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REVIEW ARTICLE

Updates on the conversion of nanosuspensions to solid oral dosage forms

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Abstract

Pharmaceutical nanosuspensions, also called nanocrystals, are heterogeneous mainly aqueous dispersions of insoluble drug particles stabilised by surfactants and/or polymers. Nanosuspensions as liquid formulations suffer from instability. Solidification of nanosuspensions to solid dosage forms is a way to combine the advantages of nanocrystals with the advantages of the solid state. In this review, advances regarding stabilisation and production of nanosuspensions are briefly covered. Updates on the methods used to convert nanosuspensions to solid oral dosage forms (e.g., powder, granules, pellets, tablets, and films) are presented in depth. From these methods, spray drying and freeze drying are widely used. Granulation and hot-melt extrusion allow straightforward downstream processing, while printing exhibits the potential for dose personalisation. Focus is given on novel formulations (e.g., nano-cocrystals, nanocrystalline solid dispersions) which could further enhance the dissolution and bioavailability of poorly soluble drugs.

Keywords: Downstream processing, Nanoparticle agglomerates, Nanosuspensions, Solidification, Solid oral dosage forms

1. Introduction

Nanotechnologies represent a highly effective approach not only for overcoming the challenge of low aqueous solubility and, consequently, poor bioavailability, but also for targeted drug delivery [1]. Consequently, the use of nanoparticles in drug delivery is receiving widespread attention, and research into nanoparticulate formulations has significantly expanded in recent years. Nanomedicine has emerged as the leading and most commercially promising technology for enhancing health [2]. Various types of nanotherapeutics have been used in the field of drug delivery, including nanocomplexes, nanoemulsions, polymeric micelles, liposomes, lipid and polymeric nanoparticles, and nanosuspensions [3].

Pharmaceutical nanosuspensions, also called nanocrystals, are heterogeneous mainly aqueous dispersions of insoluble drug particles stabilised by non-ionic surfactants, ionic stabilisers, or polymers [4]. Specifically, nanocrystals can be defined as nanoparticles consisting of pure drug, with no matrix material, and an average diameter below 1 μm (typically in the range of 200−500 nm). They can be prepared in both an aqueous and non-aqueous liquid phase as colloidal suspensions [5]. Although the term nanocrystals indicates that the particles are in the crystalline state, it has been extended to describe nano-sized suspensions of (partially) amorphous drugs [6]. Nanosuspensions have been suggested as a general drug delivery method for drugs categorised under classes II and IV of the Biopharmaceutics Classification System. The recently proposed Developability Classification System indicates that nanosuspensions are advantageous as a formulation strategy for class IIa drugs, for which the absorption rate is limited by the dissolution rate [7].

Nanosuspensions as liquid formulations suffer from instability due to nucleation and crystal

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growth. Additionally, the high surface area of the nanocrystals renders them thermodynamically unstable and promotes aggregation [8]. Conversion of nanosuspensions to solid dosage forms is a way to combine the advantages of nanocrystals with the advantages of the solid state (e.g., stability, transportation). In 2016, Malamatari et al. [6] reviewed studies on the solidification of nanosuspensions to solid oral dosage forms and inhalable drug powders. In this review, we aim to provide an update on the conversion of nanosuspensions to solid oral dosage forms, focusing on studies published from 2016 onwards. The review will briefly cover the advantages of nanosuspensions and the latest advances in their production and stabilisation. Techniques used for the solidification of nanosuspensions (i.e., spray drying, freeze drying, spray freeze drying, granulation, hot-melt extrusion, and printing) will be presented in depth (Table 1).

2. Advantages of nanosuspensions

Generally, nanosuspensions offer notable benefits, namely, (i) elevated dissolution rate and superior saturation solubility, which consequently improve bioavailability-related problems, (ii) low toxicity and (iii) enhanced chemical stability [17–19].

For drug nanosuspensions, particle size in the nanometer range may enhance the dissolution rate and saturation solubility, according to the Noyes-Whitney and Ostwald–Freundlich equations [20,21]. Especially for oral drug administration, nanosuspensions have been employed to overcome the limitation of low bioavailability and minimise the food effect when compared to micronised formulations [22,23]. In the study of Shaikh et al., the formulation of cilnidipine nanosuspensions resulted in enhanced bioavailability compared to pure drug and the marketed formulation [22]. Karakucuk et al. conducted pharmacokinetic studies of ritonavir nanosuspensions in both the fasted and fed states to assess the reduction of variability using nanosuspensions [23]. Ritonavir nanosuspensions exhibited a significant increase in oral bioavailability in the fed state compared to the coarse powder and the commercial product.

In addition to the enhanced dissolution rate, the reduced particle size of nanoparticles enhances mucosal adherence to the gastrointestinal tract, resulting in higher drug absorption [24]. A comparison between micronised suspensions and different nanosuspensions of the model drugs fenofibrate and megestrol acetate revealed that drug permeation rates from the nanosuspension with the smallest particle size were approximately three-fold higher in the dissolution-permeation study [25]. Jain et al. investigated the impact of particle size of fenofibrate nanosuspensions on biopharmaceutical performance using cellular uptake studies coupled with apparent solubility studies. The findings confirmed that mucoadhesion of nanocrystals led to extended release of the drug [26]. A ten-fold increase in rat intestinal absorption was also reported for nanosuspensions of *Kaempferia parviflora* [27].

Another advantage of nanosuspensions compared to alternative formulation techniques, is their high drug loading which may lead to higher drug delivery efficacy, effective cellular uptake, and an adequate therapeutic drug concentration at the target site, as in the case of the antitumour agent, celastrol [28]. Recently, a nanosuspension with a high loading of disulfiram was developed to improve drug stability by eliminating rapid degradation *in vivo*, in addition to increasing drug accumulation in tumor sites [29]. Formulating a drug as a nanosuspension has been suggested as a means of enhancing chemical stability in relation to solution formulations. In a recent example, curcumin nanosuspensions showed improved chemical stability compared to solubilised curcumin at pH values that mimic those of the gastrointestinal tract [30].

3. Advances in the field of stabilisation

The stability of submicron particles in the nanosuspension is mainly due to their uniform size, achieved through various manufacturing techniques. To prevent spontaneous crystal growth, the particle size of nanosuspensions must remain consistent throughout their shelf life. Preserving a uniform particle size distribution may impede the presence of variable saturation solubility, consequently preventing any crystal growth caused by Oswald ripening effect [31]. Stabilisers play a key role in the production of nanosuspensions, preserving the initial size of the nanoparticles and suppressing the free energy of the system by lowering the interfacial tension, while their steric stability and electrostatic repulsion can prevent nanoparticle aggregation, resulting in a stable formulation [32]. The progress in the development of stabilisation approaches for nanocrystals has been extensively reviewed [33–35]. It is worth noting that novel multifunctional stabilisers such as multifunctional polyethylene glycol (PEG) - chitosan and nanocaged carriers have also been employed to enhance the stability of drug nanocrystals [36,37]. Furthermore, natural bioactive ingredients such as lentinan, a β-glucan, and rubusoside have been reported as

Table 1. Advantages and limitations of the techniques used for the solidification of nanosuspensions.

Solidification technique	Advantages	Limitations	References
Spray drying	- Single-step process - Continuous process - Scalable and cost-effective compared to freeze drying and spray freeze drying - Control of particle characteristics (e.g., size, shape, morphology) - Production of powders with low moisture content, resulting in high stability upon storage - High encapsulation efficiency of drugs within polymeric carriers - The cooling effect of the evaporating solvent conserves the droplet temperature relatively low. This fact in combination with a very short contact time allows manipulation of heat-sensitive substances with negligible degradation	- Yield depends on the work scale - Using traditional spray dryers, the median particle size of the collected particles cannot be reduced below 1.5 μm - For the collection of submicron particles, nanospray driers with electrostatic particle collectors should be used	[9,10]
Freeze drying	- Drying under low temperature - Controlled moisture content - Short reconstitution time - Suitable for materials sensitive to air or O_2	- High energy and time consumption - High cost - Batch process - Vial-to-vial heterogeneity results in poor control of product quality - Optimisation and revalidation of cycles are needed upon scaling up - Requires excipients (e.g., sugars) to avoid degradation, aggregation or precipitation due to freezing and dehydration stresses - Downstream processing of freeze-dried cakes is needed prior to producing the final dosage form	[11,12]
Spray freeze drying	- Fast freezing - Control of particle characteristics (e.g., production of porous particles of low density) - High yield - Particles with excellent aerosolisation	- High complexity and time consumption - High cost - Delicate particles that may not withstand handling (e.g., mixing) - Use of liquid N_2	[12]
Granulation	Dry granulation - Suitable for moisture-sensitive materials - No cost-intensive drying steps are needed Wet granulation - Robust process - Production granules with good flow properties - Reduces segregation potential	Dry granulation - Production of large amounts of fines - High densification of the granulated material may lead to partial loss of tabletability Wet granulation - High energy and time consumption - Stability issues for moisture-sensitive and thermolabile drugs	[13]
Hot-melt extrusion	- Continuous process - Economical for drug product manufacturing - Solvent-free technique - Increases solubility and bioavailability of poorly water-soluble drugs - Useful for drug substances with low compressibility index	- Processing thermolabile compounds - Limited number of heat stable polymers - Requires raw materials with good flow properties - High energy input	[14]

Printing	- Production of various dosage forms (e.g., films, tablets) - Personalised dosage forms - Ability to manufacture dosage forms with multiple release modes - Ability to manufacture dosage forms containing multiple drugs - Printing at the point of care	- Difficult to scale up - Need for post-processing steps - Techniques such as fused-deposition modelling use intermediates (e.g., filaments) - Currently, there is limited experience with commercial products manufactured by printing	[15,16]

multifunctional stabilisers for the preparation of drug nanosuspensions and high drug loading nanocrystal-based solid dispersions [38,39]. Chen et al. successfully developed nanosuspensions of quercetin employing gypenosides as novel natural potential stabilisers with superior stabilisation efficiency in low concentrations [40]. There is also an increased interest in developing a rational methodology to select the appropriate stabiliser via computational and molecular dynamic simulations of the crystal lattice. Lattice energy framework combined with topology analysis and crystal morphology modelling have been applied to gain insight into the mechanism of particle fracture and improve the understanding of the mechanism responsible for nanocomminution and stabilisation of the drugs, as in the case of agomelatine and glimepiride nanocrystal formation [41,42].

4. Advances in the field of production

The production of nanosuspensions can be considered in two main categories: bottom-up methods, which include controlled precipitation of the nanoparticles from a supersaturated solution or with the use of an antisolvent, and top-down which use high-energy methods to decrease the particle size of crystalline drugs to the nanoscale [43]. Wet media milling (WMM) and high-pressure homogenisation (HPH) comprise the two basic top-down approaches [44]. The primary benefit of top-down methods is the ability to produce nanosuspensions with high drug loading. Furthermore, top-down methods are environmentally friendly as they do not employ harsh organic solvents [7]. Several relevant reviews have been published covering the significant advances in this field [7,45−47]. Use of bead mixtures (cross-linked polystyrene and yttrium-stabilized zirconia) as a process optimisation approach for rapid and effective development of drug nanosuspensions using WMM has been reported by Guner et al. [48]. A combination of planetary ball and pearl milling was also applied as a novel WMM procedure for the preparation of nanosized meloxicam [49]. Application of acoustic-vibratory milling was presented as a new tool for the streamlined process of developing micro/nanosuspensions [50]. Recently, much attention has been given to mechanistic modelling for the optimisation of nanosuspension preparation by WMM [51]. The microhydrodynamic approach and the stress model for stirred media mills were studied by Flach et al. to define the influence of operating parameters with respect to their applicability on process optimization of nanosuspensions [52]. Furthermore, simulation of

the temperature progression during the wet-stirred media milling by a semi-theoretical lumped parameter model was established for the process control of nanosuspensions of thermally labile drugs [53].

5. Nano-cocrystals

Nanosized cocrystals have recently been reported as a new strategy to eliminate poor aqueous solubility of BCS class II/IV drugs, taking advantage of co-crystallisation and nanocrystallisation techniques [54]. Various preparation methods have been employed for this purpose, such as WMM, spray drying, HPH, solvent evaporation and antisolvent methods [55–59]. The use of appropriate stabilisers and co-formers, aided by quality by design (QbD), has resulted in formulations with improved dissolution rate and long-term stability, as in the case of carbamazepine-nicotinamide and lamivudine-zidovudine nano-cocrystals [58,59]. A novel mechanochemical method for in situ pharmaceutical nanococrystal synthesis was suggested by Santos et al. [60], where a nano-powder of naproxen-nicotinamide was obtained in a single-step process by surfactant-assisted grinding.

The concept of nano-cocrystals has been extended to poorly soluble natural products. Specifically, baicalein-nicotinamide nanocrystals were successfully prepared using a HPH technique and demonstrated improved biopharmaceutical performance compared to baicaleine nanocrystals and baicaleine-nicotinamide cocrystals (Fig. 1) [61]. Similarly, piperine-succinic acid nano-cocrystals were obtained by WMM, resulting in a significant improvement in the solubility and dissolution rate of piperine [62].

6. Solifidification techniques

6.1. Spray drying

Spray drying is a well-established technique that can be used as a platform for both particle and crystal engineering. It is a single-step, continuous manufacturing process whereby a liquid feed is converted to a dried particulate form. The process consists of four stages: liquid feedstock preparation, atomization of the feed into a spray through a nozzle and contact with the hot drying gas, particle formation by drying of the solvent and finally separation of the dried product from the gas [63]. Spray drying has found several applications in pharmaceutics including preparation of solid dispersions, engineering of inhalable particles, encapsulation of drugs and drying of biologicals (e.g., proteins, vaccines). A review on particle engineering using spray drying has been provided by Malamatari et al. [64].

Nair et al. prepared nanosuspensions of risperidone by antisolvent precipitation with Poloxamer 68

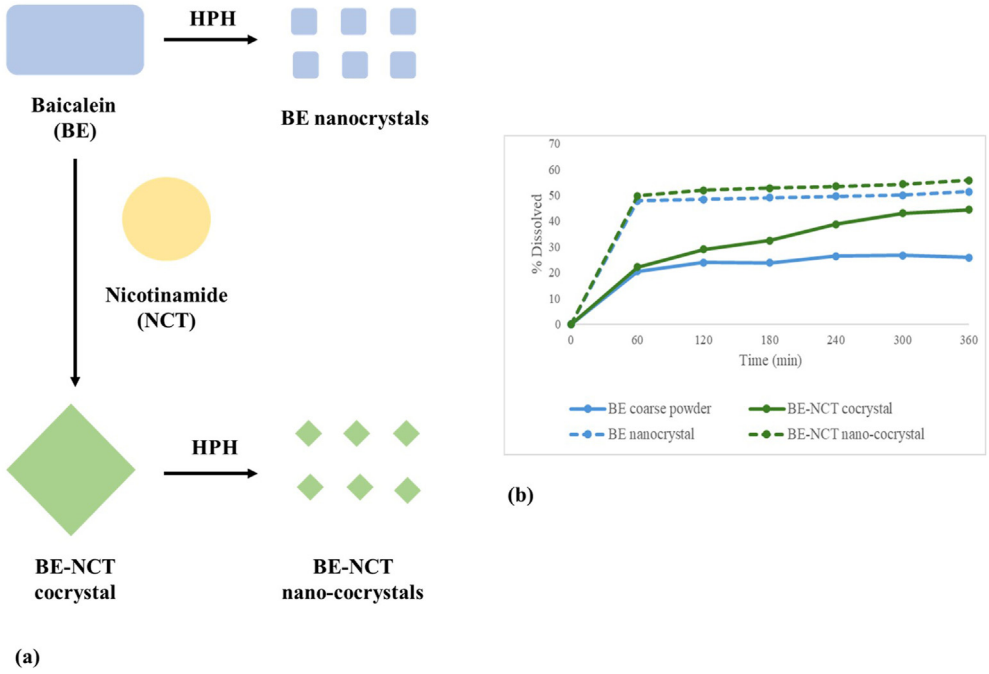

Fig. 1. (a) Formation of baicalein – nicotinamide nano-cocrystals, (b) in-vitro release in fasted state simulated intestinal fluid (FaSSIF-V2). Adapted from Ref. [61].

and Poloxamer 127 as stabilisers [65]. The nanosuspensions were spray dried after addition of mannitol and were further formulated to orally disintegrating tablets (ODTs). QbD was used to investigate the effect of inlet temperature and feed flow rate on the process yield and the particle size of nanosuspensions upon redispersion. When optimised process parameters for spray drying were obtained from the design space, the process exhibited high yield and the particle size upon redispersion was low. The crystallinity of risperidone was reduced upon spray drying. The ODTs exhibited higher dissolution than the marketed formulation, which was attributed to an increase of risperidone solubility upon spray drying.

Vardaka et al. produced nanosuspensions of agomelatine by WMM which were further solidified by spray drying [41]. It was found that agomelatine form I undergoes a polymorphic transition to form II during WMM. The spray-dried nanosuspensions were further processed to produce mini-tablets. The dissolution of agomelatine from the minitablets was rapid compared to agomelatine physical mixtures. Using the same techniques, Medarević et al. prepared spray-dried nanosuspensions of glimepiride where no polymorphic transformation was observed during WMM [42]. Redispersibility experiments showed that the spray-dried nanosuspensions stabilised with Poloxamer 188 failed to recover the initial nanoparticles. This was attributed to melting of the surfactant causing aggregation during spray drying. However, the spray-dried nanosuspensions stabilised with Poloxamer 188 exhibited the highest dissolution rate when compared to the pure drug and spray-dried nanosuspensions stabilised with cellulosic polymers. It was concluded that glimepiride dissolution was determined by the intrinsic properties of the stabiliser rather than the size of the redispersed particles.

Czyz et al. elucidated the importance of drying temperature, type, and content of matrix former and particle size for successful formulation of spray-dried nanosuspensions [66]. Nanosuspensions of naproxen and itraconazole were produced by WMM and were stabilised with Kollidon® VA 64 and sodium lauryl sulfate (SLS). They were further spray dried with lactose, trehalose, and sucrose as matrix formers at different proportions and different outlet temperatures. Outlet temperature and drug content were found to be related as parameters and to influence the redispersibility of the spray-dried nanosuspensions. Specifically, it was found that the maximum drug content that results in redispersible product is determined by the outlet temperature and the glass transition temperature of the matrix former, as well as the proportion of the matrix former and the particle size of the nanosuspensions used (Fig. 2). Thus, a compromise should be made between high dissolution rate and high drug content.

Li et al. studied the impact of dispersant on the dissolution of itraconazole spray-dried nanocomposites [67]. Superdisintegrants such as sodium starch glycolate, crospovidone and crosscarmelose sodium were co-milled with itraconazole stabilised with hydroxypropyl cellulose (HPC). The spray-dried nanocomposite containing the superdisintegrants exhibited faster dissolution compared to when sugars such as mannitol and sucrose were used as matrix formers. Their dispersant effectiveness was positively correlated with their swelling capacity, indicating a swelling-induced erosion/

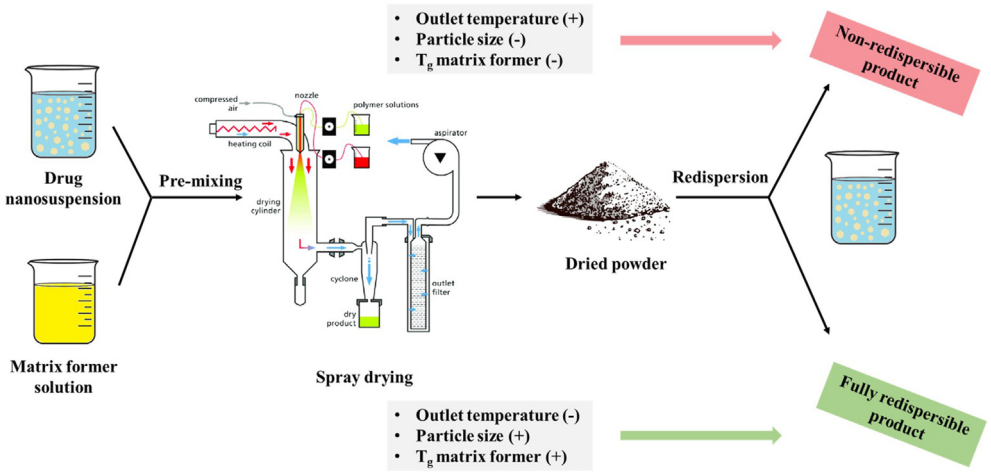

Fig. 2. Drying temperature, particle size and glass transition temperature (T_g) of matrix former as important parameters for the redispersibility of spray-dried drug nanosuspensions. Adapted from Ref. [66].

disintegration mechanism. In this way, nanocomposites with high drug loading (>60% w/w) were prepared which exhibited immediate drug release.

Rahman et al. spray dried griseofulvin nanosuspension with high Soluplus® loading (i.e., 1:1 to 1:5 drug: polymer mass ratio) [68]. This resulted in the formation of a novel class of nanocomposites known as hybrid nanocrystal-amorphous solid dispersions (HyNASDs). HyNASDs contain drug nanocrystals surrounded by molecularly dispersed drug. Hence, they are partially amorphous. The Soluplus®-based HyNASDs exhibited supersaturation of up to 300% within 20 min which was retained for up to 3 h indicating that their bioavailability could be enhanced. The increased supersaturation of the HyNASDs was attributed to the high griseofulvin-Soluplus® miscibility, the strong molecular interactions between the drug and the polymer and the nucleation/crystal growth inhibition by Soluplus®. The supersaturation achieved by HyNASDs was higher than the supersaturation exhibited by conventional spray-dried nanosuspensions. In follow-up studies it was demonstrated that while HyNASDs did not generate as high saturation as amorphous solid dispersions amorphous solid dispersions, they could boost drug release from nanoparticle-based formulation and may render them competitive to amorphous solid dispersions [69,70].

6.2. Freeze drying

Freeze drying, also known as lyophilisation, is a long-established process for removing solvents, usually water, from pharmaceutical products. It comprises three main stages: freezing, primary drying and secondary drying [71]. The final freeze-dried product usually exhibits a highly porous structure and low moisture content. Freeze drying improves the stability of labile drugs, particularly with regards to their long-term storage stability. It also facilitates the processing of compounds without causing significant damage and the production of nanosuspensions in a dry form that can be easily handled and reconstituted with water or other aqueous diluents prior to use [6,72]. Even though freeze-drying is time-consuming, costly and requires a high amount of energy, it remains a useful tool for the pharmaceutical industry. A review has been provided by Trenkenschuh and Friess on freeze drying of different types of nanoparticles with emphasis on ways to overcome colloidal instability by formulation and process optimisation [72].

Bartos et al. prepared surfactant-free nanosuspensions containing meloxicam, using freeze drying as the solidification method [73]. They studied the influence of solidification on the physical stability and drug bioavailability of the products. Meloxicam nanosuspensions were prepared by WMM and contained polyvinyl alcohol (PVA) as a protective polymer. Freeze drying resulted in amorphisation of the crystalline carrier, trehalose, and recrystallisation of meloxicam leading to increased particle size and crystallinity. Animal experiments showed that bioavailability per oral administration was five-fold higher for freeze-dried samples compared to meloxicam nanosuspensions. Solidification of nanosuspensions containing meloxicam not only increased their stability but also allowed the preparation of surfactant-free products with enhanced bioavailability and the potential to achieve rapid analgesia.

Jakubowska et al. prepared cilostazol nanosuspensions using an antisolvent precipitation-sonication method and studied the effect of freeze drying on particle size after redispersion of the product [74]. Several processing variables, such as cryoprotectants, concentration, freezing temperature, cooling rate and primary drying temperature were assessed. The optimal settings for freeze drying of cilostazol nanosuspensions were found to be: 10% w/w trehalose and 5% w/w maltodextrin or 10% PEG 1500. After processing, freeze-dried nanocrystals retained their original size, polymorphic form A of cilostazol and their enhanced dissolution rate.

Touzet et al. presented an alternative approach to freeze drying known as ‘active freeze drying’, which allows for producing lyophilised powders by progressive agitation of frozen blocks undergoing sublimation [75]. One potential application of ‘active freeze drying’ is the conversion of unstable nanosuspensions to redispersible nanocrystalline powders suitable for oral drug delivery.

Freeze drying and spray drying are the two most used techniques for the solidification of nanosuspensions due to their potential for downstream processing. Application is easy in both techniques, and they are suitable for the preparation of oral formulations [6]. The main differences between them are focused on their time consumption and the temperatures they generate. Spray drying is a quick process where high temperatures are reached (typically 120–190 °C). On the other hand, freeze-drying is a more time-consuming process, but the temperature remains low (−90 to −20 °C), meaning that it is suitable for thermolabile products. There are studies focusing on the comparison of these two techniques with respect to solidification of nanosuspensions. Ma et al. compared the two processes

for the solidification of silybin nanosuspensions, which were stabilised with polyvinylpyrrolidone (PVP–K30) [76]. Scanning electron microscopy showed that the spray-dried sample was spherical while the freeze-dried sample was rod-like with a smooth surface. Both samples presented improved dissolution rate, satisfactory redispersibility and enhanced long-term stability in comparison with the nanosuspension in the liquid form. Moreover, Medarevic et al. used both processes to solidify carvedilol nanosuspensions produced by WMM [77]. Solid state characterisation and redispersibility tests showed that redispersibility was achieved only with spray drying, while freeze drying induced irreversible particle aggregation. In addition, polymorphic transition of carvedilol occurred only with the freeze-drying process. As a result, spray drying was suggested as the technique of choice for solidification of carvedilol nanosuspensions. The superiority of spray drying compared to freeze drying as a solidification technique for aprepitant nanosuspensions has also been reported by Toziopoulou et al. (Fig. 3) [78]. Ma et al. designed a novel core–shell structure deacetyl-mycoepoxydience nanosuspension, which was solidified by spray drying and freeze drying [36]. Between the two samples, the spray-dried powder exhibited a spherical shape with a smooth surface, higher stability, smaller particle size and more rapid dissolution rate.

6.3. Spray freeze drying

Spray freeze drying (SFD) is a unique drying process, which combines the principles of spray and freeze drying. The general operating principle of SFD involves the atomisation of a liquid into droplets using a nozzle and the solidification of the atomised droplets by freezing them under cryogenic conditions. Then, the frozen droplets are lyophilised under freeze-drying conditions to remove the solvent (water) by sublimation and obtain a dry powder with particles characterised by a fine porous structure and large specific surface area. Its applications include solidifying thermosensitive drug nanosuspensions, converting them to dry powders and preparing inhalable particles with large geometric diameters for pulmonary drug delivery [79].

Braig et al. applied SFD for the preparation of redispersible powders of pure naproxen nanodispersions [80]. The nanodispersions were produced via WMM using HPC as the dispersion medium and lactose as the bulking agent. Results showed that nanoparticles prepared by SFD demonstrated enhanced redispersibility compared to the spray-dried nanodispersions. Wei et al. investigated the use of HPC as a matrix carrier for novel cage-like microparticles prepared by SFD [81]. The SFD composite microparticles exhibited excellent redispersibility which was attributed to their porous matrix and large surface area. The dissolution of the SFD composite particles was also enhanced. It was found that HPC immobilised the drug nanocrystals in its cage-like structure and prevented agglomeration upon storage.

6.4. Granulation and compaction

Wet granulation or fluid-bed granulation is another technique, which is used for the solidification of nanosuspensions due to its capability to produce homogenous granules with improved flow and compaction properties. Sahnen et al. prepared indometacin nanosuspensions by WMM and studied the solidification in solid dosage forms via fluid-bed granulation [82] They evaluated several

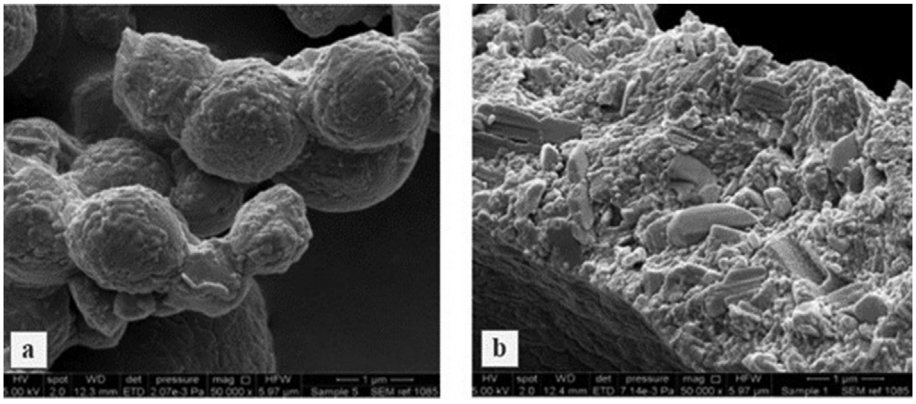

Fig. 3. Scanning electron microscopy images (magnification ×50,000) of (a) spray-dried aprepitant nanosuspensions and (b) freeze-dried aprepitant nanosuspensions. Reproduced with permission from Ref. [78].

parameters, such as the binder selection, concentrations used, spray rate and atomisation pressure. Granulation occurred with or without additional binder and the sample was dried on a carrier consisting of lactose, microcrystalline cellulose and crospovidone. Final granules were compacted into tablets, with superior dissolution performance compared to raw indometacin tablets. Horster et al. prepared solid dosage forms of poly (DL-lactide-co-glycolide) (PLGA) nanosuspensions [83]. Fluid-bed granulation with aqueous PLGA nanosuspensions and soluble carriers such as lactose was shown to be a simple and high-yield process for drying of nanosuspensions. The granules were compressed to tablets without impairing the nanoparticle size and recovery when a sufficient level of filler and low compression forces were employed.

Wewers et al. studied the influence of formulation parameters on the redispersibility of granules during solidification via fluid-bed granulation [84]. A better redispersibility of the nanoparticles from the granules was related to better dispersion of the drug nanoparticles at the surface of granules as deduced from the thickness of nanoparticle-loaded layers around the granules, studied using confocal Raman spectroscopy. Moreover, Meruva et al. developed irbesartan nanosuspensions which they solidified using spray granulation or bead layering [85]. The powders were further processed to mini tablets. Spray granulation was found superior to bead layering as a drying method.

6.5. Hot-melt extrusion

Hot-melt extrusion (HME) is a process whereby heat and pressure are applied to melt or soften materials which are extruded through a die to produce new products of uniform shape [86]. The applications of HME in pharmaceutics include taste masking of drugs, solubility enhancement of poorly soluble drugs and preparation of modified-release solid oral dosage forms [87]. Specifically, HME has been widely used as a technique for the manufacture of amorphous solid dispersions which exhibit increased dissolution rate but are also linked with stability challenges such as recrystallisation upon storage. Coupling the extruder with customised downstream auxiliary equipment (e.g., mill, pelletiser) can lead to the production of several solid dosage forms such as granules, pellets, capsules, tablets, films and reservoir rings [14]. Recently, HME has been used to fabricate the drug-loaded thermoplastic filaments that are used as the starting material for 3D printing pharmaceutics via fused-deposition modelling [86,88]. Compared to other techniques (e.g., spray drying, freeze drying), HME has the advantages of being a solvent-free, continuous process with low energy input and no time-consuming steps [14].

The first study on the extrusion of nanosuspensions to solid dosage forms was reported by Khinast et al. [89]. A novel single-step process was used for solidifying a nanosuspension via HME coupled with an internal devolatilisation process (nano-extrusion, NANEX). Specifically, a polymer, Soluplus®, was melted and fed into the extruder, after which a stable aqueous nanosuspension of titanium dioxide was added via a side-feeding device. Water was removed by devolatilisation, and the polymer solidified at the outlet. Characterisation of the extrudate revealed that it comprised nanocrystals in the de-aggregated form, embedded in the polymeric matrix [89]. The NANEX process was also employed to solidify a nanosuspension of phenytoin stabilised with Tween 80 [90]. The nano-extrudates of phenytoin exhibited increased dissolution rate compared to the raw drug and bulk extrudates. In a follow-up study, Baumgartner et al. extended the use of the NANEX process to several matrix systems (i.e., Kollidon® VA 64, Eudragit® E PO, HPMCAS and PEG 20000) [91]. It was found that a long mean residence time of the molten polymer in the extruder and low filling degrees of the screw in the degassing zone increase the amount of water that can be added to and removed from the molten material.

Ye et al. prepared nanocrystal solid dispersions of efavirenz by combining HPH and HME (Fig. 4) [92]. Specifically, a nanosuspension of efavirenz with SLS and Kollidon® 30 as stabilisers was prepared by HPH. It was then mixed with Soluplus® in the extruder barrel and the water was removed by evaporation. The nanocrystal solid dispersions exhibited an enhanced dissolution rate and were found to be stable upon storage under long-term stability conditions for six months. Gajera et al. prepared dried amorphous nanosuspensions of clotrimazole by coupling antisolvent precipitation with HME [93]. In their study the nanosuspension and the matrix-forming polymer (i.e., microcrystalline cellulose) together were directly introduced in the extruder through a separate feeding device. Such an approach can improve the drug uniformity of the extrudate which is particularly important for low-dose formulations. Moreover, they reported that a moderate inlet temperature led to efficient removal of residual moisture without compromising the redispersibility of the dried nanosuspension [93].

Using HME, Li et al. prepared HPC-based nanocrystalline solid dispersions and Soluplus®-based

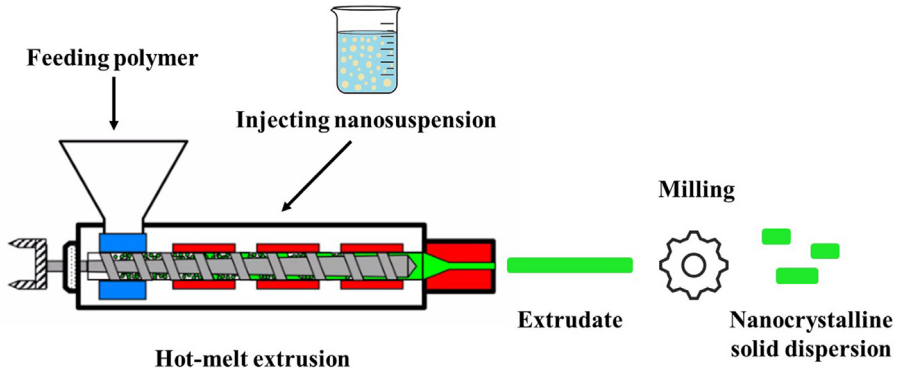

Fig. 4. Preparation of nanocrystalline solid dispersion by hot-melt extrusion. Adapted from Ref. [92].

amorphous solid dispersions of griseofulvin [94]. Comparative assessment of the two formulations demonstrated that nanocrystalline solid dispersions with hydrophilic polymers could be competitive to amorphous solid dispersion in enhancing dissolution rate of low-dose poorly soluble drugs. The extrudates of the amorphous solid dispersions required fine milling for rapid release, while only coarse milling was sufficient for the nanocrystalline solid dispersions to release low-dose drugs rapidly [95].

6.6. Printing and formation of films

Printing technologies have been used for the deposition of dissolved or dispersed drugs to produce solid oral dosage forms. Printing can be used to fabricate a wide variety of pharmaceutical dosage forms varying in shape, release profile and drug combination [96]. This makes printing a promising tool in personalised medicine. Printing of pharmaceuticals can be distinguished in two categories: 2D printing and 3D printing. The main techniques of 2D printing used for pharmaceuticals are inkjet printing and electrospray, which involve deposition of the drug onto a substrate in a x and y axis. 3D printing (also referred to as additive manufacturing) involves the deposition of the drug and excipients in a layer-by-layer manner for the construction of formulations/drug delivery systems with the use of a 3D printer equipped with an appropriate computer-aided design software. The main methods of 3D printing are based on powder solidification (e.g., selective laser sintering), liquid solidification (e.g., stereolithography) and extrusion (e.g., fused-deposition modelling) [97]. Formation of films based on nanosuspensions will also be reviewed in this section, as film formation using traditional or alternative methods shares many similarities with 2D printing of films.

Krull et al. converted griseofulvin nanosuspensions to strip films by film casting and assessed the critical material attributes of films loaded with poorly water-soluble drug nanoparticles [98–100]. For the fabrication of films, hydroxypropyl methylcellulose (HPMC) was the film-forming polymer while different plasticizers (i.e., glycerol, triacetin and PEG) were used. The type and amount of plasticizer required to form strong yet flexible films was found to have no impact on the dissolution rate of films, indicating that film mechanical properties can be effectively adjusted with minimal impact on drug release [98]. Moreover, the molecular weight of the film-forming polymer can be used to manipulate drug release with little impact on the film's mechanical properties by matching polymer solution viscosity [99]. Films with high drug loading, good mechanical properties and rapid dissolution were produced. However, it was reported that drug loadings above 40–50% w/w resulted in films with increased brittleness [100].

Several methods have been used for the conversion of drug nanosuspensions to films. Karagianni and Peltonen used film casting to prepare fast-dissolving polymeric films containing itraconazole nanocrystals [101]. Apart from film casting, alternative techniques such as the microvalve technology and electro-hydrodynamic drop-on demand printing of aqueous nanosuspensions in biocompatible films have been reported as flexible manufacturing technologies with continuous adjustability of the dose [102,103]. Stable nanosuspensions of naproxen with appropriate viscosity were used as ‘the ink’ in a consumer-grade inkjet printer and were deposited as a thin film across a wide range of concentrations [104]. Inkjet printing of drug nanosuspensions was proposed as a general approach for dispensing precise and reproducible quantities of poorly soluble drugs, an approach particularly important for the administration of low-dose (highly potent) drugs.

Germini and Peltonen used semi-solid extrusion to produce indometacin nanocrystal-loaded, 3D-printed, fast-dissolving oral polymeric films [105]. Upon printing, drug nanocrystals remained in the nanosize range (300–500 nm). Comparison of the 3D-printed films with films fabricated by film casting showed that both types of film exhibited similar behaviour. 3D printing of films was proposed as an approach to produce immediate release solid dosage forms with increased drug solubility. Using semi-solid extrusion to obtain a single-step, solvent-free, low-temperature 3D-printing method called melting solidification printing process (MESO-PP), Lopez-Vidal et al. prepared printlets with embedded albendazole nanocrystals [106]. Printlets exhibited enhanced dissolution compared to spray-dried nanocrystals while their physical and chemical stability was retained for six months upon storage.

7. Conclusions

Several methods have been used for the solidification of nanosuspensions to solid oral dosage forms (e.g., powders, granules, pellets, tablets, films). The methods include spray drying, freeze drying, spray freeze drying, granulation, hot-melt extrusion and printing. Spray drying and freeze drying remain the most widely used techniques. Granulation and hot-melt extrusion allow a straightforward downstream processing while printing exhibits the potential for dose optimisation. Recent studies build on the knowledge of previous studies and provide a mechanistic understanding of the formulation and process parameters which influence the redispersibility and dissolution of the nanoparticle agglomerates. Apart from the commonly used sugar alcohols, excipients such as superdisintegrants have been used as matrix formers. Novel formulations beyond the conventional nanocrystals have also been developed. These include nano-cocrystals and nanocrystalline solid dispersions which have the potential to further increase the dissolution and the bioavailability of poorly soluble drugs.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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