micronization methods have limitations, thus engineered particle techniques are more acceptable. They provide homogeneous particle size distribution, increased solubility and dissolution of poorly soluble pharmaceuticals, and physical modification of drug particles, such as a change in crystalline state. Every particle technology has its own value and use in enhancing the water solubility of medications that are poorly aqueous soluble. Appropriate procedures should be selected based on the qualities of the drug material to be manufactured as well as the desired dosage form.

List of Abbreviations

GIT: Gastrointestinal tract
BCS: Biopharmaceutical Classification System
HPH: High Pressure Homogenization
API: Active pharmaceutical ingredient
S-SEDDS: Solid self-emulsifying drug delivery systems
PVP: Polyvinyl pyrrolidone
PEG: Polyethylene glycol
EPR: Enhanced permeability and retention
SLN: Solid lipid nanoparticle

Author Contributions

Conceptualization, writing—original draft preparation, figure preparation: R.P.; writing—review and editing, supervision: K.P. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

Authors disclose no potential conflict of interest in the manuscript.

Funding

No external funding was received for this work.

Acknowledgment

No acknowledgement to mention

References

1. Tsume Y, Mudie DM, Langguth P, Amidon GE, Amidon GL. The Biopharmaceutics Classification System: subclasses for in vivo predictive dissolution (IPD) methodology and IVIVC. Eur J Pharm Sci. 2014; 57:152-163.
2. Kumari L, Choudhari Y, Patel P, Gupta GD, Singh D, Rosenholm JM, et al. Advancement in Solubilization Approaches: A Step towards Bioavailability Enhancement of Poorly Soluble Drugs. Life (Basel). 2023;13(5):1099.
3. Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, et al. Strategies to address low drug solubility in discovery and development. Pharmacol Rev. 2013; 65(1):315-499.
4. Krishnaiah YSR. Pharmaceutical Technologies for Enhancing Oral Bioavailability of Poorly Soluble Drugs. J Bioequiv. 2010; 2(2):028-036.
5. Hu J, Johnston KP, Williams RO 3rd. Spray freezing into liquid (SFL) particle engineering technology to enhance dissolution of poorly water soluble drugs: organic solvent versus organic/aqueous co-solvent systems. Eur J Pharm Sci. 2003; 20(3):295-303.
6. Papich MG, Martinez MN. Applying Biopharmaceutical Classification System (BCS) Criteria to Predict Oral Absorption of Drugs in Dogs: Challenges and Pitfalls. AAPS J. 2015; 17(4):948-964.
7. Reddy BBK, Karunakar A. Biopharmaceutics Classification System: A Regulatory Approach. Dissolution Technol. 2011; 18:31-37.
8. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. Int J Pharm. 2011; 420(1):1-10.
9. Leuenberger H, Lanz M. Pharmaceutical powder technology - From art to science: The challenge of the FDA's process analytical technology initiative. Adv Powder Technol. 2005; 16(1):3-25.
10. Finke JH, Kwade A. Powder Processing in Pharmaceutical

Applications-In-Depth Understanding and Modelling. Pharmaceutics. 2021; 13(2):128.
11. Davé RN, Bilgili E, Cuitino A, Jallo L. Special issue on pharmaceutical powders: Towards developing understanding of the influence of materials and processes on product performance. Powder Technol. 2013; 236:1-4.
12. Dressman JB, Vertzoni M, Goumas K, Reppas C. Estimating drug solubility in the gastrointestinal tract. Adv Drug Deliv Rev. 2007; 59(7):591-602.
13. Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, et al. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian J Pharm Sci. 2014; 9(6):304-316.
14. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012; 2012:195727.
15. Jinno J, Kamada N, Miyake M, Yamada K, Mukai T, Odomi M, et al. Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs. J Control Release. 2006; 111(1-2):56-64.
16. Pant P, Bansal K, Rao PRT, Padhee K, Sathapathy A, Kochhar PS. Micronization: An efficient tool for dissolution enhancement of dienogest. Int J Drug Dev Res. 2011; 3(2):329-333.
17. Karashima M, Sano N, Yamamoto S, Arai Y, Yamamoto K, Amano N, et al. Enhanced pulmonary absorption of poorly soluble itraconazole by micronized cocrystal dry powder formulations. Eur J Pharm Biopharm. 2017; 115:65-72.
18. Lee HJ, Kang JH, Lee HG, Kim DW, Rhee YS, Kim JY, et al. Preparation and physicochemical characterization of spray-dried and jet-milled microparticles containing bosentan hydrate for dry powder inhalation aerosols. Drug Des Devel Ther. 2016; 10:4017-4030.
19. Liversidge GG, Cundy KC. Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. Int J Pharm. 1995; 125:91-97.
20. Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery - a review of the state of the art. Eur J Pharm Biopharm. 2000; 50(1):161-177.
21. Homayouni A, Sohrabi M, Amini M, Varshosaz J, Nokhodchi A. Effect of high pressure homogenization on physicochemical properties of curcumin nanoparticles prepared by antisolvent crystallization using HPMC or PVP. Mater Sci Eng C Mater Biol Appl. 2019; 98:185-196.
22. Overhoff KA, McConville JT, Yang W, Johnston KP, Peters JI, Williams RO 3rd. Effect of stabilizer on the maximum degree and extent of supersaturation and oral absorption of tacrolimus made by ultra-rapid freezing. Pharm Res. 2008; 25(1):167-175.
23. Purvis T, Mattucci ME, Crisp MT, Johnston KP, Williams RO 3rd. Rapidly dissolving repaglinide powders produced by the ultra-rapid freezing process. AAPS PharmSciTech. 2007; 8(3):E58.
24. Babu NJ, Sanphui P, Nangia A. Crystal engineering of stable temozolomide cocrystals. Chem Asian J. 2012; 7(10):2274-2285.
25. Cho HY, Kang JH, Ngo L, Tran P, Lee YB. Preparation and Evaluation of Solid-Self-Emulsifying Drug Delivery System Containing Paclitaxel for Lymphatic Delivery. J Nanomater. 2016; 2016:3642418.
26. Deshmukh SR, Bakhle SS, Upadhye KP, Dixit GR. Formulation and evaluation of solid self-emulsifying drug delivery system of Gliclazide. Int J Pharm Pharm Sci. 2016; 8 (11):144-151.
27. Saggar S, Upadhayay A, Goswami M. Formulation and evaluation of solid self-emulsifying drug delivery system of bambuterol hydrochloride. Indian J Pharm Sci. 2019; 81(4):661-672.
28. dos Santos Lima B, Shanmugam S, de Souza Siqueira Quintans J, José Quintans-Júnior L, de Souza Araújo AA. Inclusion complex with cyclodextrins enhances the bioavailability of flavonoid compounds: a systematic review. Phytochem Rev. 2019; 18(5):1337-1359.
29. Gürten B, Yenigül E, Sezer AD, Malta S. Complexation and enhancement of temozolomide solubility with cyclodextrins. Brazilian J Pharm Sci. 2018; 54(2):e17513.
30. Kim SJ, Lee HK, Na YG, Bang KH, Lee HJ, Wang M, et al. A novel composition of ticagrelor by solid dispersion technique for increasing solubility and intestinal permeability. Int J Pharm. 2019; 555:11-18.
31. Alshweiat A, Csóka I, Tömösi F, Janáky T, Kovács A, Gáspár R, et al. Nasal delivery of nanosuspension-based mucoadhesive formulation with improved bioavailability of loratadine: Preparation, characterization, and in vivo evaluation. Int J Pharm. 2020; 579:119166.
32. Singh MK, Pooja D, Ravuri HG, Gunukula A, Kulhari H, Sistla R. Fabrication of surfactant-stabilized nanosuspension of naringenin to surpass its poor physiochemical properties and low oral bioavailability. Phytomedicine. 2018; 40:48-54.
33. Maghsoodi M, Hassan-Zadeh D, Barzegar-Jalali M, Nokhodchi A, Martin G. Improved compaction and packing properties of naproxen agglomerated crystals obtained by spherical crystallization technique. Drug Dev Ind Pharm. 2007; 33(11):1216-1224.
34. Dias RJ, Mali KK, Ghorpade VS, Havaldar VD, Mohite VR. Formulation and evaluation of carbamazepine liquisolid compacts using novel carriers. Indian J Pharm Edu Res. 2017; 51(2s):s69-s78.
35. Lee SC, Huh KM, Lee J, Cho YW, Galinsky RE, Park K. Hydrotropic polymeric micelles for enhanced paclitaxel solubility: in vitro and in vivo characterization. Biomacromolecules. 2007; 8(1):202-208.
36. Shin HC, Alani AW, Rao DA, Rockich NC, Kwon GS. Multi-drug loaded polymeric micelles for simultaneous delivery of poorly soluble anticancer drugs. J Control Release. 2009; 140(3):294-300.
37. Quader S, Liu X, Chen Y, Mi P, Chida T, Ishii T, et al. cRGD

peptide-installed epirubicin-loaded polymeric micelles for effective targeted therapy against brain tumors. J Control Release. 2017; 258:56-66.
38. Ghanbarzadeh S, Valizadeh H, Zakeri-Milani P. The effects of lyophilization on the physico-chemical stability of sirolimus liposomes. Adv Pharm Bull. 2013; 3(1):25-29.
39. Sylvester B, Porfire A, Van Bockstal PJ, Porav S, Achim M, Beer T, et al. Formulation Optimization of Freeze-Dried Long-Circulating Liposomes and In-Line Monitoring of the Freeze-Drying Process Using an NIR Spectroscopy Tool. J Pharm Sci. 2018; 107(1):139-148.
40. Soma D, Attari Z, Reddy MS, Damodaram A, Koteshwara KBG. Solid lipid nanoparticles of irbesartan: Preparation, characterization, optimization and pharmacokinetic studies. Braz J Pharm Sci. 2017; 53(1):e15012.
41. Raza A, Sime FB, Cabot PJ, Maqbool F, Roberts JA, Falconer JR Solid nanoparticles for oral antimicrobial drug delivery: a review. Drug Discov Today. 2019; 24(3):858-866.
42. Leleux J, Williams RO 3rd. Recent advancements in mechanical reduction methods: particulate systems. Drug Dev Ind Pharm. 2014; 40(3):289-300.
43. Manca ML, Lai F, Pireddu R, Valenti D, Schlich M, Pini E, et al. Impact of nanosizing on dermal delivery and antioxidant activity of quercetin nanocrystals. J Drug Del Sci Technol. 2020; 55:101482.
44. Junghanns JU, Müller RH. Nanocrystal technology, drug delivery and clinical applications. Int J Nanomedicine. 2008; 3(3):295-309.
45. Al-Kassas R, Bansal M, Shaw J. Nanosizing techniques for improving bioavailability of drugs. J Control Release. 2017; 260:202-212.
46. Slámová M, Prausová K, Epikaridisová J, Brokešová J, Kuentz M, Patera J, et al. Effect of co-milling on dissolution rate of poorly soluble drugs. Int J Pharm. 2021; 597:120312.
47. Loh ZH, Samanta AK, Heng PWS. Overview of milling techniques for improving the solubility of poorly water-soluble drugs. Asian J Pharm Sci. 2015; 10(4):255-274.
48. Han X, Ghoroi C, To D, Chen Y, Davé R. Simultaneous micronization and surface modification for improvement of flow and dissolution of drug particles. Int J Pharm. 2011; 415(1-2):185-195.
49. Strobel A, Köninger B, Romeis S, Schott F, Wirth KE, Peukert W. Assessing stress conditions and impact velocities in fluidized bed opposed jet mills. Particuology. 2020; 53:12-22.
50. Piras CC, Fernández-Prieto S, de Borggraeve WM. Ball milling: A green technology for the preparation and functionalisation of nanocellulose derivatives. Nanoscale Adv. 2019; 1: 937-947.
51. Graeser KA, Patterson JE, Zeitler JA, Rades T. The Role of Configurational Entropy in Amorphous Systems. Pharmaceutics. 2010; 2(2):224-244.
52. Keck CM, Müller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharm Biopharm. 2006; 62(1):3-16.
53. Sosna T, Mikeska M, Dutko O, Martynková GS, Škrlová K, Barabaszová KČ, et al. Micronization of Ibuprofen Particles Using Supercritical Fluid Technology. J Nanosci Nanotechnol. 2019; 19(5):2814-2820.
54. Rasenack N, Müller BW. Micron-size drug particles: common and novel micronization techniques. Pharm Dev Technol. 2004; 9(1):1-13.
55. Rogers TL, Hu J, Yu Z, Johnston KP, Williams RO 3rd. A novel particle engineering technology: spray-freezing into liquid. Int J Pharm. 2002; 242(1-2):93-100.
56. Varshosaz J, Ghassami E, Ahmadipour S. Crystal Engineering for Enhanced Solubility and Bioavailability of Poorly Soluble Drugs. Curr Pharm Des. 2018; 24(21):2473-2496.
57. Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev. 2007; 59(7):617-630.
58. Joshi K, Chandra A, Jain K, Talegaonkar S. Nanocrystalization: An Emerging Technology to Enhance the Bioavailability of Poorly Soluble Drugs. Pharm Nanotechnol. 2019; 7(4):259-278.
59. Pi J, Wang S, Li W, Kebebe D, Zhang Y, Zhang B, et al. A nano-cocrystal strategy to improve the dissolution rate and oral bioavailability of baicalein. Asian J Pharm Sci. 2019; 14(2):154-164.
60. da Fonseca Antunes AB, De Geest BG, Vervaet C, Remon JP. Solvent-free drug crystal engineering for drug nano- and micro suspensions. Eur J Pharm Sci. 2013; 48(1-2):121-129.
61. Tang B, Cheng G, Gu JC, Xu CH. Development of solid self-emulsifying drug delivery systems: preparation techniques and dosage forms. Drug Discov Today. 2008; 13(13-14):606-612.
62. Milović M, Djuriš J, Djekić L, Vasiljević D, Ibrić S. Characterization and evaluation of solid self-microemulsifying drug delivery systems with porous carriers as systems for improved carbamazepine release. Int J Pharm. 2012; 436(1-2):58-65.
63. Yan YD, Kim JA, Kwak MK, Yoo BK, Yong CS, Choi HG. Enhanced oral bioavailability of curcumin via a solid lipid-based self-emulsifying drug delivery system using a spray-drying technique. Biol Pharm Bull. 2011; 34(8):1179-1186.
64. Kang MJ, Jung SY, Song WH, Park JS, Choi SU, Oh KT, et al. Immediate release of ibuprofen from Fujicalin®-based fast-dissolving self-emulsifying tablets. Drug Dev Ind Pharm. 2011; 37(11):1298-1305.
65. Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. Adv Drug Deliv Rev. 2007; 59(7):645-666.
66. Singh A, Worku ZA, Van den Mooter G. Oral formulation strategies to improve solubility of poorly water-soluble drugs. Expert Opin Drug Deliv. 2011; 8(10):1361-1378.
67. Campos CA, Lima BS, Trindade GGG, Souza EPBSS, Mota DSA, Heimfarth L, et al. Anti-hyperalgesic and anti-inflammatory effects of citral with β-cyclodextrin and hydroxypropyl-β-cyclodextrin inclusion complexes in animal models. Life Sci.

2019; 229:139-148.
68. Carrier RL, Miller LA, Ahmed I. The utility of cyclodextrins for enhancing oral bioavailability. J Control Release. 2007; 123(2):78-99.
69. Rasheed A, Kumar C.K. A, Sravanthi VVNSS.) Cyclodextrins as drug carrier molecule: A review. Sci Pharm. 2008; 76(4):567-598.
70. Gidwani B, Vyas A. A Comprehensive Review on Cyclodextrin-Based Carriers for Delivery of Chemotherapeutic Cytotoxic Anticancer Drugs. Biomed Res Int. 2015; 2015:198268.
71. Memişoğlu E, Bochot A, Ozalp M, Sen M, Duchêne D, et al. Direct formation of nanospheres from amphiphilic beta-cyclodextrin inclusion complexes. Pharm Res. 2003; 20(1):117-125.
72. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971; 60(9):1281-1302.
73. Tekade AR, Yadav JN. A Review on Solid Dispersion and Carriers Used Therein for Solubility Enhancement of Poorly Water Soluble Drugs. Adv Pharm Bull. 2020; 10(3):359-369.
74. Thakur D, Sharma R. Solid dispersion a novel approach for enhancement of solubility and dissolution rate: a review. J Pharm Sci Bioscientific Res. 2019; 9(4):200-207.
75. Kim SJ, Lee HK, Na YG, Bang KH, Lee HJ, Wang M, et al. A novel composition of ticagrelor by solid dispersion technique for increasing solubility and intestinal permeability. Int J Pharm. 2019; 555:11-18.
76. Chin WW, Parmentier J, Widzinski M, Tan EH, Gokhale R. A brief literature and patent review of nanosuspensions to a final drug product. J Pharm Sci. 2014; 103(10):2980-2999.
77. Jacob S, Nair AB, Shah J. Emerging role of nanosuspensions in drug delivery systems. Biomater Res. 2020; 24:3.
78. Patil SV, Sahoo SK. Improvement in compressibility, flowability and drug release of glibenclamide by spherical crystallization with additives. Dig J Nanomater Biostructures. 2011; 6(4):1463-1477.
79. Kovačič B, Vrečer F, Planinšek O. Spherical crystallization of drugs. Acta Pharm. 2012; 62(1):1-14.
80. Lu M, Xing H, Jiang J, Chen X, Yang T, Wang D, et al. Liquisolid technique and its applications in pharmaceutics. Asian J Pharm Sci. 2017; 12(2):115-123.
81. Zhou Y, Wen H, Gu L, Fu L, Guo J, Du L, et al. Aminoglucose-functionalized, redox-responsive polymer nanomicelles for overcoming chemoresistance in lung cancer cells. J Nanobiotechnol. 2017; 15: Article: 87.
82. Wang Q, Liu Y, Pu C, Zhang H, Tan X, Gou J, et al. Drug-Polymer Interaction, Pharmacokinetics and Antitumor Effect of PEG-PLA/Taxane Derivative TM-2 Micelles for Intravenous Drug Delivery. Pharm Res. 2018; 35(11):208.
83. Torchilin VP. Targeted polymeric micelles for delivery of poorly soluble drugs. Cell Mol Life Sci. 2004; 61(19-20):2549-2559.
84. Gaucher G, Dufresne MH, Sant VP, Kang N, Maysinger D, Leroux JC. Block copolymer micelles: preparation, characterization and application in drug delivery. J Control Release. 2005; 109(1-3):169-188.
85. Lukyanov AN, Torchilin VP. Micelles from lipid derivatives of water-soluble polymers as delivery systems for poorly soluble drugs. Adv Drug Deliv Rev. 2004; 56(9):1273-1289.
86. Wen SN, Chu CH, Wang YC, Huang HY, Wang YJ, Lin JY, et al. Polymer-Stabilized Micelles Reduce the Drug Rapid Clearance in Vivo. J Nanomater. 2018;2018:5818592.
87. Kargar M, Moghimipour E, Ramezani Z, Handali S. Application Potential of Liposomal Delivery Systems Prepared by Lipids Extracted from E. coli Cultures. Annu Res Rev Biol. 2014; 4:1319-1329.
88. Hussain A, Singh S, Sharma D, Webster TJ, Shafaat K, Faruk A. Elastic liposomes as novel carriers: recent advances in drug delivery. Int J Nanomedicine. 2017; 12:5087-5108.
89. Olusanya TOB, Haj Ahmad RR, Ibegbu DM, Smith JR, Elkordy AA (2018) Liposomal Drug Delivery Systems and Anticancer Drugs. Molecules 23(4):907. doi: 10.3390/molecules23040907.
90. Mohammed AR, Weston N, Coombes AG, Fitzgerald M, Perrie Y. Liposome formulation of poorly water soluble drugs: optimisation of drug loading and ESEM analysis of stability. Int J Pharm. 2004; 285(1-2):23-34.
91. Zhang JA, Anyarambhatla G, Ma L, Ugwu S, Xuan T, Sardone T, et al. Development and characterization of a novel Cremophor EL free liposome-based paclitaxel (LEP-ETU) formulation. Eur J Pharm Biopharm. 2005; 59(1):177-187.
92. Yang T, Cui FD, Choi MK, Cho JW, Chung SJ, Shim CK, et al. Enhanced solubility and stability of PEGylated liposomal paclitaxel: in vitro and in vivo evaluation. Int J Pharm. 2007; 338(1-2):317-326.
93. Mehnert W, Mäder K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev. 2001; 47(2-3):165-196.