Expert Opinion

1. Introduction
2. New strategies in solid dispersion manufacturing methods
3. Conclusions
4. Expert opinion

Solid dispersions, Part II: new strategies in manufacturing methods for dissolution rate enhancement of poorly water-soluble drugs

Dimitrios N Bikiaris
Aristotle University of Thessaloniki, Laboratory of Polymer Chemistry and Technology, Department of Chemistry, Thessaloniki, Greece

Introduction: The absorption of poorly water-soluble drugs, when presented in the crystalline state to the gastrointestinal tract, is typically dissolution rate-limited, and according to BCS these drugs belong mainly to class II. Both dissolution kinetics and solubility are particle size dependent. Nowadays, various techniques are available to the pharmaceutical industry for dissolution rate enhancement of such drugs. Among such techniques, nanosuspensions and drug formulation in solid dispersions are those with the highest interest.
Areas covered: This review discusses strategies undertaken over the last 10 years, which have been applied for the dissolution enhancement of poorly water-soluble drugs; such processes include melt mixing, electrospinning, microwave irradiation and the use of inorganic nanoparticles.
Expert opinion: Many problems in this field still need to be solved, mainly the use of toxic solvents, and for this reason the use of innovative new procedures and materials will increase over the coming years. Melt mixing remains extremely promising for the preparation of SDs and will probably become the most used method in the future for the preparation of solid drug dispersions.

Keywords: electrospinning, melt mixing, microwave irradiation, nanocomposites, poorly water-soluble drugs, solid dispersions, solubility enhancement, supercritical

Expert Opin. Drug Deliv. (2011) 8(12):1663-1680

1. Introduction

In recent years, the number of active pharmaceutical ingredients (API) having high therapeutical impact but low water solubility is estimated to be around 25 – 40% of the total drugs. This poor solubility lowers their gastrointestinal tract absorption and ultimately limits their clinical utility. To improve the solubility and dissolution rate of these drugs several technological methods have been reported such as: i) reducing particle size to increase surface area, ii) solubilization in surfactant systems, iii) formation of water-soluble complexes, iv) use of prodrug and drug derivatization approaches, such as strong electrolyte salt forms and v) decreasing crystallinity of the drug substance or preparation of amorphous dispersions through formation of solid solutions [1,2].

The strategy of reducing the particle size of an API by micronization has been applied in the pharmaceutical industry for several decades. Until recently, however, the ability of existing particle size reduction techniques was limited to sizes within the micron range, because of the rapid agglomeration of sub-micron drug particles due to the presence of cohesive forces [3]. The existing technologies for reducing particles size

informa healthcare

10.1517/17425247.2011.618182 ISSN 1742-5247

Article highlights.

- Several techniques can be used for the preparation of solid drug dispersions.
- Melt mixing is a continuous and simple process that does not require the use of any kind of solvent.
- CO_2 is used as solvent for the preparation of solid dispersions (SDs) in supercritical conditions, which is not toxic and easily evaporated.
- Microwave irradiation (MW) is also proved to be a viable, fast and alternative technique to prepare solvent-free SDs.
- Electrospinning is also a new method for the preparation of SDs in the form of nanofibers with extreme high drug dissolutions rates.
- SDs using inorganic nanoparticles (layered double hydroxide (LDH), fumed silica and mesoporous silica) have the advantage that the drug is dispersed in high surface area.

This box summarizes key points contained in the article.

can be divided into so-called 'top-down' (jet milling, pearl mill and spiral jet milling) and 'bottom-up' technologies [4]. However, none of the top-down technologies are ideal for the formation of nanocrystal particles, because they are usually inefficient due to high-energy input or pharmaceutical contamination and denaturation during the milling process. This is crucial since in drug nanocrystals the particle size is reduced to its absolute minimum (> 1 μm) which causes increased dissolution rates [5,6]. Currently, industrial-scale production of drug nanocrystals falls mainly into the category of bottom-up approaches, in particular precipitation-based processes, such as spray drying and supercritical antisolvent (SAS) process, spray freeze drying into liquid, evaporative precipitation into aqueous solution and liquid solvent change process, etc. [7,8].

Besides the formation of drug nanocrystals the dissolution rate of poorly water-soluble drugs can be increased by the formation of a high-energy but stabilized amorphous form [9,10]. This can be achieved mainly with the dispersion of a drug in a polymer matrix and with evolved hydrogen bonding. Amorphous drugs can more easily dissolve, compared with crystalline, and, thus, dissolution rate can be enhanced. Drug formulation in solid dispersions (SDs) is one of the first and most commonly used techniques up to this day for the dissolution rate enhancement of poorly water-soluble drugs. Generally, SDs may be defined as pharmaceutical dosage forms in which the drug is dispersed in a biologically inert matrix. The formulation of hydrophobic drugs as SDs is a significant area of research aiming to improve their dissolution and bioavailability. The SDs consists of a poorly water-soluble drug and a hydrophilic excipient that may be either water-soluble or water-insoluble. However, in SDs the drug can also be dispersed in nanocrystalline form and in that case the dissolution enhancement is due to the wetting characteristics of the used carrier or due to the drug particle size reduction. In both cases, the carrier properties influence the dissolution rate of the drug [11]. New and optimized manufacturing processes for producing effective SDs are desired [12].

There are a lot of methods for the preparation of SDs. Some of them are very old and rather simple, such as solvent evaporation and kneading methods. However, these are time consuming and in some cases the used solvent may be toxic or remain at high levels in the final formulation. In the past years, a lot of progress has been made in the methods used for the preparation of SDs and new techniques have been applied solving a lot of problems. This review focuses on describing the new strategies and the evolution of some SD manufacturing methods. Emphasis is also given on the application of new techniques.

2. New strategies in solid dispersion manufacturing methods

2.1 Melt mixing

Although hot-melt extrusion (HME) is a well-known technique in the field of food and plastics industry for more than a century, it has only recently gained increased acceptance in the pharmaceutical industry for the preparation of SDs. Compared with other techniques, HME has a lower environmental impact (absence of solvents), reduced cost (few processing steps, continuous operation) and can be used to provide sustained, modified, targeted drug delivery and drug formulations with improved bioavailability [13-17]. The technique is rather simple. The drug is physical premixed with the appropriate drug carrier(s) and this mixture is introduced into rotating screws that convey the powder into a heated zone. Shear forces are imparted into the mixture, compounding the materials until a molten mass is achieved. The drug is dissolved into the polymer melt and this is extruded from the die. After cooling, the drug is dispersed in semicrystalline or amorphous form into the polymer matrix. The used machines for melt mixing, the screws configuration, the mechanism for drug dissolution into polymer melt and the extruded products are presented in **Figure 1**.

In SDs prepared by HME, the drug is in most formulations dispersed at a molecular level. This was verified in ritonavir drug melt extrudates [18]. In the case of poly(vinyl pyrrolidone) (PVP) and bicalutamide (BL) SDs prepared by HME at drug-to-polymer ratios of 1:10, 2:10 and 3:10 (w/w), it was found that all hot melt extrudates had a single glass transition temperature (T_g) between the T_g of amorphous BL and PVP [19]. This indicates miscibility of BL with PVP and the formation of SDs in which the drug was dispersed at a molecular level. Experimentally observed T_g values of physical mixtures (PM) were shown to be significantly higher than those calculated using the Gordon–Taylor equation suggesting the formation of strong intermolecular interactions between BL and PVP [19]. So it seems that HME gives sufficient energy for such interactions to take place. These are responsible for drug amorphization and enhanced dissolution properties, as

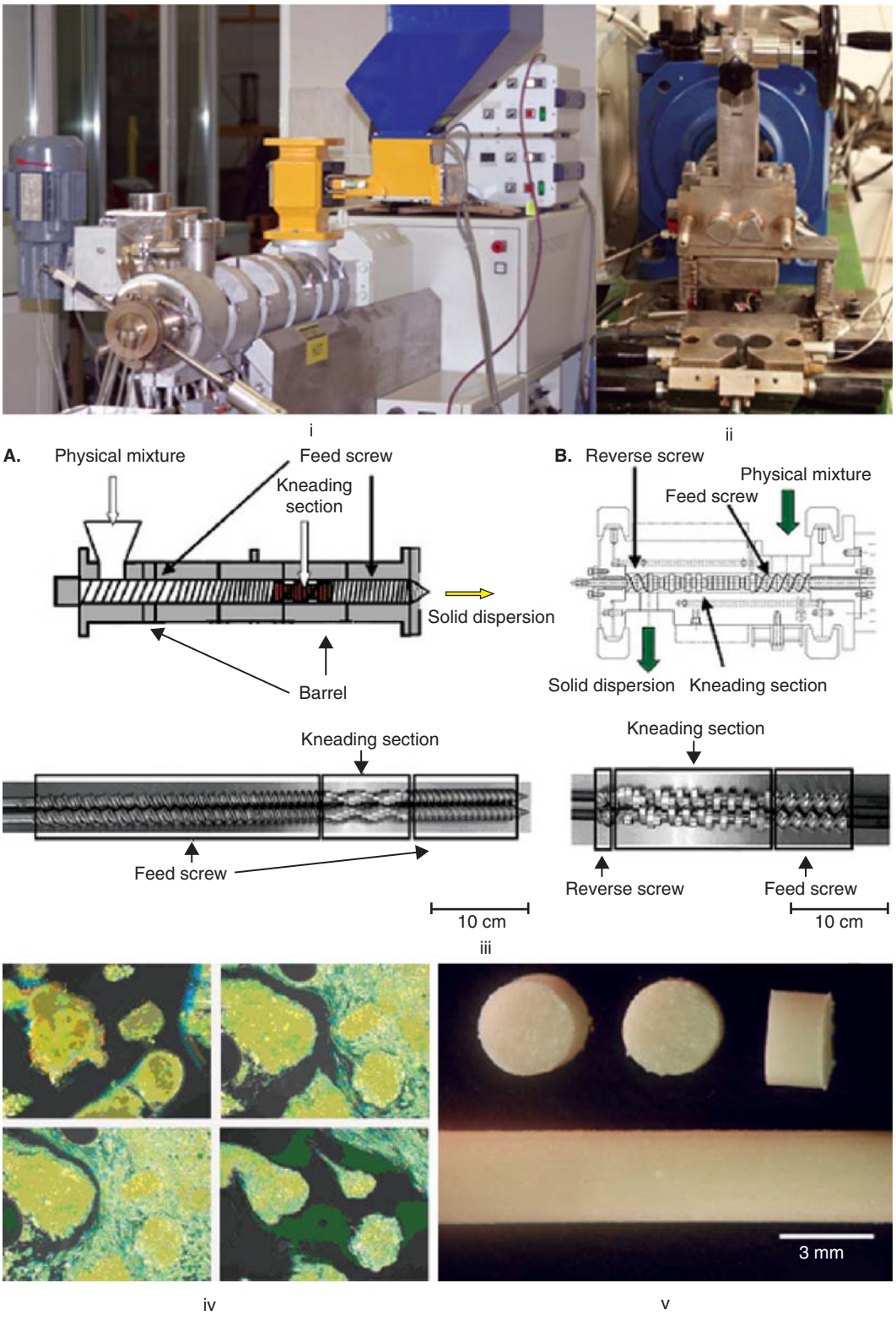

Figure 1. (i) Twin screw extruder; (ii) a batch mixer with roller screws used for solid dispersions (SDs) preparation with melt mixing procedure; (iii) schematic view of the (A) extruder and (**B**) kneader; (iv) drug dissolution in polyethylene glycol melt at different temperatures; (v) optical images of SDs extrudates from hot-melt extrusion.
Reproduced with permission from [26].

in the case of the solvent evaporation technique. The mechanism of dissolution enhancement is also similar to that of solvent evaporation [11]. It was found that dispersion of melt extrudates in aqueous medium gives rise to nano/micro-dispersions and, thus, its dissolution enhancement. Dissolution testing of itraconazole SDs conducted at sink conditions revealed that the dissolution rate of the micronized particles was improved by HME due to particle deaggregation and enhanced wetting [20].

The HME process, whether it results in a glassy solid solution or in a crystalline suspension, mainly depends on the evolved interactions, the temperature settings of the barrel segments, the used carrier and the drug amount [21]. Formulation of API in high-energy amorphous form is desired in SDs prepared by HME if it is stable. However, this is not always the case and in polyethylene oxide (PEO)/acetaminophen (APAP) SDs it was found that the drug tended to recrystallize on cooling to room temperature for all the drug loadings investigated [22]. This is due to the crystalline nature of the drug carrier which causes a heterogeneous crystallization of the drug. Besides recrystallization, polymorphism may also take place during melt mixing, as verified from a previous study, and this can affect the dissolution rate of the used drug [23,24].

The importance of processing parameters during melt extrusion for the preparation of SDs was revealed in indomethacin (INM) and Eudragit® E PO (EPO) extrudates [15]. In this paper, the effects of three process parameters – set mixer temperature, screw rotating speed and residence time – were studied. The reported results showed that the dissolution rate increased with increasing the mixer set temperature, or the screw rotating speed. This was because the dissolution of the drug in the polymer melt is a convective diffusion process, and laminar distributive mixing can significantly enhance the dissolution rate. In another study, it was found that by increasing the temperature during HME and reducing the drug loading in PVP/vinylacetate (VA) (Kollidon® VA64) nimodipine (NM) SDs, NM could be obtained in an amorphous state [25]. Higher temperature can lead to better solubility of the drug into the polymer melt, while decreasing the drug's amount means that the drug cannot be crystallized. In all reported formulations dramatically higher dissolution rates were found. Besides heating temperature and screw rotation speed, the retention time of the samples in the extrusion machines also plays an important role in the preparation of SDs. In a recent study of CrosPVP/INM SDs, it was found that although SDs were prepared by heating at 125°C for 30 min, it was more useful to be able to continuously prepare powdered SDs by heating below the melting point (140°C) in a short time (4 min) using an extruder or a kneader from the viewpoint of manufacturing [26].

From all the reported studies till today in literature it can be seen that PVP and polyethylene glycols (PEGs) are the most used carriers for the preparation of SDs during HME. PEGs are widely used because of their low melting point and higher wettability. However, the drug in such SDs is often present in the crystalline form or it recrystallizes over time, resulting in unstable formulations with lower dissolution rates. PVPs are amorphous polymers with glass transition temperatures between 110 and 180°C. This relatively high glass transition temperature limits the applicability of PVP for the preparation of SD by the melting method. For this reason, PVP can be used in combination with PEG as in the case of valdecoxib drug [27]. *In vitro* dissolution studies performed in 0.1 N HCl showed a significant increase in dissolution rate when PEG 4000 and PVP K30 were used in combination. Improved drug dissolution by both carriers may be attributed to the improved wettability, reduction in drug crystallinity and solubilizing effects. Similar polymer mixtures of PEG 1500 and the polymers PVP, polyvinylpyrrolidone-co-vinylacetate (PVP/VA) and Eudragit EPO were also used in order to prepare SDs by a melting method [28].

While this manufacturing method has many advantages over solvent-based methods, it does have some limitations. During processing, drug substances are exposed to elevated temperatures for prolonged periods of time (2 – 10 min) and this can induce decomposition of thermally unstable drugs. When these processing issues are encountered new strategies can be used, such as the addition of processing aids, like plasticizers, which may allow processing to be carried out at a lower temperature [29]. Furthermore, there is a possibility that the API, the polymer or both may degrade if excessively high temperature is needed in the melt extrusion process. To solve this problem in a recent study a novel method was reported wherein the API was first converted to an amorphous form by solvent evaporation and then melt-extruded with a suitable polymer at a drug load of at least 20% w/w [30]. By this mean melt extrusion could be performed at temperatures below the melting point of the drug. Since the glass transition temperature of the amorphous drug was lower than that of the polymer used, the drug substance itself served as the plasticizer for the polymer. The melt extruded amorphous formulations showed higher oral bioavailability than the crystalline formulation.

Besides the traditional melt techniques recently a new fusion-based process was developed to prepare SDs by imparting high shear and frictional forces without external heat input, named KinetiSol® Dispersing (KSD) [16,31]. The technique is conducted using a custom-built compounder designed for pharmaceutical processing applications by DisperSol Technologies, L.L.C. (Austin, TX, USA). Briefly, the unit consists of a product containment vessel containing a rotating shaft with processing blades extending outward from the shaft. During operation, the blades rotate at a high rotational velocity rapidly processing the material through the development of heat generated by shear and frictional motion of product within the vessel. This method of heat generation is unique among fusion-possessing technologies and no external heat input is required during production.

When comparing manufacturing techniques, it was found that KSD provided a threefold increase in a BCS (Biopharmaceutics Classification System) class II drug recovery over HME for Eudragit L100-55 compositions, without the need for plasticizer or micronized drug. Furthermore, compositions prepared by HME contained crystalline drug and high levels of impurities, whereas KSD compositions were substantially amorphous and contained fewer impurities. It was clearly demonstrated that KSD is an effective method of forming dissolution-enhanced amorphous solid solutions of chemically and thermally unstable compounds due to the ability to rapidly process compositions [16]. Previous studies conducted by DiNunzio *et al.* have illustrated clear advantages of KSD over HME, including the preparation of plasticizer-free Eudragit L100-55 compositions leading to enhanced physical stability and the successful processing of hydrocortisone [31]. Furthermore, the method is more appropriate compared with traditional method when thermally sensitive drugs are used. In a recent paper it was reported that manufacturing process control studies using hot melt extruded compositions of hydrocortisone and PVP/VA showed that increased temperatures and residence times negatively impacted product potency due to decomposition [32]. Using KSD to reduce residence time and to facilitate lower temperature processing it was possible to produce SDs with improved product potency. The study clearly demonstrated the importance of carrier selection to facilitate lower temperature processing, as well as the effect of residence time on product potency. Furthermore, KSD provided significant advantages over HME due to the reduced residence times and lower processing temperatures required. This allowed for the production of SDs with enhanced product potency.

2.2 Supercritical processes used for solid dispersion preparations

Most SD formulations are prepared by solvent evaporation. However, some of these solvents, such as chloroform, dichloromethane, etc., are toxic. As an alternative supercritical carbon dioxide ($scCO_2$) can be used for drug dissolution enhancement, which is a non-conventional compressible solvent [33]. CO_2 has high dissolution capability, low toxicity, low-cost, large availability, excellent biocompatibility and low environmental impact and for all these has become nowadays an important commercial and industrial solvent. Furthermore, because CO_2 attains the critical point under mild conditions (7.38 MPa and 31°C), $scCO_2$ maybe most suitable for preparing pharmaceutical products compared with other solvents. Supercritical micronization processes, such as rapid expansion of a supercritical solution (RESS) [34], SAS (**Figure 2**) [35], gas antisolvent process (GAS) [4,36], particles from gas saturated solutions (PGSS) [37] and precipitation with compressed fluid antisolvent (PCA) [38], have gained increasing attention and may be considered as interesting alternatives and most effective processes for the micronization of SDs.

In the RESS technique, the material to be processed must be dissolved at high pressure in CO_2 and after expansion drug nanocrystals can be prepared. Depending on the solvent and the pre- and post-expansion conditions, particles can be produced with a mean diameter of 100 – 200 nm and the improved dissolution behavior is influenced by particle size, surface area and wettability of the processed powders, as well as by the pH value of the dissolution media [39]. The used drug carrier is very important for the formed size and shape of nanocrystals in the RESS process [40]. Needle-like flurbiprofen (FP) fine particles were obtained, which adhered to the surface of lactose particles. The number of FP particles that adhered to the surface of particles decreased with an increase in the ratio of lactose added, leading to a markedly improvement of the dissolution rate. This improvement was caused not only by the increase in the specific surface area, but also by the improvement of the dispersibility of FP in water. However, except for nanocrystals, amorphous SDs can also be prepared, as in the case of cefuroxime axetil (CFA) [41]. The effects of process parameters, such as the temperature of nozzle (50 – 70°C) and extraction port (60 – 90°C), on the properties of the formed particles were investigated. The lowest particle size was seen in the sample prepared with nozzle temperature 60°C and extraction temperature 90°C. More than 90% of the partly nano-sized CFA formulations were dissolved in 3 min and complete dissolution occurred within 20 min.

An interesting modification of the RESS process is RESSAS (Rapid Expansion of Supercritical Solution into Aqueous Solution) that consists of two steps. The first is to expand the supercritical solution into a liquid solution instead of a gas and the second is to use surfactants to stabilize the particles in aqueous solutions [42,43]. The advantage of this procedure is that nanoparticles with lower particle sizes and, thus, higher dissolution rates, can be prepared. This was verified in a recent paper where the applications of RESS and RESSAS were used comparative for the production of submicron particles of the poorly water-soluble drug naproxen (NP) [44]. The experimental results show that the RESS processing of NP leads to particles in the range of 0.56 – 0.82 μm, which is about 22 times smaller than the unprocessed powder. However, in the RESSAS experiment the stabilized NP particles have an average diameter of 0.3 μm for drug concentrations up to 1 g/dm^3 in 0.4 w/w PVP solution, which is much smaller than that produced with RESS.

Similar results were also obtained with the SAS method using cilostazol drug and different additives, including poloxamer 188, poloxamer 407, D-α-tocopheryl polyethylene glycol (TPGS) 1000, Gelucire® 44/14 and Gelucire 50/13 [45]. Interestingly, the morphology of SAS particles processed with TPGS 1000, Gelucire 44/14 and Gelucire 50/13 changed to plate or leaflet shape. Poloxamer 188 and 407 were superior in increasing the dissolution rate due to decreased particle size, the resulting increased surface area and improved wettability. However, micronized and nano-sized drug particles produced with SAS have a high tendency to agglomerate leading to disadvantages of decreased drug solubility, dissolution rate or bioavailability

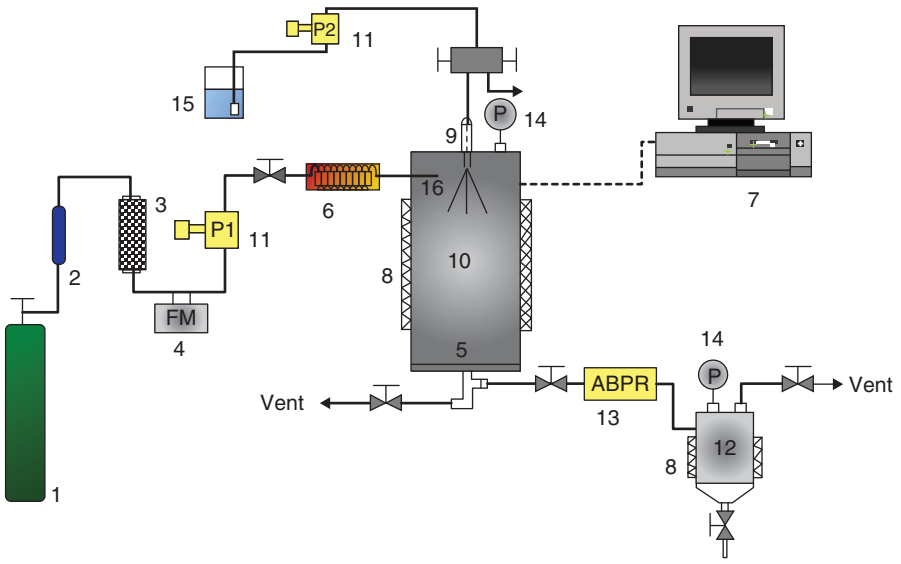

Figure 2. Schematic diagram of a Thar Technologies' Co USA supercritical antisolvent (SAS) laboratory apparatus for co-precipitation. (1) CO_2 cylinder; (2) filter; (3) cooler; (4) mass flow meter; (5) metal frit; (6) preheater; (7) computer; (8) heating jackets; (9) solvent nozzle; (10) precipitator vessel; (11) high-pressure pumps; (12) separator; (13) automatic back-pressure regulator (ABPR); (14) pressure gauges; (15) drug solution; (16) CO_2 nozzle.

Reproduced with permission from [35].

[46]. To overcome this, SAS-drug excipient mixing (SAS-DEM) method for micro/nano-drug particle formation and prevention of drug–drug particle agglomeration was proposed [47]. Using this method, nevirapine (NEV) drug microparticles were prepared using excipients such as lactose and microcrystalline cellulose. It was found that the SAS-DEM treatment was effective in overcoming drug–drug particle aggregation and did not affect the crystallinity or physicochemical properties of NEV. Due to this treatment, a three- to fourfold dissolution increase was obtained. This high drug dissolution rate was attributed to efficient de-agglomeration and mixing, as well as sufficient wetting of drug particles, due to surrounding excipient particles. However, compared with other techniques, which are able to prepare amorphous formulations, SAS, due to the formed nanocrystals, may not be so effective for drug dissolution enhancement. This was verified in oxeglitazar SDs prepared by SAS and spray-freezing (SF) [48]. Oxeglitazar freeze-dried formulations consisted of porous spherical particles with high amorphous content (94.2 – 100%) and, thus, higher dissolution rate than nanocrystals prepared with SAS.

Experimental parameters in the supercritical process, such as temperature, autoclave pressure, air pressure, flow rate of carbon dioxide and percentage of used drug were also examined for the preparation of SDs. The PGSS process was recently used to produce microparticles of SDs containing PEG 4000, PEG 400, poloxamer 407 and YNS3107, which is a new poorly water-soluble chemical entity [49]. From this study it was found that the main relevant parameters were the autoclave temperature and pressure. Optimum conditions for producing the smallest SD within the experimental domain were found for T = 62°C and p = 177 bar. Under these conditions, microparticles were formed with a volume weighted mean diameter of 30.4 ± 2.3 µm (I.D. nozzle = 1 mm).

PCA using supercritical CO_2 is one of the most investigated processes for the design of pharmaceutical drug–polymer co-formulations for solubility enhancement. A particular advantage of using the PCA technique is that not only are the particles formed organic solvent-free but also no further purification or separation in solvent removal is required in the formation of powdered blends, thin films and microcapsules. PCA can be used for the preparation of amorphous drug SDs, instead of nanocrystalline that were reported with the other supercritical methods, as in the case piroxicam in PVP [37]. Such co-formulations of the sparingly soluble anticonvulsant phenytoin and the water-soluble polymer excipient PVP K30 have been prepared by PCA [50]. Co-formulations with phenytoin concentrations below 40 wt% were fully amorphous and similar to pure PVP in morphology, while phenytoin was also present in crystalline form in products with higher drug contents. For the system under consideration, phenytoin solubility in PVP of about 40 wt% has been determined.

In the above-mentioned methods drugs were mixed with polymers used as drug matrices, which were already prepared in a previous step. However, in a recent study it was found that a polymer–drug SD can be prepared with a single pot process by performing the surfactant-assisted polymerization of 1-vinyl-2-pyrrolidone (VP) in $scCO_2$ in the presence of the piroxicam drug [36]. Under proper operative conditions, the polymer–drug composite was obtained in the form of sub-micron spherical particles with relatively narrow particle

size distribution (**Figure 3**). Drug loadings higher than 12% (w/w) were obtained and X-ray diffraction (XRD) and Raman spectroscopy suggest that the anti-inflammatory agent is dispersed in the matrix with a non-crystalline structure. The dissolution rate of the drug from the composites was significantly faster both than that of the pure compound and of its PM with the polymer.

2.3 Electrospinning

Electrospinning is derived from 'electrostatic spinning' and is a simple, versatile and useful technique for fabricating nanofibers from a rich variety of functional materials. The produced fibers are exceptionally long and uniform in diameter. Concerning the drug delivery, electrospinning has gained popularity in the last 5 years due to an increased interest in nanoscale properties and technologies. During the electrospinning process a polymer solution is ejected from a needle tip by surface tension. The application of an electric field using a high-voltage source results in charge being induced within the polymer solution, which causes the initiation of a jet. As this jet travels the solvent's evaporation is rapid and an appropriate collector can be used to capture the polymer fiber (**Figure 4**). As an outcome, non-woven filament mats are quickly formed and this leads to a decrease in drug mobility. This method has been transferred successfully in recent years in pharmaceutical technology application and regained more attention for the preparation of drug SDs, in order to increase their dissolution properties [51]. When solvent evaporation is complete the drug molecules are dispersed in the polymer fibers matrix. In a recent review, it was demonstrated that poorly water-soluble drugs can be incorporated during the electrospinning process to produce electrospun fibers with enhanced drug solubilities [52].

The concrete advantages of electrospun nanofiber-based SDs for effective delivery of poorly water-soluble drugs include: i) a one-step top-down easy manufacturing process that can be used for further developed and mass production, ii) very large surface area-to-volume ratio, iii) high porosity with very small pore size and iv) three-dimensional (3D) continuous web structure which give higher available surface area [53]. One additional advantage of electrospinning process is that minimum solvent remains in the final products. In these formulations there are several factors that can affect the drug release from electrospun fibers: fiber construct geometry and thickness, fiber diameter and porosity, fiber composition, fiber crystallinity, fiber swelling, drug loading, drug state, drug molecular weight, drug solubility in the release medium and drug–polymer–electrospinning solvent interactions [54].

Semicrystalline and amorphous polymers can be used for nanofibers production and drug loading. Based on the possibly favored interactions between the drug and polymer, as well as due to the fast evaporation of the used solvent, a crystal lattice is not created in the fiber matrix. Therefore, amorphous SDs of APIs may be produced through a simple and straightforward one-step process. For example, SDs of ketoprofen in the form of nanofibers were prepared using electrospinning process with PVP K30 as drug carrier [55]. Characterization results from differential scanning calorimetry (DSC), XRD and scanning electron microscopy (SEM) demonstrated that ketoprofen was distributed in the PVP nanofibers with a diameter of 0.4 – 0.6 nm on a molecular scale. Fourier transform infrared spectroscopy (FTIR) results demonstrated that ketoprofen had fine compatibility with PVP due to the hydrogen bonding formed between them. *In vitro* dissolution tests showed that ketoprofen in the nanofibers could be exhausted within 30 s after they were put into the dissolution medium.

The type of the polymer and the used solution concentrations are also very important for the preparation of nanofibers [56]. It was found that hydroxypropylmethylcellulose (HPMC) is not appropriate for preparing suitable formulations for dissolution enhancement of donepezil HCl drug at any concentration. Water solutions of PVA–PEG graft copolymer were more successful. This is maybe because HPMC has lower solubility than PVA and PEG. Such fibers can be used for oral fast-dissolving drug delivery formulations, as in the case of ibuprofen (IBU) and PVP K30 nanofibers [57]. It was found that 84.9 and 58.7% of IBU was released in the first 20 s for formulations with a drug-to-PVP ratio of 1:4 and 1:2, respectively. According to this procedure, in another poorly water-soluble drug like ferulic acid (FA), *in vitro* dissolution and permeation tests showed that the nanofiber-based SDs could release all the contained FA within 1 min and had a 13-fold higher permeation rate across sublingual mucosa compared with crude FA particles [58]. Recently, Yu *et al.* compared SDs of acetaminophen/PVP using different processes and the results demonstrated that electrospun nanofiber-based SDs showed better dissolution effects compared with SDs films prepared by solvent evaporation [59].

In the electrospinning process there are a number of processing parameters that can influence the electrospinning ability of polymer solutions and, correspondingly, the properties of the generated fibers. These parameters include the solution properties, such as viscosity, elasticity, conductivity and surface tension; the systematic variables such as hydrostatic pressure in the capillary tube, electric potential at the capillary tip and the distance between the tip and the collecting screen and ambient conditions such as temperature, humidity and air velocity in the electrospinning chamber. Among all the parameters the influence of temperature on the electrospinning process and the quality of the prepared fibers seems to have received least attention. It was reported that ultrafine fibers of polymer or polymer blends could be prepared using an elevated temperature electrospinning process [60]. An electric heating film for heating the co-dissolving solutions in the glass syringe can be used. With a similar process helical drug was used in order to increase its dissolution rate [53]. Helicid has poor solubility at ambient temperature, not only in water, but also in common organic solvents such as ethanol, methanol, acetone and chloroform. No common solvents are readily available for making homogeneous solutions

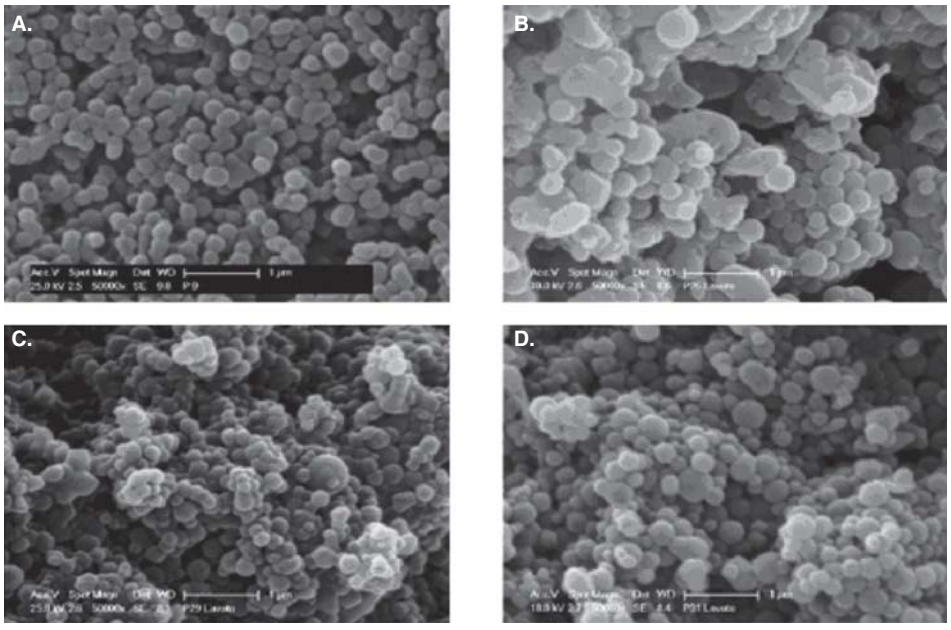

Figure 3. Poly(vinyl pyrrolidone) particles synthesized in supercritical carbon dioxide in the presence of different piroxicam concentrations and density of the polymerization medium. Initial drug concentration (%, w/w with respect to the monomer) and density (g/ml) respectively are: 0 and 0.94 (A), 5 and 0.93 (B), 10 and 0.93 (C), 15 and 0.94 (D).
Reproduced with permission from [36].

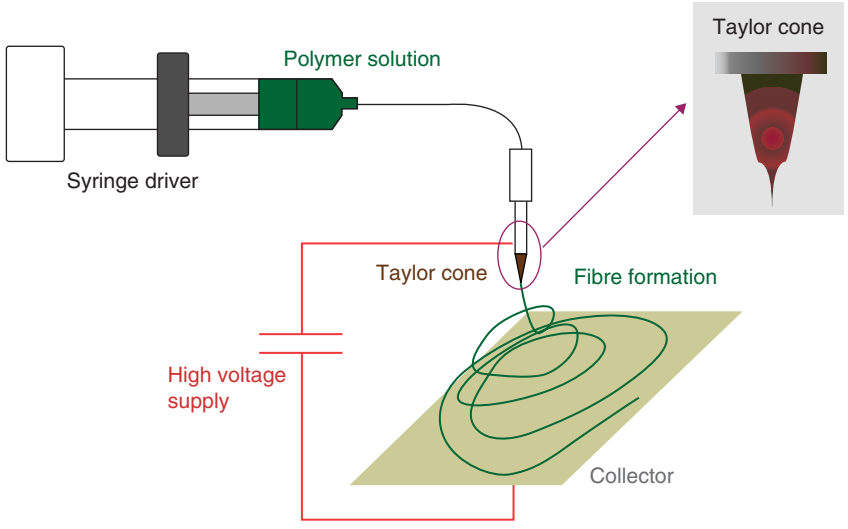

Figure 4. Schematic representation of electrospinning procedure.

suitable at room temperature for electrospinning. For this reason, the drug–polymer solution was heated before electrospinning [53]. The optimum operating temperature was fixed at 70°C, because i) temperatures of 80°C or higher are near the boiling point of water and may lead to clogging of the spinning head of the needle's capillary tube due to fast evaporation and ii) high drug dissolution rate was achieved, which was over 26-fold faster than that of crude helicid.

2.4 Microwaves irradiation

Microwave irradiation (MW) is electromagnetic irradiation located between the infrared (IR) and radio frequencies in the range of 0.3 – 300 GHz, which corresponds to wavelengths of 1 cm to 1 m. To avoid disruptions with radar and telecommunications, all domestic and industrial microwave devices operate at a frequency of 2.45 GHz (corresponding to a wavelength of 12.25 cm). Microwaves, with their ability to penetrate any

substance, allow the production of heat at any point of the sample at the same time. This is due to the presence of molecules characterized by a dipolar moment, able to absorb microwave energy and convert it into heat [61-63]. Therefore, it is possible to achieve a rapid and uniform heating, even in materials exhibiting low heat conductivity, like polymers, because transfer of energy does not rely on heat diffusion.

In recent years, microwave-assisted organic chemistry has received considerable attention and nowadays more and more research chemists are applying microwave technology to organic reactions, especially for drug synthesis [61-63]. Except for drug synthesis, other potential uses of microwaves in the pharmaceutical industry are still at early stages of development, but interest is growing [64]. New microwave reactors have been prepared and one of the most promising microwave applications in pharmaceutical technology is the improvement of the dissolution rate of poorly water-soluble drugs. The application of microwaves in the preparation of solid drug dispersions appears to present a number of desirable attributes. Apart from the improvement of drug dissolution, the lower thermal treatment, which corresponds to a reduced risk of decomposition of heat-sensitive drug substances, and the shorter preparation time, make MW application a promising alternative to conventional methods for preparation of solid drug dispersions. The first attempt in this area probably is the dissolution rate enhancement of felodipine drug from SDs by heating the PM of the drug and the carrier (amorphous silicon dioxide (SiO_2)) either in a vacuum dryer or in a microwave oven [65].

In a recent study, microwave was applied for the preparation of SDs of the poorly water-soluble drug tibolone (Tibo) in PEG (**Figure 5**) [66]. The morphology, physicochemical characteristics and drug release properties of the microwave-prepared SDs were investigated and compared with those of SDs prepared by the respective conventional (solvent evaporation or melting) methods. The drug content assay results, as measured by high-performance liquid chromatography, showed that the use of MW did not significantly affect the stability of the drug. The enhancement of drug dissolution rate by microwaves for the PEG/Tibo dispersions (**Figure 5C**) is probably due to the lower size of Tibo particles (**Figure 5B**) in the dispersions prepared by MW.

Bergese *et al.* [67] developed a method based on MW induced diffusion (MIND) for generating activated drug/3D-matrix nanocomposites. MIND experiments were performed by single- and multimode applicators on various combinations of water-insoluble drugs (IBU, nimesulide (NMS) and nifedipine) and 3D-matrices (crospovidone and h-cyclodextrin). It was demonstrated that MW processing allows for a significant transformation of the drug from microcrystals to (matrix embedded) molecular clusters. Excellent results (residual crystallinity lower than 30%) have been obtained with all the drug/matrix combinations, with a wide variety of processing conditions and both the applicators. This reduction could be appropriate for dissolution enhancement of the used drugs.

Microwave technology has also been employed in order to prepare an enhanced release dosage form for the poorly water-soluble drug NMS, employing Gelucire 50/13 and poloxamer 188 (Lutrol® F 68) as surfactant carriers [68]. After the irradiation treatment an amorphization form of the drug in SD systems was obtained. In order to assess the improvement of NMS dissolution rate by preparing MW activated systems, *in vitro* dissolution profiles of SDs with both carriers were compared with those of pure drug and their corresponding PM. All the performed SD formulations showed a remarkable enhancement of the *in vitro* drug dissolution rate. In particular, SD NMS:Gelucire 50/13 1:2 w/w was able to produce 90% of the drug in solution within 13 min, while at the same time only 74% of the drug was released from the respective PM. The corresponding percentage for the pure drug was only 18%.

MW was used to prepare fast release SDs or sustained release SDs of IBU (drug characterized by a low melting point) with PVP/VA 60/40 (PVP/VA 64) and hydroxypropyl-β-cyclodextrin (HP-β-CD) hydrophilic carriers [69]. It was proven that this technique is a viable and alternative mean to prepare solvent-free binary systems. The physical characterization of the MW activated systems attested a complete amorphization of the drug and no formation of polymorphic forms was found. From the dissolution profile of the MW systems with both polymers employed, a remarkable improvement of the dissolution rate of IBU was evident, compared with that of the pure drug. In fact, as reported in SD IBU:PVP/VA treated at 600 W for 6 min, 90% of the drug was released, while at the same time only 55% of the drug was released from the PM where the drug was separately treated with pulse methylprednisolone therapy (PMT) IBU:PVP/VA and 38% from the PM IBU:PVP/VA. The corresponding percentage for the pure drug was 20%.

In a recent study, MW was applied for preparation of SDs of the poorly water-soluble drug atorvastatin calcium (ATR) with PEG 6000. The *in vivo* performance of the SDs prepared by the microwave-induced fusion method showed an enhancement in the solubility and dissolution rate of ATR from SDs compared with plain ATR and, thus, significantly enhance its bioavailability ($p < 0.05$) [70]. This was attributed to the increased wetting and solubilizing effect of PEG 6000, as well as the molecular dispersion of the drug in SDs and alteration of the surface properties of the drug's particles. Hydrogen bonds that formed during MW irradiation can also enhance the dissolution properties of a poorly water-soluble drug. Moneghini *et al.* [71] describes the influence of MW on the preparation and properties of solvent-free SDs employing vitamin E TPGS 1000 succinate, with itraconazole as model drug. The XRD data confirmed the absence of phase transitions in the solid state of the drug subjected to MW alone. All the SDs showed an improvement in the solubility and dissolution profile of the drug, with the best results obtained in the case of the 1:3 w/w SD. This was related to an interaction between the drug and the carrier, with a

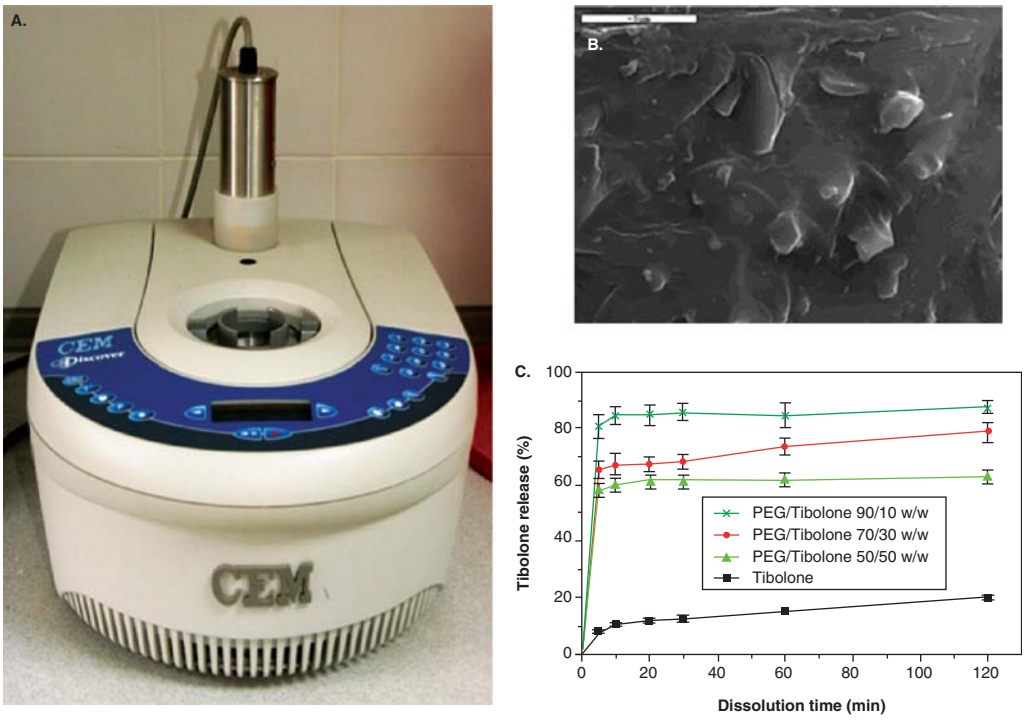

Figure 5. (A) Microwave reactor (CEM), **(B)** scanning electron microscopy of polyethylene glycol/tibolone 70/30 w/w prepared by microwave procedure and **(C)** release rate of tibolone from poly(ethylene glycol)/tibolone solid dispersions prepared with melt mixing during microwave irradiation.
Reproduced with permission from [66].

complex formed due to favorable H bonds, as demonstrated by DRIFT (Diffuse Reflectance Infrared Fourier Transform) analysis. In this study, it was demonstrated that the amorphization of the drug led to an increase in wettability and a significant improvement in bioavailability.

2.5 Solid dispersions using inorganic nanoparticles and nanocomposites

2.5.1 Layered double hydroxide

Layered double hydroxide (LDH) is natural anionic clay that can be prepared by co-precipitation of M^{2+} and M^{3+} metal ions (e.g., Mg^{2+} and Al^{3+}). The LDHs are represented by the general formula $[M^{II}_{1-x}\ M^{III}_{x}(OH)_2]^{x+}(A^{n-})_{x/n}{\cdot}yH_2O$, where M^{II}, M^{III} and A^{n-} are di-, tri-valent metal cations and interlayer anions, respectively. It consists of layers of edge-sharing hydroxyl octahedral with net positive charge balanced by anions in the interlayer. Due to LDHs' anionic exchange capacity, many pharmaceutically active compounds with negative charge at the physiological pH can be intercalated into the LDH interlayers, in order to prolong drug action or to enhance their dissolution rate [72]. The inorganic solid acts as a matrix to prepare systems with controlled drug release properties or increased drug solubility [73].

As an example a recent paper deals with a new hydrotalcite-like compound used as a matrix to improve dissolution rate of the poorly water-soluble drug gliclazid, which is a second-generation sulfonylurea compound used in the treatment of type II diabetes mellitus [74]. The gliclazide–hydrotalcite-like clay nanohybrid was prepared via ion exchange in its nitrate form. The drug loading resulted was 42.9% (w/w). As a consequence of the intercalation, the interlayer distance of the host increased from 0.89 nm (interlayer distance of nitrate form) to 1.5 nm. A remarkable improvement of the apparent solubility and dissolution rate in comparison with the crystalline drug was observed in acid fluids (pH 1.2 and 3). In a similar study, ursodeoxycholic acid (UDCA), a poorly water-soluble drug, was intercalated into an inorganic nanovehicle, the LDHs, to improve the stability and aqueous solubility of UDCA [75]. After intercalation the UDCA molecules were distributed in a molecular level and stabilized through electrostatic interaction, without structural deformation and chemical decomposition of UDCA molecules. The UDCA–LDHs coated with an anionic polymer, Eudragit S100, showed that the total fraction of dissolved UDCA during the first 2 h increased up to threefold in a simulated biological fluid compared with that of intact UDCA.

NP and flurpibrofen (FB) are non-steroidal anti-inflammatory drugs (NSAIDs) of 2-arylpropionic acid derivatives and have been used as host organic drugs to be intercalated into LDH applying reconstruction and co-precipitation techniques [73]. From drug loading, thermal analysis and XRD measurements it was found that co-precipitation technique is better than reconstruction technique to obtain intercalated

monophasic nanocomposites. The new gallery heights in XRD patterns indicate that the drugs have been stacked as monolayer particles perpendicular to the LDH plane, in a staggered inter-digitated method, as can be seen from the schematic diagram for FP in **Figure 6**. In acidic medium, LDH dissolved and the intercalated drug starts to release in a molecular form which is suitable for adsorption. Furthermore, it was found that LDH improves the drug solubility and its dissolution rate.

The dissolution rate increase, as was described before, is due to the hosting properties of LDH and the dispersion of the drug inside the plates of pyruvate dehydrogenase (PDH), mainly molecular dispersion. Such intercalation and characterization of pravastatin and fluvastatin drugs in Mg^{2+}/Al^{3+} LDHs, to form novel nanohybrid hydroxides through the co-precipitation technique, was recently reported [76]. Structural characterization, computed results and atomic force microscopy image analysis demonstrate that the fluvastatin anions are attached with the brucite as a monolayer, whereas the pravastatin anions form a multilayer. The shift in the stretching frequency of carboxylate anion of statin drugs provides evidence that the drugs are electrostatically bonded to LDHs.

A nanostructural drug–inorganic clay composite involving a pharmaceutically active compound captopril (Cpl) intercalated Mg-Al-LDH (Cpl-LDHs) with Mg/Al molar ratio of 2.06 has been assembled by co-precipitation method [77]. Powder XRD, FTIR and Raman spectra analysis indicate a successful intercalation of Cpl between the layers, with a vertical orientation of Cpl disulfide-containing S–S linkage. SEM photo indicates that as-synthesized Cpl-LDHs possess compact and non-porous structure with approximately and linked elliptical shape particles of ca. 50 nm. Thermogravimetric-differential thermal analysis (TG-DTA) suggests that the thermal stability of intercalated organic species is largely enhanced due to host–guest interaction involving the hydrogen bond compared with the pure form before intercalation. The *in vitro* release studies show that both the release rate and release percentages markedly decrease with increasing pH from 4.60 to 7.45, due to possible change of release mechanism during the release process. Similar dissolution enhancement was reported in bezafibrate and clofibric acid drugs with LDH [78]. This is because the drugs have been stacked into LDH as a monolayer with a staggered inter-digitated arrangement.

2.5.2 *Silicon dioxide*

An alternative drug carrier that has been used for the improvement of the dissolution rate of poorly water-soluble drugs is SiO_2 nanoparticles [79]. The principal advantage of utilized silica materials as an implantable delivery vehicle is that the sol–gel method is non-toxic, uncomplicated, inexpensive, takes place at room temperature and it does not require the use of pharmaceutically unacceptable solvents. These materials are biocompatible *in vivo*, cause no adverse tissue reactions and degrade in the body to silicic acid, that is, $Si(OH)_4$, which is eliminated through the kidneys [80]. In comparison, crystalline silica is 10 times less soluble than amorphous silica [81]. Silicas having many silanol groups (Si-OH) on their surfaces are capable of forming hydrogen bonds with drug molecules. Thus, the drug is molecularly dispersed on the silica's surface and dissolution enhancement can be achieved. The SD particles of tolbutamide (TBM) were prepared by formulating non-porous Aerosil® 200 (hydrophilic) and Aerosil R972 (hydrophobic) or porous Sylysia 350 (hydrophilic) and Sylophobic 200 (hydrophobic) silica as a carrier and applying the spray drying (SD-Micro™ Spray Dryer) or evaporation (Eva) method [82]. The dissolution property of TBM in the SD particles prepared with hydrophilic silica was remarkably improved compared with those of the original TBM crystals (Form I) or spray-dried TBM without silica (Form II). In the case of hydrophobic silica, the release rate of TBM from the SD particles was much slower than that of original TBM.

Nanosilica particles can be used together with a polymer in ternary SD systems with different drugs like carvedilol (CAR) and simvastatin (SIM), showing a significant improvement of the drug release profile in both cases [83,84]. The dissolution rate of both drugs was improved by adsorbing solutions of the drugs in hydrophilic non-volatile or volatile solvents onto carriers with a large surface area. This was accomplished by dissolving the drug in methanol or the non-toxic hydrophilic liquids PEG 400 or 2-pyrrolidone, and adsorbing these solutions onto the surface of silica (Aerosil) or cross-linked PVP (Kollidon CL-M) [79]. The drug release from the adsorbent systems was enhanced when compared with micronized drug and was independent of the drug loading in the investigated range. Similar SD systems of Tibo with PVP, fumed SiO_2 nanoparticles and their corresponding ternary systems (PVP/SiO_2/Tibo) were prepared and studied in a recent study in order to produce formulations with enhanced drug dissolution rates [85]. From the results it was concluded that PVP as well as SiO_2 can be used as appropriate carriers for the amorphization of Tibo, even when the drug is used at high concentrations (20 – 30%, w/w). This is due to the evolved interactions taking place between the drug and the used carriers. At higher concentrations the drug was recrystallized. Similar are the observations on the ternary PVP/SiO_2/Tibo SDs. The dissolution profiles of the drug in PVP/Tibo and SiO_2/Tibo SDs are directly dependent on the physical state of the drug. Thus, immediate release rates are observed in SD with low drug concentrations, in which Tibo was in an amorphous state.

Combination of SD and surface adsorption techniques has been attempted to overcome the limitations of spray drying technique for amorphization of low T_g drugs, such as SIM [84]. Dichloromethane suspensions of SIM either alone or in combination with PVP (1:1 or 1:2 parts by weight) were spray dried containing also Aerosil 200 (1:1, 1:1:1, 1:2:2 parts by weight of SIM, Aerosil 200 and PVP, respectively). Based on powder characteristics, drug content, saturation solubility and feasibility of processing into tablets, SD 1:2:2 was selected as the optimized formulation. During initial characterization, SEM, DSC and XRD analyses confirmed the presence of

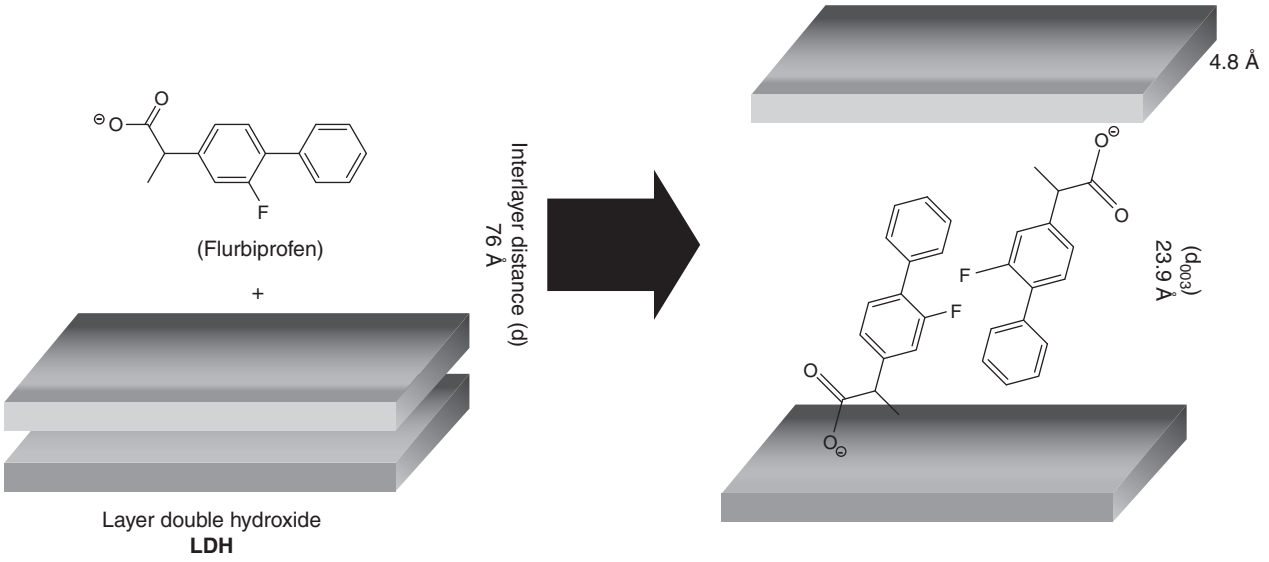

Figure 6. Systematic diagram of flurpibrofen–layered double hydroxide (LDH) intercalation process.
Reproduced with permission from [73].

amorphous form in SD 1:2:2. IR spectroscopy revealed the possibility of hydrogen bonding interaction between SIM and PVP in SDs. Also, there was a dramatic improvement in rate and extent of *in vitro* drug release of SD 1:2:2. Furthermore, *in vivo* study in rats also justified the improvement in therapeutic efficacy of SD 1:2:2 over pure SIM. Similar dissolution enhancement was also mentioned using CAR drug, which is also a low T_g drug, in SDs 1:2:2 parts by weight of CER, Aerosil 200 and PVP, respectively [83]. However, in this case the amorphous SD was produced by melt quenching technique.

Silica nanoparticles can also be used in combinations with other polymers and additives to prepare new drug formulations. A silica-lipid hybrid (SLH) microcapsule system for oral delivery of poorly water-soluble drugs was recently reported (**Figure 7**) [86]. For the model drug celecoxib (CEL), SLH microcapsules were composed of medium-chain triglycerides, lecithin and silica nanoparticles. These have an internal porous matrix structure and offer several physicochemical and biopharmaceutical advantages in comparison with unmodified drug, lipid emulsion, dry emulsion and the commercial product, Celebrex®. DSC and XRD analyses confirmed non-crystalline CEL in SLH microcapsules. Dissolution under sink conditions revealed a two- to fivefold increase in dissolution efficiencies (%DE) and significantly reduced $t_{50\%}$ (≥ 50-fold) for CEL formulated as SLH microcapsules.

2.5.3 *Mesoporous silica*

The term mesoporous designates porous materials that possess pores with diameters between 2 and 50 nm. In recent years, mesoporous silica nanoparticles (MSNs) have attracted increasing consideration as a dynamic drug carrier system [87-89]. This is due to their unique properties, which render them suitable carriers for API; pore diameters that can be tuned between 2 and 30 nm and high specific surface areas (up to 1500 m^2/g), creating a high potential for adsorption. In addition, the high pore volume (up to 1.5 cm^3/g) and the high surface area facilitate the adsorption of large active substances amounts. Also, by adjusting the pore size to dimensions slightly larger than those of the drug molecules, MSNs can serve as a versatile host of various substances. Finally, the silanol-containing surface can be functionalized to induce better control over drug loading and release properties.

Nowadays, MSNs nanomaterials are widely used in several biopharmaceutical applications, since these nanoparticles demonstrated very low cytotoxicity [90]. Furthermore, due to large specific surface area these materials have found applications as immediate formulations for enhancing the dissolution rate of poorly water-soluble drugs. Takeuchi *et al.* [91] reported that the SD on MSNs could improve the dissolution properties of INM and TBM. The produced nanoparticles displayed large specific surface area (~ 765 cm^2/g), with an average particles size of 120 nm. In a recent study, MSNs were loaded with telmisartan (TEL), in order to improve the dissolution rate and enhance the drug loading capacity [92]. Spherical MSNs were synthesized using an organic template method in an oil/water phase and large pore diameter MSNs were functionalized with aminopropyl groups through post-synthesis. The total pore volume and the pore diameter of MSNs were the two main factors limiting the maximum drug loading capacity. MSNs allow a very high drug loading of about 60% in weight. The dissolution profile of pure crystalline TEL, along with the TEL release profiles from TEL-MSNs and TEL-AP-MSNs are presented in **Figure 8**. As can be seen the dissolution rate of TEL released from TEL-MSNs was faster compared with the

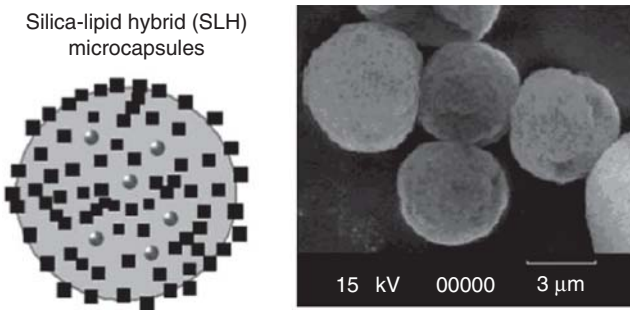

Figure 7. Schematic representation of silica-lipid hybrid (SLH) microcapsule composed of medium-chain triglycerides, lecithin and silica nanoparticles and its scanning electron micrograph.
Reproduced with permission from [86].

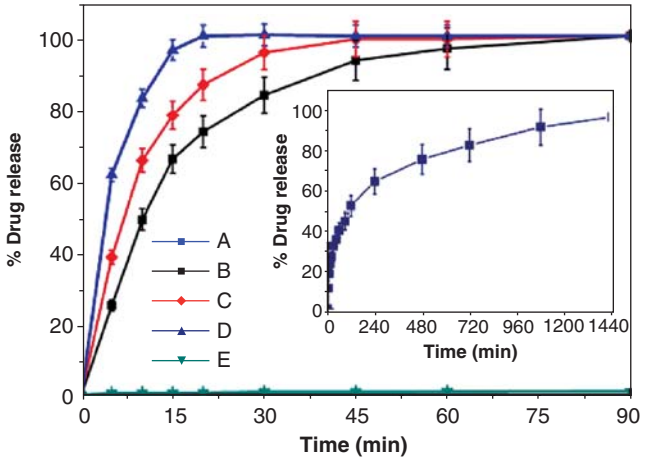

Figure 8. Release profiles of TEL from TEL-AP-MSNs (A, inset) and TEL-MSNs (the BJH pore diameters of MSNs for the sample B, C and D were 3.6, 7.8 and 12.9 nm, respectively) as well as pure crystalline TEL (E) at enzyme-free simulated intestinal fluid (pH 6.8).
Reproduced with permission from [92].
BJH: Barrett–Joyner–Halenda; MSNs: Mesoporous silica nanoparticles; TEL: Telmisartan.

dissolution rate of pure TEL. The amounts of dissolved TEL in the release medium at sampling times of 5, 15 and 30 min accumulated to 61.3, 96.2 and 100.3% for TEL-MSNs. The release rate of TEL from MSNs with a pore diameter of 12.9 nm was found to be effectively increased and the release rate of TEL from the functionalized MSNs was effectively controlled compared with that from the unmodified MSNs. The TEL molecules were able to form weak hydrogen bonds with the silanol groups on the pore walls of the MSNs. Therefore, the drug release from TEL-MSNs was not expected to be differentiated by the chemical interaction of the TEL molecules with the carrier but by the different pore diameters of the MSNs.

The pore diameter of MSNs is very critical for the physical state of the drug and, thus, for the dissolution rate behavior. The SDs of spironolactone (SPI) with porous silica (Sylysia 730 and 350) were prepared by the solvent method [93]. The results of XRD and DSC indicated that SPI adsorbed on the surface of Sylysia and the molecular state of the adsorbed SPI changed from crystalline to amorphous state. Although the decrease in the SPI concentration increased with the amorphous fraction in the SD, the diffraction peaks due to SPI crystals still remained in the SD of the Sylysia 730:SPI system in a weight ratio of 1:1, indicating that the mean pore diameter and specific surface area of an additive are some of the important factors for the amorphization of SPI crystals. The dissolution property of the SPI from the SDs was remarkably improved in comparison with that of SPI crystals.

In all the mentioned studies it seems that the drugs' amorphization during SDs preparation with MSNs is the main factor for the dissolution rate enhancement. However, it has also been reported that increased dissolution rate can be achieved even in the case when the drugs are dispersed in nanocrystalline state [94].

3. Conclusions

Polymeric carriers are extensively and successfully used for the preparation of SDs. In these formulations the drug can be dispersed in an amorphous or semicrystalline state. The drug dissolution enhancement is due to the finer drug particles distribution and the wetting characteristics of the polymer carriers. Such dispersions can be prepared by melt mixing and supercritical conditions. Both methods, due to the absence of used solvents, have significant advantages compared with traditional methods, such as solvent evaporation. Furthermore, except polymer carriers, inorganic nanoparticles, such as LDH, fumed silica and mesoporous silica, can be used alone or in combination with different polymers for drug dissolution enhancement. This is due to the fact that the drug is dispersed on a very large surface area as nanocrystals or as amorphous dispersion. Nowadays, even newer processes are used for SDs, such as electrospinning and MW, with very promising results. According to the reported literature, all the described methods can be used successfully to solve the solubility problems of poorly water-soluble drugs.

4. Expert opinion

Particle size in the range of nanometers is very important for drug dissolution enhancement, but the physical state of the drug also plays a crucial role. Thus, the SD of drug in amorphous polymer at a molecular level is the most desired. Such formulation provides extended surface area of a drug that increases its dissolution rate, while resolving wettability issues occurring in conventional particle size reduction. The amorphous system formation and its physical stability can be enhanced by the dispersion process into amorphous polymer matrix and by the selection of appropriate matrix components. However, except amorphization, poorly water-soluble compounds need novel approaches for the preparation of SDs with enhancement of bioavailability and therapeutic efficacy. In recent years, a lot of progress has been made and new methods and processes have been introduced in the pharmaceutical technology for the preparation of SDs. The advantage of these methods and the progress that has been done in the last 5 years is discussed in an extended review. The first part of this review is dealing with formulations like solvent evaporation, kneading, wet milling, spray drying and cyclodextrins complexation [95]. In the present part, a lot of different methods are presented and discussed.

HME, which has gained wide acceptance as an alternative process for the preparation of SDs, is a continuous and rather simple process that does not require the use of any kind of solvent. The advantage of this process is that the drug is dissolved in the polymer melt that is used as drug carrier, instead of a solvent. Concerning the drug's physical state in such formulations, the evolved interactions play the most important role, as well as the used drug carrier. Additional factors that can affect the physical state of the drug in HME are the used barrel temperature, rotation speed and the remaining time in the barrel. The dissolution enhancement mechanism is also similar to solvent evaporation and is affected by the drug's physical state. Compared with other techniques, such as spray drying and ball milling, it was reported that HME can prepare SDs with higher dissolution rates [96]. This procedure has also some limitations, since it cannot be used with thermally unstable drugs. However, these drugs can be treated with the presence of plasticizers, which can reduce their melting point. Besides the traditional melt techniques, recently a new fusion-based process was developed to overcome such limitations, named KSD.

The applications of supercritical fluid processes in pharmaceutical technology are also increasing, particularly in the field of particle formation and drug delivery systems, such as SDs. This is because CO_2 is used as solvent in supercritical conditions, which is not toxic and easily evaporated. Furthermore, the applied processes have a lot of advantages over conventional SD formulation methods in terms of improved control, flexibility and ease of operation. The used process depends on the available applied conditions to prepare drug nanocrystals or amorphous SDs. New strategies, such as rapid expansion of supercritical solution into aqueous solution and polymerization of vinyl monomers in the presence of the drug in one single process with $scCO_2$, can also be used for the preparation of SDs. Supercritical fluid processes today offer an opportunity to address the issues associated with BCS class II molecules and are extensively used in pharmaceutical technology. However, its application is very difficult for the production of SDs in large scales.

MW has also proven to be a viable and alternative technique to prepare solvent-free binary systems. Due to the high irradiation frequencies it is possible to achieve a rapid and uniform heating, even in materials having low heat conductivity, like polymers and drugs, which can melt, and prepare stable SD formulations. An advantage of the method is that it requires extremely low processing time (1 – 2 min) for the preparation of the melt, since it works under pressure and high power, and thus the polymer–drug system is melted at lower temperatures than is usually required. This is very effective in the case when a drug decomposes during or after melting and cannot be formulated in SDs with HME. Furthermore, it was found that microwave energy has been more appropriate to change the crystalline state of a drug to amorphous, instead of conventional heating. It is a new technique and its application for the preparation of SDs will be evaluated in the future.

Electrospinning is also a new method for the preparation of SDs, since it was not used in pharmaceutical technology, but mainly for the preparation of polymer nanofibers. However, some very promising applications for the preparation of SDs with enhanced drug dissolution rates were recently found. This is because the drug is dispersed mainly in an amorphous phase in the polymer matrix, which has the form of nanofibers

with a mean diameter size of 5 – 20 nm. Thus, the drug is dispersed in a high surface area and is rapidly dissolved. An additional advantage that can be reported is the extremely low levels of remaining solvents. Compared with other techniques the main drawback is that the preparation of SDs requires a lot of time, due to the low flow rate of the used solutions.

In all the above-mentioned procedures, polymers are mainly used as drug carrier for drug dispersion. However, inorganic nanoparticles, such as LDH, fumed silica and mesoporous silica, can also be used alone or in combination with polymers for drug dissolution enhancement. In the case of LDH, drugs can be inserted between the inorganic layers, preparing intercalating organic/inorganic hybrids in which the drug is dispersed at a molecular level. In silica nanoparticles, like SiO_2 and mesoporous silica, the drug can be dispersed in the particles surface or inside the pores, which have a diameter between 2 and 50 nm. In all these SD formulations the drug is dispersed on an extremely high surface area, since the specific area of these nanoparticles ranges between 200 and 1000 m^2/g. This results in the dispersion of drug in an amorphous state or in nanocrystals, both of which can give formulations with enhanced dissolution properties, which is the main advantage of the use of such nanoparticles. Compared with other techniques the use of solvents for drug loading remains its main drawback.

All the above-described formulations are promising and alternative to conventional methods for the preparation of solid drug dispersions. Some of them are used for the first time in SDs and their development is still in progress. Many problems still need to be solved, mainly the use of toxic solvents, and for this reason the use of innovative procedures and materials will increase in the following years. To my opinion, melt mixing remains extremely promising for the preparation of SDs and will probably become the most used method in the future for the preparation of solid drug dispersions.

Declaration of interest

The author states no conflicts of interests and has received no payment for the preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Amidon GL, Lennernas H, Shah VP, et al. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res 1995;8:413-20

•• **One of the first approaches for drugs classification according to their dissolution.**

2. Lipinski C. Poor aqueous solubility-an industry wide problem in drug delivery. Am Pharm Rev 2002;5:82-5

3. Kesisoglu F, Panmai S, Wu Y. Nanosizing-oral formulation development and biopharmaceutical evaluation. Adv Drug Deliv Rev 2007;59:631-44

4. Cho E, Cho W, Cha KH, et al. Enhanced dissolution of megestrol acetate microcrystals prepared by antisolvent precipitation process using hydrophilic additives. Int J Pharm 2010;396:91-8

5. Hu J, Johnston KP, Williams RO III. Nanoparticle engineering processes for enhancing the dissolution rates of poorly water soluble drugs. Drug Dev Ind Pharm 2004;30:233-45

•• **Effect of particle size on drug dissolution rates.**

6. Keck CM, Muller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharm Biopharm 2006;62:3-16

7. Van Eerdenbrugh B, Van den Mooter G, Augustijns P. Top-down production of drug nanocrystals: nanosuspension stabilization, miniaturization and transformation into solid products. Int J Pharm 2008;364:64-75

8. Dong Y, Ng WK, Hu J, et al. A continuous and highly effective static mixing process for antisolvent precipitation of nanoparticles of poorly water-soluble drugs. Int J Pharm 2010;386:256-61

9. Sethia S, Squillante E. Solid dispersions: revival with greater possibilities and applications in oral drug delivery. Crit Rev Ther Drug Carrier Syst 2003;20:215-47

10. Kaushal AM, Gupta P, Bansal AK. Amorphous drug delivery systems: molecular aspects, design, and performance. Crit Rev Ther Drug Carrier Syst 2004;21:133-93

11. Karavas E, Georgarakis E, Sigalas MP, et al. Investigation of the release mechanism of a sparingly water-soluble drug from solid dispersions in hydrophilic carriers based on physical state of drug, particle size distribution and drug–polymer interactions. Eur J Pharm Biopharm 2007;66:334-47

•• **Release mechanism of sparingly water-soluble drug from solid dispersions.**

12. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today 2007;12:1068-75

13. McGinity JW, Zhang F, Koleng JJ, et al. Hot-melt extrusion as a pharmaceutical process. Am Pharma Rev 2001;4:25-37

• **The article describes the application of Hot-Melt Extrusion in Pharmaceutical technology.**

14. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur J Pharm Biopharm 2002;54:107-17

15. Liu H, Wang P, Zhang X, et al. Effects of extrusion process parameters on the dissolution behavior of indomethacin in Eudragit® E PO solid dispersions. Int J Pharm 2010;383:161-9

16. Hughey JR, DiNunzio JC, Bennett RC, et al. Dissolution enhancement of a drug exhibiting thermal and acidic decomposition characteristics by fusion processing: A comparative study of hot melt extrusion and KinetiSol®

Dispersing. AAPS PharmSciTech 2010;11:760-74,2010

- **The article describes the application KinetiSol® Dispersing as new melt technique for the preparation of SDs.**

17. Repka MA, Majumdar S, Battu SK, et al. Applications of hot-melt extrusion for drug delivery. Expert Opin Drug Deliv 2008;5:1357-76

- **The article describes the application of Hot-Melt Extrusion in Pharmaceutical technology.**

18. Tho I, Liepold B, Rosenberg J, et al. Formation of nano/micro-dispersions with improved dissolution properties upon dispersion of ritonavir melt extrudate in aqueous media. Eur J Pharm Sci 2010;40:25-32

19. Andrews GP, Abudiak OA, Jones DS. Physicochemical characterization of hot melt extruded bicalutamide–polyvinylpyrrolidone solid dispersions. J Pharm Sci 2010;99:1322-35

20. Miller DA, Mc Conville JT, Yang W, et al. Hot-melt extrusion for enhanced delivery of drug particles. J Pharm Sci 2007;96:361-76

21. Albers J, Alles R, Matthée K, et al. Mechanism of drug release from polymethacrylate-based extrudates and milled strands prepared by hot-melt extrusion. Eur J Pharm Biopharm 2009;71:387-94

22. Yang M, Wang P, Huang CY, et al. Solid dispersion of acetaminophen and poly(ethylene oxide) prepared by hot-melt mixing. Int J Pharm 2010;395:53-61

23. Docoslis A, Huszarik KL, Papageorgiou GZ, et al. Characterization of the distribution, polymorphism, and stability of nimodipine in its solid dispersions in polyethylene glycol by micro-Raman spectroscopy and powder X-Ray diffraction. AAPS J 2007;9:E361-70

- **Micro-Raman Spectroscopy was used to evaluate the physical state of the drug in SDs.**

24. Papageorgiou GZ, Bikiaris D, Karavas E, et al. Effect of physical state and particle size distribution on dissolution enhancement of nimodipine/PEG solid dispersions prepared by melt mixing and solvent evaporation. AAPS J 2006;8:E623-31

- **The article describes the effect of physical state and particle size distribution on drug dissolution Enhancement.**

25. Jijun F, Lili Z, Tingting G, et al. Stable nimodipine tablets with high bioavailability containing NM-SD prepared by hot-melt extrusion. Powder Techn 2010;204:214-21

26. Shibata Y, Fujii M, Sugamura Y, et al. The preparation of a solid dispersion powder of indomethacin with crospovidone using a twin-screw extruder or kneader. Int J Pharm 2009;365:53-60

27. Shah J, Vasanti S, Anroop B, et al. Enhancement of dissolution rate of valdecoxib by solid dispersions technique with PVP K 30 & PEG 4000: preparation and in vitro evaluation. J Incl Phenom Macrocycl Chem 2009;63:69-75

- **PVP and PEG were used as carriers for SDs prepared by melt mixing.**

28. Bley H, Fussnegger B, Bodmeier R. Characterization and stability of solid dispersions based on PEG/polymer blends. Int J Pharm 2010;390:165-73

29. Schilling SU, Shah NH, Malick AW, et al. Citric acid as a solid-state plasticizer for Eudragit RS PO. J Pharm Pharmacol 2007;59:1493-500

30. Lakshman JP, Cao Y, Kowalski J, et al. Application of melt extrusion in the development of a physically and chemically stable high-energy amorphous solid dispersion of a poorly water-soluble drug. Mol Pharm 2009;5:994-1002

31. DiNunzio JC, Brough C, Miller DA, et al. Fusion processing of itraconazole solid dispersions by KinetiSol® dispersing: a comparative study to hot melt extrusion. J Pharm Sci 2009;99:1239-53

32. DiNunzio JC, Brough C, Hughey JR, et al. Fusion production of solid dispersions containing a heat-sensitive active ingredient by hot melt extrusion and Kinetisol® dispersing. Eur J Pharm Biopharm 2010;74:340-51

33. Yeo SD, Kiran E. Formation of polymer particles with supercritical fluids: a review. J Supercr Fluids 2005;34:287-308

34. Vemavarapu C, Mollan MJ, Needham TE. Coprecipitation of pharmaceutical actives and their structurally related additives by the RESS process. Powder Techn 2009;189:444-53

35. Lim RTY, Ng WK, Tan RBH. Amorphization of pharmaceutical compound by co-precipitation using supercritical anti-solvent (SAS) process (Part I). J Supercr Fluids 2010;53:179-84

36. Galia A, Scialdone O, Filardo G, et al. A one-pot method to enhance dissolution rate of low solubility drug molecules using dispersion polymerization in supercritical carbon dioxide. Int J Pharm 2009;377:60-9

37. De Sousa ARS, Silva R, Tay FH, et al. Solubility enhancement of trans-chalcone using lipid carriers and supercritical CO2 processing. J Supercr Fluids 2009;48:120-5

38. Wu K, Li J, Wang W, et al. Formation and characterization of solid dispersions of piroxicam and polyvinylpyrrolidone using spray drying and precipitation with compressed antisolvent. J Pharm Sci 2009;98:2422-31

- **Comparison between spray drying and precipitation with compressed antisolvent.**

39. Turk M. Manufacture of submicron drug particles with enhanced dissolution behavior by rapid expansion processes. J Supercr Fluids 2009;47:537-45

40. Sonoda R, Hara Y, Iwasaki T, et al. Improvement of dissolution property of poorly water-soluble drug by supercritical freeze granulation. Chem Pharm Bull 2009;57:1040-4

41. Varshosaz J, Hassanzadeh F, Mahmoudzadeh M, et al. Preparation of cefuroxime axetil nanoparticles by rapid expansion of supercritical fluid technology. Powder Techn 2009;189:97-102

42. Türk M, Lietzow R. Formation and stabilization of submicron particles via rapid expansion processes. J Supercr Fluids 2008;38:346-55

43. Hezave AZ, Esmaeilzadeh F. Investigation of the rapid expansion of supercritical solution parameters effects on size and morphology of cephalexin particles. J Aerosol Sci 2010;41:1090-112

44. Turk M, Bolten D. Formation of submicron poorly water-soluble

drugs by rapid expansion of supercritical solution (RESS): results for naproxen. J Supercr Fluids 2010;55:778-85

45. Kim MS, Kim JS, Hwang SJ. Enhancement of wettability and dissolution properties of cilostazol using the supercritical antisolvent process: effect of various additives. Chem Pharm Bul 2010;58:230-3
46. Kale K, Hapgood K, Stewart P. Drug agglomeration and dissolution-what is the influence of powder mixing. Eur J Pharm Sci 2009;72:156-64
47. Sanganwar GP, Sathigari S, Babu RJ, et al. Simultaneous production and co-mixing of microparticles of nevirapine with excipients by supercritical antisolvent method for dissolution enhancement. Eur J Pharm Sci 2010;39:164-74
48. Badens E, Majerik V, Horvαth G, et al. Comparison of solid dispersions produced by supercritical antisolvent and spray-freezing technologies. Int J Pharm 2009;377:25-34
- **Comparison of solid dispersions produced by supercritical antisolvent and spray-freezing technologies.**
49. Brion M, Jaspart S, Perrone L, et al. The supercritical micronization of solid dispersions by Particles from Gas Saturated Solutions using experimental design. J Supercr Fluids 2009;51:50-6
50. Kluge J, Fusaro F, Muhrer G, et al. Rational design of drug–polymer co-formulations by CO2 anti-solvent precipitation. J Supercr Fluids 2009;48:176-82
51. Yu DG, Zhu LM, White K, et al. Electrospun nanofiber based drug delivery systems. Health 2009;l:67-75
- •• **Applications of electrospinning method for drug delivery systems.**
52. Ignatious F, Sun L, Lee CP, et al. Electrospun nanofibers in oral drug delivery. Pharm Res 2010;27:576-688
53. Yu DG, Gao LD, White K, et al. Multicomponent amorphous nanofibers electrospun from hot aqueous solutions of a poorly soluble drug. Pharm Res 2010;27:2466-77
54. Natu MV, De Sousa HC, Gil MH. Effects of drug solubility, state and loading on controlled release in bicomponent electrospun fibers. Int J Pharm 2010;397:50-8
55. Yu DG, Branford-White C, Shen XX, et al. Solid dispersions of ketoprofen in drug-loaded electrospun nanofibers. J Disper Sci Technol 2010;31:902-8
56. Nagy ZK, Nyúl K, Wagner I, et al. Electrospun water soluble polymer mat for ultrafast release of donepezil HCl eXPRESS. Polym Lett 2010;4:763-72
57. Yu DG, Shen XX, Branford-White C, et al. Oral fast-dissolving drug delivery membranes prepared from electrospun PVP ultrafine fibers. Nanotechnology 2009;20:055104
58. Yu DG, Yang JM, Branford-White C, et al. Third generation solid dispersions of ferulic acid in electrospun composite nanofibers. Int J Pharm 2010;400:158-64
- **Extremely high dissolution rates from solid dispersions prepared by electrospinning.**
59. Yu DG, Branford-White C, White K, et al. Dissolution improvement of electrospun nanofiber-based solid dispersions for acetaminophen. AAPS PharmSciTech 2010;11:809-17
60. Chen HM, Yu DG. An elevated temperature electrospinning process for preparing acyclovir-loaded PAN ultrafine fibers. J Mater Process Technol 2010;210:1551-5
61. Lehmann H, La Vecchia L. Evaluation of microwave reactors for prep-scale synthesis in a kilolab. JALA 2005;10:412-17
62. Mavandadi F, Pilotti A. The impact of microwave-assisted organic synthesis in drug discovery. Drug Discov Today 2006;11:165-74
63. Kappe CO, Dallinger D. The impact of microwave synthesis on drug discovery. Nat Rev 2005;5:51-63
64. Wong TW. Use of microwave in processing of drug delivery systems. Curr Drug Deliv 2008;5:77-84
- **In this paper the application of microwave process for drug delivery systems preparation is described.**
65. Kerc J, Srcic S, Kofler B. Alternative solvent-free preparation methods for felodipine surface solid dispersions,. Drug Dev Ind Pharm 1998;24:359-63
- **One of the first papers that describes the application of microwaves for preparation of SDs.**
66. Papadimitriou SA, Bikiaris D, Avgoustakis K. Microwave-induced enhancement of the dissolution rate of poorly water-soluble tibolone from poly (ethylene glycol) solid dispersions. J Appl Polym Sci 2008;108:1249-58
- **One of the first papers that the microwave conditions for the preparation of SDs are evaluated.**
67. Bergese P, Colombo I, Gervasoni D, et al. Microwave generated nanocomposites for making insoluble drugs soluble,. Mater Sci Eng 2003;23:791-5
68. Moneghini M, Zingone G, De Zordi N. Influence of the microwave technology on the physical–chemical properties of solid dispersion with nimesulide. Powder Techn 2009;195:259-63
69. Moneghini M, Bellich B, Baxa P, et al. Microwave generated solid dispersions containing Ibuprofen. Int J Pharm 2008;361:125-30
70. Maurya D, Belgamwar V, Tekade A. Microwave induced solubility enhancement of poorly water soluble atorvastatin calcium. J Pharm Pharmacol 2010;62:1599-606
71. Moneghini M, De Zordi N, Solinas D, et al. Characterization of solid dispersions of itraconazole and vitamin E TPGS prepared by microwave technology. Future Med Chem 2010;2:237-46
72. Del Arco M, Fernandez A, Martin C, et al. Solubility and release of fenbufen intercalated in Mg, Al and Mg, Al, Fe layered double hydroxides (LDH): the effect of Eudragits S 100 covering. J Solid State Chem 2010;183:3002-9
73. Berber MR, Minagawa K, Katoh M, et al. Nanocomposites of 2-arylpropionic acid drugs based on Mg-Al layered double hydroxide for dissolution enchancement. Eur J Pharm Sci 2008;35:354-60
74. Ambrogi V, Perioli L, Ciarnelli V, et al. Effect of gliclazide immobilization into layered double hydroxide on drug release. Eur J Pharm Biopharm 2009;73:285-91
75. Choi G, Lee JH, Oh YJ, et al. Inorganic-polymer nanohybrid carrier for delivery of a poorly-soluble drug,

ursodeoxycholic acid. Int J Pharm 2010;402:117-22

76. Panda HS, Srivastava R, Bahadur D. In-vitro release kinetics and stability of anticardiovascular drugs-intercalated layered double hydroxide nanohybrids. J Phys Chem B 2009;113:15090-100

77. Zhang H, Zou K, Guo S, et al. Nanostructural drug-inorganic clay composites: Structure, thermal property and in vitro release of captopril-intercalated Mg–Al-layered double hydroxides. J Solid State Chem 2006;179:1792-801

78. Berber MR, Hafez IH, Minagawa K, et al. Nanocomposite formulation system of lipid-regulating drugs based on layered double hydroxide: synthesis, characterization and drug release properties. Pharm Res 2010;27:2394-401

79. Friedrich H, Fussnegger B, Kolter K, et al. Dissolution rate improvement of poorly water-soluble drugs obtained by adsorbing solutions of drugs in hydrophilic solvents onto high surface area carriers. Eur J Pharm Biopharm 2006;62:171-7

80. Kortesuo P, Ahola M, Kangas M, et al. In vitro release of dexmedetomidine from silica xerogel monoliths: effect of sol–gel synthesis parameters. Int J Pharm 2001;221:107-14

81. Finnie KS, Waller DJ, Perret FL, et al. Biodegradability of sol–gel silica microparticles for drug delivery. J Sol-Gel Sci Technol 2009;49:12-18

• **In this paper the biodegradability of silica nanoparticles is described.**

82. Takeuchi H, Nagira S, Yamamoto H, et al. Solid dispersion particles of tolbutamide prepared with fine silica particles by the spray-drying method. Powder Techn 2004;141:187-95

83. Pokharkar VB, Mandpe LP, Padamwar MN, et al. Development, characterization and stabilization of amorphous form of low Tg drug. Powder Tech 2006;167:20-5

84. Ambike AA, Mahadik KR, Paradkar A. Spray-dried amorphous solid dispersions of dimvastatin, a low Tg drug: In vitro and in vivo evaluations. Pharm Res 2005;22:990-8

85. Papadimitriou S, Bikiaris D. Dissolution rate enhancement of the poorly water-soluble drug tibolone using PVP, SiO_2, and their nanocomposites as appropriate drug carriers. Drug Dev Ind Pharm 2009;35:1128-38

• **In this paper polymer/silica nanocomposites are used for drug dissolution enhancement.**

86. Tan A, Simovic S, Davey AK, et al. Silica-lipid hybrid (SLH) microcapsules: a novel oral delivery system for poorly soluble drugs. J Control Release 2009;134:62-70

87. Slowing II, Vivero-Escoto JL, Wu CW, et al. Mesoporous silica nanoparticles as controlled release drug delivery and gene transfection carriers. Adv Drug Deliv Rev 2008;60:1278-88

88. Vallet-Regi M, Balas F, Arcos D. Mesoporous materials for drug delivery. Angew Chem Int Ed 2007;46:7548-58

•• **In this paper the application of mesoporous materials for drug delivery is described.**

89. Wang S. Ordered mesoporous materials for drug delivery. Micropor Mesopor Mater 2009;117:1-9

90. Thomas MJK, Slipper I, Walunj A, et al. Inclusion of poorly soluble drugs in highly ordered mesoporous silica Nanoparticles. Int J Pharm 2010;387:272-7

91. Takeuchi H, Nagira H, Yamamoto H, et al. Solid dispersion particles of amorphous indomethacin with fine porous silica particles by using spray-drying method. Int J Pharm 2005;293:155-64

92. Zhang Y, Zhi Z, Jiang T, et al. Spherical mesoporous silica nanoparticles for loading and release of the poorly water-soluble drug telmisartan. J Control Release 2010;145:257-63

93. Uchino T, Yasuno N, Yanagihara Y, et al. Solid dispersion of spironolactone with porous silica prepared by the solvent method. Pharmazie 2007;62:599-63

94. Van Speybroeck M, Barillaro V, Thi TD, et al. Ordered mesoporous silica material SBA-15: A broad-spectrum formulation platform for poorly soluble Drugs. J Pharm Sci 2009;98:2648-58

95. Bikiaris D. Solid dispersions, Part I: recent evolutions & future opportunities in manufacturing methods for dissolution rate enhancement of poorly water soluble drugs. Expert Opin Drug Deliv Sep 2011. [Epub ahead of print]

• **In this review different methods for the preparation of SDs are presented and discussed such as solvent evaporation, kneading, wet milling, spray drying and cyclodextrins complexation.**

96. Patterson JE, James MB, Forster AH, et al. Preparation of glass solutions of three poorly water soluble drugs by spray drying, melt extrusion and ball milling. Int J Pharm 2007;336:22-34

Affiliation

Dimitrios N Bikiaris
Aristotle University of Thessaloniki,
Laboratory of Polymer
Chemistry and Technology,
Department of Chemistry,
GR-541 24 Thessaloniki, Greece
E-mail: dbic@chem.auth.gr