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Recent advances in techniques for enhancing the solubility of hydrophobic drugs

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Abstract: Numerous hydrophobic compounds are important ingredients for drug discovery and development. Hydrophobicity has been a major hurdle limiting the therapeutic efficacy of drugs. Drugs with low solubility are biopharmaceutically classified as class II and class IV drugs. Other challenges facing the pharmaceutical industry include low bioavailability, poor dissolution and erratic absorption of various compounds. In recent years, several technologies and methods have been developed to improve the solubility of drugs, meanwhile various mechanisms of improving solubility of compounds have been proposed. This review explores recent advances and techniques used to enhance solubility of lipophilic or low-solublility drugs. We summarize several strategies, such as rotor stator colloid mill, jet mill, ball mill, spray drying, hot melt extrusion, supercritical fluid and structural modification, including salt formation, and co-crystallization.

Keywords: Hydrophobic drugs, solubility enhancement, recent advances.

INTRODUCTION

Arithmetically, about 40% of all drugs are hydrophobic ones. This has been an intractable challenge in formulation and development of oral therapeutic drugs (Kalepua and Nekkanti, 2015). Oral administration of drugs is currently the leading and most important route of drug administration. It increases patient compliance to take the medication - as well as gives an upper hand in drug formulation. Oral administration of drugs is superior to the non-oral routes of administration such as injections in terms of safety (Green *et al.,* 2017). Orally administered drugs are majorly absorbed by passive diffusion through the gastrointestinal (GI) cellular membranes. As such, they face many barriers in the gastrointestinal tract such as harsh, acidic conditions in the stomach, a mucus layer and intestinal microflora that prevent adequate absorption of the drug. This reduces the therapeutic efficacy of the medication (Vong and Nagasaki, 2017). Besides the physiological factors affecting drug absorption, the properties of the drugs are equally important. The imperative factors affecting the bioavailability or therapeutic effectiveness of the drug are solubility and permeability (Nainwal *et al.,* 2019). Cognizant to this, understanding the drug solubility potential is key to its formulation (Thelen *et al.,* 2019).

Solubility is a phenomenon which occurs in dynamic equilibrium. As stated in International Union of Pure and Applied Chemistry (IUPAC), "Solubility is the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. Solubility is defined in various units such as, molarity, mole fraction, mole ratio and mass (solute) per volume (solvent) (IUPAC, 1997). Quantitatively, a compound having a solubility of 0.1g/L or above is considered to be adequately soluble while that having a solubility of less than or equal to 0.01 g/L is considered to be poorly soluble (Stegemann *et al.,* 2007). Solubility of drugs is affected by many factors, such as the particle size that determines the specific surface area and the polarity that affects the dipole-dipole interaction (Dickmann *et al.,* 2016; Galamba *et al.,* 2019). size. Moreover, the influence of polymorphs on solubility has also drawn much attention. A crystal is made up of atoms, ions or molecules in a regular geometric lattice in three dimensional repeating units. Polymorphs can also differ in terms of their melting points thus impacting on the solubility of a substance (Loschen and Klamt, 2015). The biopharmaceutical classification system (BCS) also classifies drugs according to their solubility. BCS segregates drugs into four classes based on their solubility and permeability factor (Takagi *et al.,* 2006). The system has been endorsed by regulatory organizations and agencies such as European Medicines Agency, 2010, ICH M9 on BCS based biowaivers, 2018, WHO Biowaiver list, 2018 and U.S. FDA, 2017. Moreover, the system has been incorporated in biowaiver granting guidelines (Charalabidis *et al.,* 2019). The four classes under this classification system, as showed in fig. 1, are: I (high solubility, high permeability), II (low solubility, high permeability), III (high solubility, low permeability) and IV (low solubility, low permeability). The system defines a drug by "high solubility" when the highest dose strength is soluble in 250 ml or less of aqueous media over a pH range of between 1 and 7.5 (Amidon *et al.,* 1995). There are solubility challenges in Class II and Class IV drugs. Dissolution of the drugs in these classes, affected by the particle size, is the limiting stage. As such, formulation of Class II and Class IV drugs is of great

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interest. Herein, recent advances of the imperative pharmaceutical techniques in enhancing the solubility of hydrophobic drugs are described. Their principle mechanisms are further described using suitable case studies.

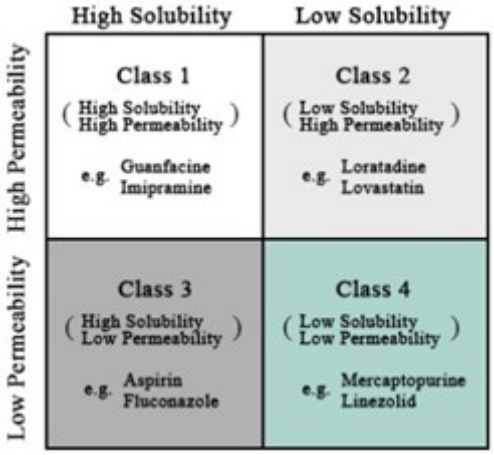

Fig. 1: BCS Classification System and Example

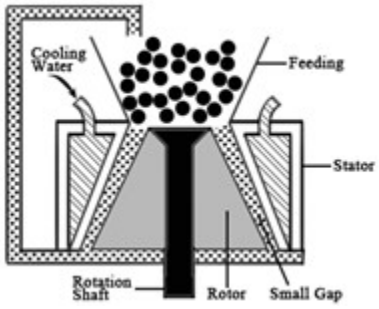

Fig. 2: Scheme of the Colloid Mill

Particle size reduction

Particle size intrinsically affects the dissolution process of any substance. The smaller the particle size, the larger the surface area available for the solute and solvent to interact thus leading to facilitate dissolution. For nano-sized particles, the influence of particle size on solubility can be explained through an equation described as follows (Kesisoglou *et al*., 2007).

$$\ln\frac{S}{So} = \frac{2\gamma V}{R\,T\,r}$$

Where S is the saturation solubility of nano-sized particles, S_o is the solubility of infinitely large particles, V is the molar volume, γ is the surface tension of solid, R is the gas constant, T is the absolute temperature and r is the radius of nanoparticles.

The milling technique also reduces the particle size thus increasing the surface area (Huang and Tong, 2004). As such, it overcomes the major pharmaceutical hurdle by increasing the dissolution rate and bioavailability of the drug based on the Noyes-Whitney equation (Fernandes *et al.,* 2018; Han *et al.,* 2011 and Fu *et al.,* 2015). Mechanical techniques which enhance micronization are majorly the attrition or milling techniques such as the rotor stator colloid mill, jet mill and ball mill (table 1).

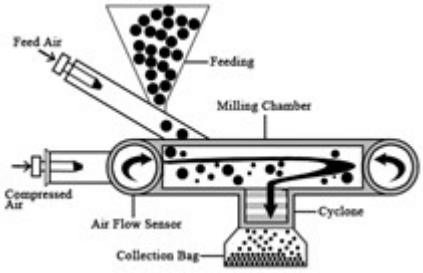

Fig. 3: Scheme of the Jet Mill

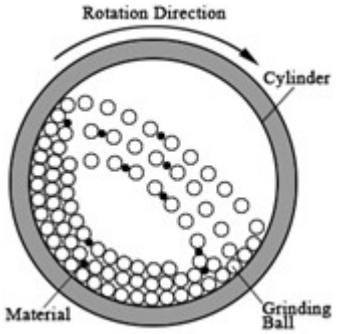

Fig. 4: Scheme of the Ball Mill

Rotor Stator Colloid Mill

A colloid is a mixture composed of particles in a dispersing medium. It is defined by the size of the particles involved. If the particles in a mixture are on the scale of individual molecules of close to 1 nanometer, it is defined as a solution. If the particles are larger than 1,000 nanometers, it is a suspension. Anything in between a solution and a suspension is a colloid (Clay, 2020). Rotor stator colloid mill is pharmaceutically useful in micronization of solid particles or droplets size of a liquid present in suspensions or emulsions (Alam *et al.,* 2009; Clavijo-Romero *et al.,* 2019). It consists of the stationary surface commonly known as the stator, and a high shear rotating surface called the rotor. The product is passed through a small gap between the stator and the rotor. The consequence of the following mechanical and hydraulic forces is the micronization of the product (fig. 2) (King and Keswani, 1994). Compared with gear juicer, colloid mill processing generates smaller particle sizes with a more disrupted microstructure. This contributes to higher content of target compounds in mill juice when applied in plant medicine (Li *et al.,* 2016). However, the technique is not satisfactory because it leads to denaturing of the materials. This is caused by the lack of constant flow as a result of centrifugal movement, further leads to generation of heat by the stator and the materials which in turn denatures the materials. This further causes structural degradation in the shear gap thus significantly reducing its effect (King and Keswani, 1994; Weidendorfer and Hinrichs, 2008).

Table 1: Summary of examples obtained from literature on the use of milling for the production of drug

Drug	Process Description	Minimum/avg Particle Size (μm)	Method	Equipment Used	Ref
Efavirenz	10% (w/v) efavirenz, mill time 60 min, using 0.2% Hydroxypropyl methylcellulose (HPMC) in spray dried process.	D(10)=1.136 D(50)=4.262 D(90)=11.427	Colloid mill	REX (Meteor, Brazil)	Hoffmeister *et al*., 2017
Peptide	Feed rate 1 g/min, feeding pressure 60 psi, grinding pressure 70 psi, batch size 20 g.	D(10)=0.8 D(50)=2.2 D(90)=4.6	Jet mill	00-Jet-O-Mizer (Fluid Energy, Telford, PA)	Zhang *et al*., 2020
Salbutamol sulphate	Injection pressure 6 bar, milling pressure 3 bar.	D(10)=0.65±0.03 D(50)=2.65±0.08 D(90)=6.35±0.19	Jet mill	Spiral Jet Mill 50AS (Hosokawa Alpine AG, Germany)	Zellnitz *et al*., 2019
Olmesartan medoxomil	Feed rate 5 g/min, grinding nozzle pressure 0.50 MPa.	D(10)=0.730 D(50)=3.136 D(90)=9.327	Jet mill	RICH-RC75A, (Shanghai Rich Machine Manufacture Co., Ltd., Shanghai, China)	Chai *et al*., 2019
Dronedarone	Feed rate 1 kg/h, micronization pressure 1.2 bar, injector pressure 3 bar.	D(90)=12.74	Jet mill	LaboMill (F.P.S. Food and Pharma Systems srl)	Kordić *et al*., 2018
Felodipine	2.5% (w/w) felodipine in 2% (w/w) DSPE-mPEG-2000, rotational speed 700 rpm, rotational time 3 h.	D(50)=0.3	Ball mill	Fritsch Pulverisette 7 ball mill (Fritsch, Idar-Oberstein, Germany)	Carling and Brulls, 2021
Atorvastatin	Atorvastatin-naringin molar ratio of 1:1, rotational speed 400 rpm, rotational time 3 h.	D(90)=18.80	Ball mill	Retsch PM 100 planetary ball mill (Retsch GmbH, Germany)	Nair *et al*., 2020
Pioglitazone HCl	1.25 g of pioglitazone HCl mix with 4.9% (w/w) pluronic F-127 and 0.05% sodium deoxycholate, rotational speed 500 rpm, rotational time 20 min.	D(90)=7.28±1.74	Ball mill	Fritsch Pulverisette 7 ball mill (Fritsch, Idar-Oberstein, Germany)	Alshora *et al*., 2020
Levodopa	Levodopa-sodium hyaluronate ratio (1:0.5), rotational time 60 min, rotational speed 400 rpm.	D(50)=9.248±0.212	Ball mill	Retsch PM 100 (Retsch GmbH, Haan, Germany)	Bartos *et al*., 2018
Meloxicam	Containing 0.5% Polyvinyl alcohol (PVA), rotational speed 437 rpm, rotational time 43 min.	D(10)=0.067±0.001 D(50)=0.130±0.005 D(90)=0.371±0.010	Ball mill	Retsch PM 100 (Retsch GmbH, Haan, Germany)	Bartos *et al*., 2018
Aceclofenac	Containing 0.25% PVA and 200 mg of aceclofenac which was milled for 4 h using balls of size 5mm, rotational speed 400 rpm.	D(90)=0.485±0.054	Ball mill	PM100 (Retsch Inc., Newtown, PA, USA)	Narayan *et al*., 2017

Table 2: Summary of examples obtained from literature on the use of spray drying for the production of drug

Drug	Carrier	Process Description	Solubilizing Effects	Equipment Used	Ref
Simvastatin	Polyvinylpyrrolidone (PVP)	Inlet temperature 350°C, outlet temperature 26-280°C, feed rate 6-8 ml/min, atomization pressure 2 kg/cm^2 and aspiration -200 mm.	Pure simvastatin has saturation solubility 16±0.77 μg/ml while solid dispersion carried PVP 85±2.49 μg/ml.	Lab-ultima (Mumbai, India)	SreeHarsha *et al*., 2020)
Nifedipine	Cholesterol	Liposomes were prepared, the liposomes were subjected to spray drying to obtain proliposomes at inlet temperature 130°C.	The solubility of nifedipine is improved 24.8 time s after forming proliposomes.	/	Bi *et al*., 2020
Florfenicol	HPMC, Sodium dodecyl sulfate (SDS), PVP	Mixed solution ground at 2500rpm for 60 minutes then spray drying, inlet temperature 195°C, outlet temperature 84°C, feed rate 7.0mL/min.	Average particle size 276.4±19.4 nm, significantly increased the solubility.	/	Fang *et al*., 2020
Fenofibrate	Polyvinyl pyrrolidone vinyl acetate	Feed rate 112g/min, inlet temperature 167°C, outlet temperature 61°C, atomization pressure 30 psi.	D(10)=1 μm, D(50)=3 μm, D(90)=6 μm	Niro pharmaceutical spray dryer (PSD-1)	Ekdahl *et al*., 2019
Ziprasidone	Soluplus® Eudragit® R1or Eudragit® S100 or EthylCellulcse)	The flow rate of disperse air was set at 12L/min, inlet temperature 180°C, outlet temperature 80°C.	More than 80% of the loaded drugs were released within 2h, while the physical mixtures only achieved around 40%.	Mono Disperse Spray Dryer (Nantong Concept New Co., Ltd. China)	Liu *et al*., 2019
Ibuprofen	Hydroxypropylmethyl cellulose acetatesuccinate (HPMCAS)	Atomization gas flow rate of ~357 NL/h (P=1013.25 mbar and T=273.15 K), inlet temperature 55°C, feed rate 4.5 ml/min.	Ibuprofen microparticles around 55% of the loaded drugs were released in 10 min, while pure ibuprofen only achieved 15%.	Mini-spray drier Buchi290 (Buchi, Switzerland)	Ziaee *et al*., 2019
Atorvastatin calcium	Sodium Lauryl Sulphate (SLS)	Inlet temperatures 160°C, flow rate of 6-8 ml/min.	Revealing a release of 99% in 15 min.	Lab Plant laboratory-scale spray-dryer	Da Silva *et al*., 2019
Orphan	/	Inlet temperature 50 °C, atomization air flow rate 670 L/h, feed flow rate 1.5 ml/min, drying air flow rate 35 m^3/h.	D(50)=9.72±0.12 μm, D(90)=19.75±1.85 μm, solubility was further increased to 0.59±0.01 mg/ml.	Mini-spray drier Buchi290 (Buchi, Switzerland)	Gonzalez *et al*., 2019
Lacidipine	Soluplus®, SDS	Inlet temperature 60 °C, atomizing flow rate 600 L/h and 100% aspirator (35 m^3/h) with solution pumped at 2 ml/min.	Pure drug insoluble in pH 6.8 medium and water, while spray dried products dissolve about 50% and 70% respectively in 15 min.	Mini-spray drier Buchi290 (Buchi, Switzerland)	Guan *et al*., 2019
Praziquantel	Human serum albumin	Outlet temperatures 59-64 °C, atomization flow rate 50 mm on the rotameter (i.e. 601 L/h), feed rate of 4% (i.e. 1.5 ml/min).	The solubility of raw praziquantel was 168.5±2.2 μg/mL and the produced particles were about 450 μg/ml.	Mini-spray drier Buchi290 (Buchi, Switzerland)	Yamasak *et al*., 2019

Table 3: Summary of examples obtained from literature on the use of HME for production of drugs

Drug	Carrier	Process Description	Solubilizing Effects	Equipment Used	Ref
Ketoconazole	Eudragit L100-55, polyethylene glycol 3000 (PEG 3000)	Mixed with Eudragit L100-55, PEG 3000 in 1:8:1 (w/w) ratio of drug: Eudragit L100-55: PEG 3000, screw rate of 100 rpm at temperatures of 140°C, feeding rate 2 g/min.	The pure API was almost insoluble, while the extrudate was up to 400µg/ml in non-sink dissolution experiment at 30 min.	ZE 12 Three-Tec 12 mm co-rotating twin screw extruder (Seon, Switzerland)	Monschke *et al.*, 2021
Loratadine	Shellac, HPMC	Mixed with shellac, HPMC in 2:1:7 (w/w) ratio of drug: shellac: HPMC, screw rate of 100 rpm at temperatures of 105°C, feeding rate 1g/min.	The dissolution of loratadine in pH 6.8 phosphate buffer at 45 min was less than 5%, while the extrudate was approximately 80%.	Twin-screw extruder (Three Tec, Seon, Switzerland)	Kapote and Wagner, 2021
Indomethaci	Soluplus®	Mixed with Soluplus® in 1:4 (w/w) ratio of drug:carrier, screw rate of 70 rpm at temperatures of 125°C.	Saturation solubility of pure API 55.7µg/ml, extrudate induced significantly higher solubility (145.7µg/ml).	Co-rotating twin-screw extruder (Pharma 11; Thermo Fisher Co., Shanghai, China)	Shi *et al.*, 2019
Ketoprofen	Soluplus®, Kollidon®SR	Screw speed 100 rpm, feeding rate 415 g/h, melt temperature 115°C.	An extended release of ketoprofen was accomplished 84.3% drug release at 10h and 100% release at 12h.	Nano 16 from Leis-tritz (Somerville, NJ, USA)	Restrepo-Uribe *et al.*, 2019
Aripiprazole	Kollidon® 12 PF	Screw speed 120 rpm, melt temperature 120°C.	The dissolution of aripiprazole in water at 10 min was less than 10%, while the extrudate was more than 90%.	Twin-screw extruder (Process 11, Thermo Fisher Scientific)	McFall *et al.*,2019
Indomethacin	PVA	Screw rate 50 rpm, Melt temperature 156°C.	The extrudate reached a peak of approximately 90µg/ml in 15min, while the API was approximate 10%.	HAAKE Mini CTW (Thermo FisherScientific K.K., MA, USA)	Mori *et al.*, 2019
Efavirenz	Soluplus® and Kollidon® VA 64	Screw rate 75 rpm, melt temperatures 140°C, further preparation into tablet.	About 100% drug was released in less than 1 h, whereas pure API took 60 min to show 20% drug release.	Single-screw Lab Hot Melt Extruder (S.B. Panchal and Co., India)	Pawar *et al.*,2018
Lapatinib ditosylate	Soluplus®, poloxamer 188	Screws rate 30 rpm, melt temperatures 145°C.	Saturation solubility of pure API 0.007 mg/mL, extrudate induced higher solubility (0.088 mg/ml).	Mini CTW twin screw extruder (ThermoFisher, Waltham, USA)	Hu *et al.*, 2018
Nimodipine	HPMCAS	Screw speed 50 rpm, melt temperature 110°C, further preparation into tablet (dry granulation).	The dissolution of Nimotop® (RLD, tablet) was approximate 60% at pH 6.8, while the extrudate was up to 87% and extrudate tablet was up to 75%.	Haake Mini Lab II Micro Compounder with a co-rotating twin-screw (Thermo Fisher Co. Ltd., Germany)	Zhang *et al.*, 2018
Carvedilol	Kollidon®VA64, Acconon®C-50	Screw speed 200 rpm, barrel temperature 160°C.	The dissolution of physical mixture was 60% at 120 min, while the dissolution of extrudate was up to 90%.	Twin-screw extruder (Thermo Scientific Inc., Waltham, MA)	Vasoya *et al.*, 2019

Table 4: Classification of supercritical fluid technology

Function of CO_2	Abbreviation	Method
Solvent	RESS	Rapid expansion of supercritical solution
	RESS-N	Rapid expansion of supercritical solution with a nonsolvent
	RESS-SC	Rapid expansion of supercritical solution with solid cosolvent
	RESS-C	Continuous-rapid expansion of supercritical solution
	US-RESSAS	Ultrasonic-assisted rapid expansion of supercritical solution into aqueous solution
Anti-solvent	GAS	Gas anti-solvent
	SAS	Supercritical anti-solvent
	PCA	Precipitation with compressed anti-solvent
	ASES	Aerosol solvent extraction system
	SEDS	Solution enhanced dispersion by supercritical fluid
	SAS-EM	Supercritical anti-solvent with enhanced mass transfer
	SEDS-EM	Solution enhanced dispersion by supercritical fluid with enhanced mass transfer
	SFEE	Supercritical fluid extraction of emulsions
Solute	PGSS	Particles from gas saturated solutions
	GAMA	Gas assisted melting atomization
Co-solute	CAN-BD	Carbon dioxide assisted nebulization with a bubble dryer
	SAA	Supercritical fluid assisted atomization
	SAA-HCM	Supercritical fluid assisted atomization introduced by hydrodynamic cavitation mixer

Jet Mill

Jet mill, also known as fluid energy mill, is the pioneer technique for the micronization of solid materials. It operates on compressed air or high pressure and super-heated steam. Product particles are fed through the venturi injector into the milling chamber. High velocity air is then introduced through jet nozzles which are distinctly placed around the circular chamber of the mill. Recurrent collision collapses the particles into small particles until the accumulated energy is reduced to negligible values. These micronized particles are further carried to the aspirating units (fig. 3) (Eskin *et al.,* 1997). It provides a reliable explanation for the observed response of reduced particle size to changes in solids feed rate, gas mass flow rate, mill geometry, gas physical properties, and material properties (MacDonald *et al.,* 2016). The sticky active pharmaceutical ingredient (API) can also ensure that the required particle size for pharmaceutical processing is obtained. Mixing of API at low dosage strength with the product particles can increase their dissolution rate after jet milling (Nakach *et al.,* 2019). Some mathematical models are used for the simulation of comminution process in jet mill to describe the relationship between the key process parameters and particle size thus replacing experience and blindness (Datta and Rajamani, 2002; Rodnianski *et al.,* 2019). The agglomerates in ultrafine powders can be effectively eliminated by the jet milling. The jet-milled ultrafine powders have a low lattice strain and a tight particle size distribution (Sun *et al.,* 2019).

Ball Mill

Ball milling is industrially known as media milling or pearl milling. It aids in grinding of API or suspensions to achieve micronization. The operative body consists of a hollow cylinder containing balls. The cylinder is mounted on a metallic frame and can be rotated along its longitudinal axis. This rotation causes stress that leads to abrasion or attrition of the material to be micronized (fig. 4) (Colombo *et al.,* 2009). These grinding balls or pearls are made of ceramic, agate, silicon nitride, sintered corundum, zirconia, chrome steel, tungsten carbide or plastic polyamide. They are available in different sizes that can be mixed and matched to achieve a steady material flow. Smaller pearls lead to finer particles as the availability of void spaces decreases and more surface area is available. Similarly, larger balls or pearls produce coarser material after attrition (Suryanarayana, 2001). The milling process variables such as milling speed, milling time, amount of ball, ball-to-powder mass ratio and filling ratio of the vessel are critical process parameters that significantly impact on the particle size (Sharma *et al.,* 2016, Mojarrad *et al.,* 2016). Vibrational ball milling of carvedilol and meloxicam exhibit a comminution function. It further serves as an intensive mixing technique capable of producing co-ground drug-excipient mixtures comprising amorphous drug forms intimately mixed with suitable hydrophilic excipients at molecular level (Loh *et al.,* 2015; Bolourchian *et al.,* 2019 and Bartos *et al.,* 2018).

Spray drying

Spray drying is a technology with wide range of applications in pharmaceutics. It converts crystalline products to amorphous products. It is particularly useful in the microparticulate drug delivery systems (Vishali *et al.,* 2019). It is a constructive single step operation which produces dry powders and aid with gaining control over parameters such as particle size and morphology (Lee *et al.,* 2019). The major working principle for this technology is the atomization of a solution, suspension or emulsion into spray. Although the technology has constantly being modified and its equipment has been optimized, the principle has not changed much. High pressure pump atomizes the solution, suspension or emulsion into a heated and insulated tower. Droplets loose moisture rapidly and flash dry when they come in contact with hot stream. The dried micronized particles are then separated from the tower using a cyclone or a filter bag (fig. 6) (Bellinghausen, 2019; Azad *et al.,* 2015; Vehring, 2008).

In the process of contact between small droplets and hot air, water evaporation can be completed instantly. The drying process is very fast compared with traditional drying methods and others such as freeze-drying (Ran *et al.,* 2019; Pang *et al.,* 2017). During spray drying, materials come into direct contact with hot air. However, most of the heat is used to evaporate the moisture in the liquid. As such, the material temperature is not too high to affect its stability (Zanoni *et al.,* 2020; Edueng *et al.,* 2019). By changing the process parameters, the powder can be produced in a highly efficient way that meets the precise powder characteristics of particle size, shape, density, dispersion, polymorphism and flow characteristics (Potharaju *et al.,* 2020; Ekdahl *et al.,* 2019; Browne *et al.,* 2019).

Nevertheless, the high consumption of hot air in spray drying leads to high energy consumption, thus limiting its application in pharmaceutics (Velić *et al.,* 2003). Cognizant to this, various successful studies reported that exhaust air heat recovery system, novel spray drying technique such as flame spray drying, and monodisperse droplet generation systems in spray drying change process parameters such as increased feed dry matter content thus effectively reducing energy consumption (Julklang and Nekkanti, 2015; Piatkowski, 2015; Atuonwu and Stapley, 2017; Wittner *et al.,* 2019).

The atomizer is the core component of spray drying. The atomization performance is a critical factor in determining the particle size, dissolubility, uniformity and other qualities of the product. The atomizer can be an airflow atomizer, pressure nozzle atomizer or a rotary atomizer

based on structure and principle differences. Different atomizer designs affect the airflow pattern and temperature distributions which result in different droplet size distributions and atomization efficiency (Sarrate *et al.,* 2015). The new B-90 type nano spray drying equipment developed by Buchi company (Swiss) can produce particle size range of materials as low as 0.3-0.5 µm (Arpagaus, 2012).

Spray-freeze drying is a unique drying technology combined with spray technology and freezing technology. The methods comprise of three steps: dispersion of bulk liquid solutions into droplets, droplet freezing and sublimation drying of the frozen material which may comprise particles or a film that can be subsequently pulverized (Wanning *et al.,* 2015). The particle morphology obtained by spray-freeze drying is superior to those obtained by spray drying or freeze-drying. Droplets with good size distribution are obtained and water leaves tiny pores inside the particles during the freeze-drying process. The formation of these microporous structures increases the specific surface area of the particles and greatly improves the wettability and solubility of the products (Hadipour e*t al.,* 2018; Adeli, 2017). The strategy of forming solid dispersions during spray drying provides a new idea for increasing the solubility of insoluble drugs. The carrier materials used to prepare solid dispersion include mannitol and polyvinylpyrrolidone (Thakur *et al.,* 2020; SreeHarsha *et al.,* 2020; Ekdahl *et al.,* 2019). A summary of examples obtained from literature on the use of spray drying for drug production is presented in table 2.

Hot melt extrusion

Hot melt extrusion (HME) is a technology used in an array of pharmaceutical manufacturing. In recent years, it has been modified to enhance drug dissolution rates (Hughey *et al.,* 2010; Pina *et al.,* 2014; Feng and Wang, 2019). HME technology was first applied in plastics, rubber products, and food industry (Saerens *et al.,* 2014). HME has been widely used in the pharmaceutical industry to produce various products such as tablets, capsules, films, and implants administered via oral, transdermal, and transmucosal routes (Kallakunta *et al.,* 2019). HME equipment is divided into feed zone, transition zone and metering zone which dissolves or disperses the drug in molten polymer (fig. 6) (Maniruzzaman *et al.,* 2012; Grimard *et al.,* 2016). The major parts include:

(1) Feeding hopper: it feeds to the extruder.
(2) Barrels (with heating and cooling device): they melt and mix the hydrophobic substance along with polymer.
(3) Single or twin screws: they mix, reduce the size and convey the mass to the die and screw driving unit.
(4) Die and screw driving unit: the mass flow through the unit to obtain the extrudates. Dies decide the shape of the extrudates.
(5) Conveyer belt: product is conveyed and cooled down on the conveyer belt.

HME technology has numerous advantages such as solvent-free, shorter production time, fewer processing steps and better content uniformity in extrudates. Moreover, the technology is suitable for sustained, controlled and targeted drug release systems (Sahoo1 *et al.,* 2019; Gajda *et al.,* 2018; Park *et al.,* 2013; Van Renterghem *et al.,* 2019; Cheng *et al.,* 2018; Gately *et al.,* 2017). However, the advantages of HME in increasing the solubility and dissolution of hydrophobic drugs are most attractive to formulation scientists. When the drug is dissolved at molecular level with the polymer, one-phase referred to as solid solution is obtained. If the drug forms microcrystalline dispersion which is a two-phase system with the polymer, it is referred to as a solid dispersion (Baghel *et al.,* 2016). In both scenarios, the wettability of the hydrophobic drug increases and deagglomeration as well as micellization of the drug with hydrophilic polymers are achieved. This leads to enhanced bioavailability of the hydrophobic drug (Huang *et al.,* 2019). In this entire process, the major factors that stabilize the drug and the carrier are the intermolecular interactions of the hydrophobic drug and the polymer, and the viscosity of the polymer or the carrier used along with the insoluble component (Hormann *et al.,* 2018).

HME has been widely used to improve the solubility of hydrophobic drugs. The adjustment of critical process parameters and carrier polymer screening are important factors that determine the properties of hydrophilicity and dissolution of the final product (Wesholowski *et al.,* 2019; Thakkar *et al.,* 2020). Higher barrel temperature provides more energy to break the crystal lattice of crystalline drugs to help the mixture melt as well as reduce the viscosity of the mixture to improve its extrudability (Reitz *et al.,* 2013; Maniruzzaman *et al.,* 2012). However, increasing the barrel temperature has a negative effect on the stability of the drug, especially for the thermosensitive drugs (Alsulays *et al.,* 2015; Ma *et al.,* 2019). The effect of screw speed on product properties is a complex behavior. It is one of the most important parameters which affect the convection and residence time of materials in the barrel. Increase in screw speed generates more heat in the barrel. The viscosity, mixing uniformity, stability and crystal state of materials may change with the adjustment of screw speed. Keeping the screw speed in a suitable range is the optimal strategy (Fan *et al.,* 2020). Fast cooling of extrudates prevents potential phase separation and drug nucleation thus yields amorphous solid dispersions that improve the solubility of the drug (Lang *et al.,* 2014; Chamsai and Sriamornsak, 2016). The macromolecules carrier used in HME not only affects the drug forming, but also inhibits the formation and growth of drug crystal nucleus thus inhibiting the recrystallization of the product. This plays a crucial role in improving the

solubility (Crowley *et al.,* 2007). These macromolecules are either naturally derived, semi-synthetically modified or synthetically manufactured depending on source. Based on the difference in drug solubility, carriers can be divided into either being hydrophilic or hydrophobic. They can be used for the preparation of immediate release dosage forms and modified release dosage forms respectively (Thakkar *et al.,* 2020). The combination of hydrophilic carriers and hydrophobic drugs can increase the wettability of drugs and improve the solubility and dissolution of drugs. Hydrophilic carriers such as povidone, cellulose, polyethylene glycol, polyacrylic resin, and surfactants are widely used in HME technology are showed in table 3.

Supercritical fluid

Supercritical fluids (SCF) are fluids whose temperature and pressure are greater than their critical temperature and critical pressure. This allows them to possess the properties of a gas and liquid (fig. 7) (Yasuji *et al.,* 2008; Chakravarty *et al.,* 2019). Supercritical fluids were first described in experiments in 1822. Superficial matter also exists in nature, for example, the high pressure and high temperature of underwater volcanoes lead to the supercritical state of water (Knez *et al.,* 2014). As a special phase state of matter, supercritical fluids have the characteristics of liquid and gas such as strong dissolving ability because they have a density similar to that of liquids and conducive for mass transfer because of viscosity and expansion coefficient similar to that of gases (Davies *et al.,* 2008, Kalani and Yunus, 2011). Supercritical fluids have many other advantages such as being non-toxic, economical and environmentally friendly (Djas and Henczka, 2018; Patel *et al.,* 2019). With the deepening research of SCF theory and continuous innovation of equipment, SCF technology has been applied in many fields such as medicine, food, textile, and petroleum industry among others (García-González *et al.,* 2015; Kankala *et al.,* 2017; Hofstetter *et al.,* 2019; Khosravi-Darani, 2010; Liu *et al.,* 2020; Banchero, 2013; Thiebaut, 2012). The application of SCF in the field of medicine focuses on aspects of extraction of natural drugs, enantio-separation of chiral drugs and chromatographic analysis (Molino *et al.,* 2020, Zhao *et al.,* 2019; Duval *et al.,* 2019). The selection and control of fluid medium is the critical process parameter of an SCF technology. Theoretically, any kind of gas and liquid can form supercritical fluid under the appropriate temperature and pressure conditions. Compounds such as H_2O, N_2, Xe, SF_6, N_2O, CHF_3, ethylene, propylene, propane, ammonia, n-pentane, ethanol, and CO_2 have been tried as SCF, while CO_2 is the best choice among the list (Rabinarayan *et al.,* 2013; Kompella and Koushik, 2001). Safety and low cost are the most significant benefits of using CO_2 as supercritical fluid. Compared with other fluids, low critical temperature (31.1 °C) and pressure (74 bar) are the excellent characteristics of CO_2 as a widely used supercritical fluid (Machado *et al.,* 2013).

Supercritical fluids are highly compressible at or near critical temperature. This causes moderate changes in pressure to further alter the density and mass transport characteristics of fluids. This causes drug particles to solubilize or precipitate under supercritical fluid conditions. The drug particles could further be recrystallized at immensely reduced particle size (Martin and Cocero, 2008; Almeida *et al.,* 2016). As one of the novel nonionizing and solubilization technology where particle size reduction is achieved, SCF has different principles as per different processes. These processes can be classified according to the role of the supercritical fluid in the process i.e. solvent, anti-solvent, solute or co-solvent as showed in table 4 (Oliveira *et al.,* 2013). The principle of rapid expansion of supercritical solution (RESS) states that the solubility of drugs changes with the density of SCF. Similarly, the solubility is also very sensitive to the change of pressure. Cognizant to this, the drugs can be rapidly precipitated to form microparticles by adjusting the pressure (Leeke *et al.,* 2014). The low solubility of most drugs in SCF is the main limitation of RESS (Shariat and Peters, 2002). Adding non-solvent (RESS-N) or co-solvent (RESS-SC) attempted to solve this problem but caused a new problem of residue formation (Sodeifian *et al.,* 2018). Supercritical antisolvent technology (SAS) can effectively ameliorate the defects of solvent residues and significantly reduce the particle size of drugs under mild conditions (Djerafi *et al.,* 2015). SCF added into the system of drugs and organic solvents as an antisolvent result in the expansion of volume of the liquid phase thus reducing the solubility of drugs. This further leads to rapid precipitation of the drugs into solid particles. In contrast to RESS, insoluble drugs in SCF is the basis of SAS (Sodeifian and Sajadian, 2018). There are many innovations in supercritical anti-solvent technology. These innovations arise after combining the technology with ultrasound, atomization, emulsification and other technologies as showed in table 4. In the process of particles from gas saturated solutions (PGSS), SCF dissolves the drug in the molten state as solute and forms a "gas saturated solution" after reaching saturation. This solution contains about 5-50% SCF. The molten mixture is atomized, expanded through decompression and then cools rapidly. The aim is to make the drug form many crystal nuclei and grow into solid particles instantly (Weidner, 2009). However, it is not suitable for the preparation of thermosensitive drugs and drug loaded particles because the process requires the drugs to melt. In recent years, the technology of supercritical fluid assisted atomization (SAA) using SCF as co-solute and auxiliary atomization medium has been developed. In this process, SCF is initially mixed with aqueous and organic phases containing the drug and dissolved as solute.

Table 5: Summary of examples obtained from scientific literature on the use of SCF for the production of drug

Drug	Carrier	Method	Solubilizing Effects	Ref
Posaconazole	4-aminobenzoic acid	GAS	The average particles size of cocrystals of posaconazole and 4-aminobenzoic acid was less than 45 μm.	Long *et al.*, 2021
Withaferin A	/	RESS	The optimum particle size of withaferin A nanoparticles were 20.5 nm.	Karimi and Raofie, 2020
Baicalein	Hydroxypropyl-β-cyclodextrin	PCA	Inclusion complex particle size 0.295±0.035 μm, the dissolution of pure API was less than 15% at 15 min, while the inclusion complex was exceeding to 90% at 15 min.	Yan *et al.*, 2019
Trans-resveratrol	HPMC/poloxamer 407	SAS	Composite nanoparticles produced particle size 258.5±19.5 nm and trans-resveratrol particle size 2631.4±203.1 nm, the solubility of trans-resveratrol was dramatically increased.	Ha *et al.*, 2019
Praziquantel	Cetyl palmitate	SFEE	Praziquantel-solid Lipid Nanoparticles particle size 23.78±4.52 nm.	Andrade *et al.*, 2019
Thymol	/	RESS	The micronization process led to a reduction of 77.5 times in particle size and an increase of 37.28% in solubility.	Martello *et al.*, 2019
Gambogic acid	/	RESOLV	The dissolution rate of the nanosized gambogic acidparticles (approximately19 μg/ml, 110 min) was enhanced in comparison to the raw API (approximately 9 μg/ml, 110 min).	Xiang *et al.*, 2019
Puerarin	β-cyclodextrin	SEDS	The accumulated release rate of inclusion complex nanoparticles of puerarin reached 98 % within 5 min, markedly higher than that of the puerarin powder and its physical mixture.	Lei *et al.*, 2019
Loratadine	/	US-RESSAS	The API particles were observed to become nanosized from the original average size of 32.6 μm to 26 nm, dissolution rates enhancement of 3.5 folds after the US-RESSAS process.	Sodeifian and Sajadian, 2019
Amiodarone hydrochloride	PVP	RESOLV	Nanoparticles particle size 53.3 nm, the dissolution of pure API was approximately 30% at 60 min, while the dissolution of nanoparticles was exceeding to 80% at 30 min.	Sodeifian and Sajadian, 2019
Gefitinib	/	SEDS	The dissolution of pure API was approximately 20% at 60 min, while the dissolution of microparticles was exceeding to 70% at 60 min.	Zhang *et al.*, 2019
Ibuprofen	Kollidon CL-SF	RESS	In the first 5 min, 83.7% of the ibuprofen in the solid dispersions was dissolved, these values 22.3 times of pure ibuprofen.	Han *et al.*,2019
Carvedilol	PVPKollidon®30	RESS	The dissolution of crude API was less than 25% at 10 min, while the dissolution of solid dispersions was exceeding to 80% at 10 min.	Djuris *et al.*, 2019
Berberine	β-cyclodextrin	SEDS	In vivo pharmacokinetic studies showed that oral bioavailability increased by about 86% when the dissolution rate of inclusion complex was increased by 83%.	Jia *et al.*, 2018
Lonidamine	/	RESS	The dissolution of pure API was approximately 20% at 48 h, while the dissolution of nanoparticles was approximately 20% at 48 h.	Chen *et al.*, 2018
Letrozole	Menthol	RESS-SC	Letrozole Nanoparticles particle size 19.0 nm, the dissolution of pure API was less than 30% at 60 min, while the dissolution of nanoparticles was approximately 80% at 60 min.	Sodeifian and Sajadian, 2018
Naringenin	/	SEDS	The dissolution of unprocessed API only less than 20% at 60 min while over 70% of the microparticles was released. At the end of the experiment (240 min), approximately 85% of the microparticles had dissolved, while only 25% of the unprocessed API had dissolved.	Miao *et al.*, 2018

Table 6: Major advantages and disadvantages of different methods

Methods	Advantages	Disadvantages
Rotor Stator Colloid Mill	Materials with high viscosity and large particles are applicable.	The friction between the rotor-stator and the material produces heat, which makes the material denatured and mechanical wear.
Jet Mill	Clean compressed air can prevent materials from being polluted. Uniform particle size distribution is obtained after cyclone separation.	Materials with large oil, water and fiber are not applicable and dust exposure in the air is caused by poor sealing.
Ball Mill	Both dry grinding and wet grinding are suitable for mass production, beside, the equipment is well sealed to avoid dust exposure.	The operation of equipment requires high energy consumption and complex cleaning procedures.
Spray drying	Different particle size distribution can be obtained by controlling spray drying parameters. Application to heat sensitive materials due to fast drying speed.	Air heating leads to high energy consumption. The heat was diffused into the drying materials by air convection which makes the heat efficiency low.
Hot melt extrusion	Absence of solvents avoids residual organic solvents and uniform dispersion of disperse solids in the molten mass.	High heat input is not suitable for heat sensitive drugs and excipients are needed.
Supercritical fluid	The particle size reduction of low solubility drugs is suitable. Mild conditions and environmental friendliness are observed during the operation.	The equipment is expensive and complicated to operate due to the requirement of high pressure resistance.
Salt formation	Salt forms of drugs can be obtained by a simple process.	Non-ionic drugs are not applicable. The changes of pharmacological action and the increase of toxicity were observed occasionally.
Co-crystallization	Acid, basic and non-ionic drugs are applicable. Abundant co-formers provide a wide range of options and show remarkable safety.	The thermodynamic stability of co-crystal system and the purity of final product are main challenges.

The mixture is then atomized. The atomization effect is significantly enhanced because of the decompression expansion of SCF (Reverchon *et al.,* 2015). The most significant advantage of SAA and other related technologies such as supercritical fluid assisted atomization introduced by hydrodynamic cavitation mixer (SAA-HCM) is that they are suitable for aqueous systems and thermosensitive drugs (Hong *et al.,* 2018). Notably, SCF enhance drug solubility by reduce drug particle size and forming composite microparticles of the hydrophilic carrier and drug as showed in table 5.

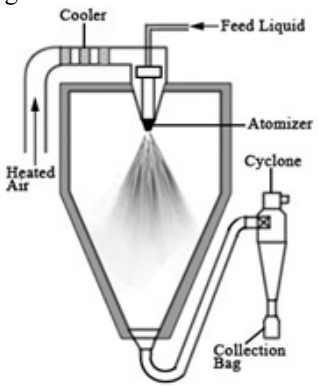

Fig. 5: Scheme of Spray Drying

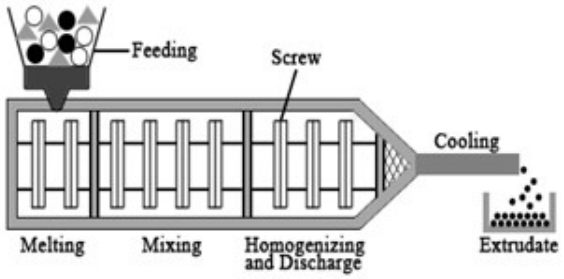

Fig. 6: Scheme of Hot Melt Extrusion

Chemical modification

Chemical modification of hydrophilic substances can enhance their solubility and dissolution rates. These modifications can either be salt formation, or co-crystallization.

Salt formation

Salt formation is an effective and common method of increasing solubility and dissolution rates of hydrophilic substances. A cursory search of the U.S. Patent and Trademark Office database revealed that over 24,000 issued U.S. patents contain the term "pharmaceutically acceptable salt" in one or more claims (Trask, 2007). The targeted drugs with this technique are either acidic or basic in nature. As such, the physicochemical properties of non-ionic drugs cannot be changed through salt formation (Thakuria and Nangia, 2013). The salt forming process of drugs is to introduce guest molecules to change the molecular arrangement and stacking mode of API (Stanton and Bak, 2008). The change of intermolecular force and lattice energy results in the alteration of physicochemical properties such as melting point, solubility, stability and bioavailability after salt formation (Rodríguez-Hornedo *et al.,* 2006). Accumulating evidence suggests that the solubility and dissolution of drugs increase significantly after salt formation.

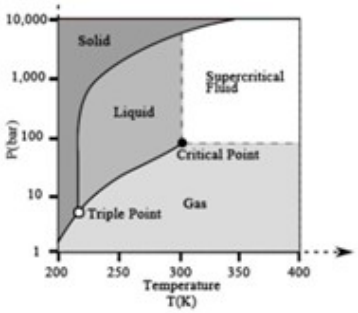

Fig. 7: Phase diagram of CO_2

The solubilization ability is related to the inherent properties of drugs and the types of salts. It was reported that the solubility of delveridine mesylate is 2238 times greater than that of the free base (Stephenson *et al.,* 2011). In the same line, researchers reported that the solubility of adamantylamine increased approximate 200 times when combined with sulfonate derivatives (especially, methane-sulfonate) because of the high solubility and low molecular weight of these counterions (Martins *et al*., 2019). The comparative study on the solubility of telmisartan hydrochloride and telmisartan showed that the solubility of the salt form was significantly higher than that of the free base in various media (in distilled water the solubility was 1243.17µg/mL vs. 0.09µg/mL, 1404.46 µg/mL vs. 125.41µg/mL and 86.92µg/mL vs. 0.05 µg/mL in distilled water, SIF (pH 1.2) and SIF (pH 6.8) respectively (Park *et al.,* 2019). Application of sodium saccharinate and sodium cyclamate not only solved the problem of benexate's bad taste, but also increased the solubility by 5 and 1.5 times relative to the marketed form of benexate (Dwichandra *et al.,* 2018). The Orange Book contains 1356 molecular entities listed up to 2006. More than half of them are in salt form. The most commonly used anion are chloride and sulfate while sodium accounts for 75.3% of all basic salts (Paulekuhn *et al.,* 2007, Lam *et al.,* 2010). According to the Orange Book, the commonly used salts include sodium, hydrochloride, sulfate, phosphate, lactate, hydro-bromate, methane-sulfonate, maleate and tartrate.

Co-crystallization

Co-crystals are crystalline materials composed of two or more different molecules within the same crystal lattice. The molecules are bonded together by hydrogen bonds, van der Waals forces, π stacking, halogen bond and other non-covalent forces. Co-crystallizing agents are solids at room temperature thus making the process very stable (Lara-Ochoa and Espinosa-Pérez, 2007). There seems to be a similarity between salt formation and co-crystallization. Actually, the difference between co-crystals and salt lies in the degree of proton transfer (Das

and Baruah, 2011). If the API and its co-former have aΔpKa (pKa (base) - pKa (acid)) less than 1, there is less substantial proton transfer. In this case, the API-co-former entity should be classified as a co-crystal (Mukherjee and Desiraju, 2014; Cerreia *et al.,* 2017). The design of co-crystals is mainly based on the principles of supra-molecular chemistry and crystal engineering.

It is therefore necessary to fully analyze the possible functional groups in the API and select the appropriate co-formers. Co-formers include pharmaceutical excipients, food additives, vitamins, preservatives and amino acids. API can also be used as co-formers (Almarsson and Zaworotko, 2004). Compared with salt, polymorph and solvate, the physicochemical properties such as melting point, stability, solubility, dissolution and bioavailability of the drug eutectic can also be improved (Vemuri and Lankalapalli, 2019). For example, to increase the solubility of nitrofurantoin, the co-crystal was mixed with citric acid in 1:1 stoichiometric ratio and the solid dispersion consisted of 30% w/w nitrofurantoin and 70% w/w HPMC as the carrier system. Dissolution studies showed a greater initial dissolution rate in co-crystal than solid dispersion despite the possible presence of amorphous content in the solid dispersion system (Teoh *et al*., 2019). The dynamic solubility of co-crystals containing DL-tartaric acid in the ratios 1 : 1, 1 : 2 and 2 : 1 increased by fold 1.39, 1.66, 6.01 as compared to pure zoledronic acid, respectively (Varmaa *et al.*, 2019). Theophylline is a typical representative co-former, which forms co-crystal with various drugs such as nicotinamide (Srinivasan *et al*., 2021), apigenin and daidzein (Huang *et al*., 2019), sulfathiazole (Yeh and Lee, 2018), diflunisal and diclofenac (Surov *et al*., 2014); flufenamic acid (Aitipamula *et al*., 2014). Many co-crystals combinations have been proved to be effective in improving solubility by the formulator, including bis(demethoxy)curcumin and hydroxyquinol (Wunsche et al., 2021), sulfamethazine and 3-methylsalicylic acid (Ahuja *et al*., 2020), Lamotrigine with malonic acid (Chappa *et al*., 2019), meloxicam with succinic acid (Ogienko *et al*., 2018), naproxen with nicotinamide (Abbas *et al*., 2018), ticagrelor with nicotinamide (Inam *et al*., 2018), carbamazepine with saccharin (Abd Rahim and Amanina, 2018), paracetamol with caffeine (Latif *et al*., 2018) and atorvastatin calcium with isonicotinamide (Wicaksono *et al.*, 2017). Co-crystallization can be applied to all kinds of API, including acids, bases and nonionic compounds, and thus it can find wide application in drug development.

CONCLUSION

Solubility and dissolution are the most important parameters governing drug bioavailability. Optimal concentration of drug at the site of action depends of these two factors. Solubility of hydrophobic drugs decreases bioavailability and hence it is considered during drug formulation and development. This paper reveals that selection for enhancing the solubility of hydrophobic drugs should be done according to the nature of drug, compatibility, interaction of drug with other excipients, stability of the product and the yield obtained. In addition, the major advantages and disadvantages of different methods should also be considered (table 6). In conclusion, the technologies or advancements discussed above are likely to transform the pharmaceutical industry in terms of improving the solubility of hydrophobic drugs, either as single drugs or as combinations.

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