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Recent strategies in spray drying for the enhanced bioavailability of poorly water-soluble drugs

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Abstract

Poorly water-soluble drugs are a significant and ongoing issue for the pharmaceutical industry. An overview of recent developments for the preparation of spray-dried delivery systems is presented. Examples include amorphous solid dispersions, spray dried dispersions, microparticles, nanoparticles, surfactant systems and self-emulsifying drug delivery systems. Several aspects of formulation are considered, such as pre-screening, choosing excipient(s), the effect of polymer structure on performance, formulation optimisation, ternary dispersions, fixed-dose combinations, solvent selection and component miscibility. Process optimisation techniques including nozzle selection are discussed. Comparisons are drawn with other preparation techniques such as hot melt extrusion, freeze drying, milling, electro spinning and film casting. Novel analytical and dissolution techniques for the characterisation of amorphous solid dispersions are included. Progress in understanding of amorphous supersaturation or recrystallisation from solution gathered from mechanistic studies is discussed. Aspects of powder flow and compression are considered in a section on downstream processing. Overall, spray drying has a bright future due to its versatility, efficiency and the driving force of poorly soluble drugs.

Keywords: Spray drying; Solid dispersion; Amorphous; Poorly soluble drugs; Formulation

INTRODUCTION

Spray drying is an excellent technique for the rapid removal of solvent from a system, yielding particles with various properties that can be specifically designed. In this review, there is a focus on the ability to produce drug-containing particles with an enhanced bioavailability. Due to the large number of poorly water-soluble drugs present in today's market (and the even larger proportion currently under development), methods for generating drug particles with enhanced solubility are of crucial importance.

Poorly water-soluble drugs:

Poorly water-soluble drugs are now accounting for 40% of existing drugs and 70% of new chemical entities(Brouwers et al., 2009; Nagabandi et al., 2014; Williams et al., 2013). The solubility performance of drugs remains one of the most challenging aspects in formulation development today(Leuner and Dressman, 2000). The BCS classification system was introduced in 1995 as a systematic way of classifying drugs according to solubility and permeability properties(Amidon et al., 1995). Class II drugs are highly permeable and poorly soluble, but class IV drugs have low permeability and low solubility (Figure 1).
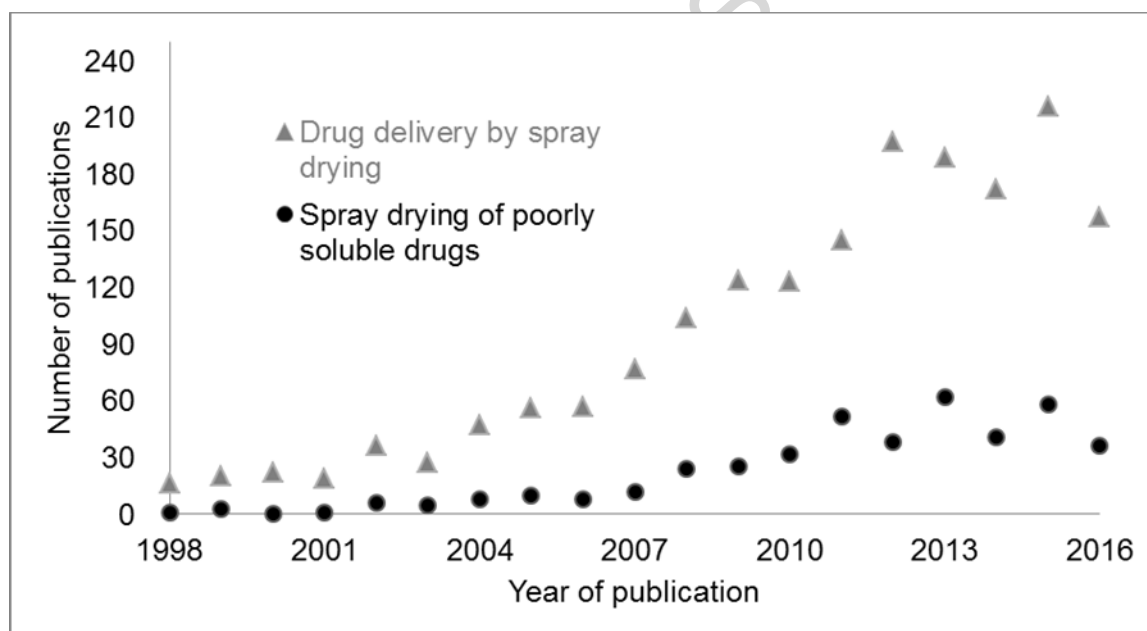
Figure 1. Trend in the spray drying of drugs and poorly soluble drugs since 1998, source Scopus[®]

A variety of techniques for producing drug formulations with enhanced solubility are available(Savjani et al., 2012). Physical modifications include particle size reduction like micronisation or nano-sizing(Mosharraf and Nyström, 1995); modifications of the crystal habit include preparation of the amorphous form(Yoshioka et al., 1994) or preparing an alternative polymorph or co-crystal(Blagden et al., 2007). Drug dispersions can include eutectic mixtures(Law et al., 2003), solid dispersions(Leuner and Dressman, 2000), solid solutions and cryogenic techniques. Chemical modifications include changes in pH, using a buffer, derivatisation, complexation and salt formation(Serajuddin, 2007). Other methods involve the use of surfactants, solubilisers, the supercritical fluid processes, cosolvency, hydrotrophy and new excipients(Fahr and Liu, 2007). Several preparation methods designed to produce formulations with enhanced solubility relative to the untreated drug are of interest, particularly hot melt extrusion(Crowley et al., 2007), electrospinning(Kenawy et al., 2009),

rotary evaporation(Van Eerdenbrugh and Taylor, 2010), milling(Chieng et al., 2009), freeze drying(Dontireddy and Crean, 2011) and others, but here the primary focus will be on spray drying and the substantial level of research work taking place in this area.

Spray drying

Spray drying can be used to make amorphous solid dispersions, solid dispersions, microparticles, nanoparticles, self-emulsifying delivery systems, eutectic mixtures and other powdered products. The process has been described in many excellent articles and reviews and will not be described here in great detail(Cal and Sollohub, 2010; Paudel et al., 2013; Singh and Van den Mooter, 2016; Sollohub and Cal, 2010; Vehring, 2008). Essentially, a liquid solution (or suspension) is converted to a powdered solid. Liquid feed is usually pumped into a drying chamber *via* a nozzle where fine droplets rapidly encounter a hot drying gas. The wet gas and dry particles are then separated by a cyclone and / or bag filter and the powdered product is dispensed into a collection vessel and / or bag filter (Figure 2). Many different permutations of the spray drying apparatus exist, such as nozzle variations (two-fluid, pressure, rotary, vibrating), drying chamber geometry differences (height, width, material), direction of flow (counter-current and co-current), cyclone design, drying gas type and of course, scale. Critical process parameters include inlet temperature, outlet temperature, drying gas velocity, liquid feeding rate, feed concentration, feed viscosity and several others(Vehring, 2008).

PRE-SCREENING OF FORMULATIONS

The purpose of formulation pre-screening is to minimise the risk and cost associated with development. Pre-screening is particularly important during pharmaceutics research because of the high cost and limited availability of new chemical entities. A variety of practical, mathematical, and *in silico* approaches exist, with differing pros and cons.

Practical methods like solvent casting (Davis et al., 2015) have the advantage of representing a real system, encountering problems that might be missed in mathematical assumptions or computer models. Only small quantities of drug and solvent are required to rapidly produce a variety of permutations whilst keeping costs and solvent levels relatively low. A design of experiment approach can also reduce the overall number of runs required for a specific formulation(Iannuccelli et al., 1998). Nevertheless, the Holy Grail continues to be computational or mathematical models to represent real systems as these can be performed much faster and with fewer requirements for resources. Examples of progress in these areas are mentioned later on.

Not all practical pre-formulation techniques will adequately represent a commercial production outcome, so a variety of techniques are required. Atomic force microscopy and confocal Raman microscopy were used as tools to compare particles generated from a drying kinetics analyser with particles from a conventional spray drier(Whiteside et al., 2013). Griseofulvin was taken as a model drug at loadings of 2.5% and 20% with PEG 6000. With this model system, particles were found to be physically and chemically equivalent, indicating that single levitated droplet drying offers a viable pre-formulation technique for screening drug-polymer combinations.

Improvement of mathematical equations to predict formulation behaviour is ongoing(Chatterjee et al., 2001; Tian et al., 2014). The Arrhenius equation can be used to measure the rate of degradation reactions from amorphous dispersions and predict stability.

Patterson *et al.* monitored the stability of dispersions of HPMC-AS for 6 months using HPLC(Patterson et al., 2015). Although the data reflected the impact of temperature and RH levels, it was clear that these terms alone did not account for all of the variability in the data. An extension to the Arrhenius equation to include a term for polymer chemistry improved the fit of the model.
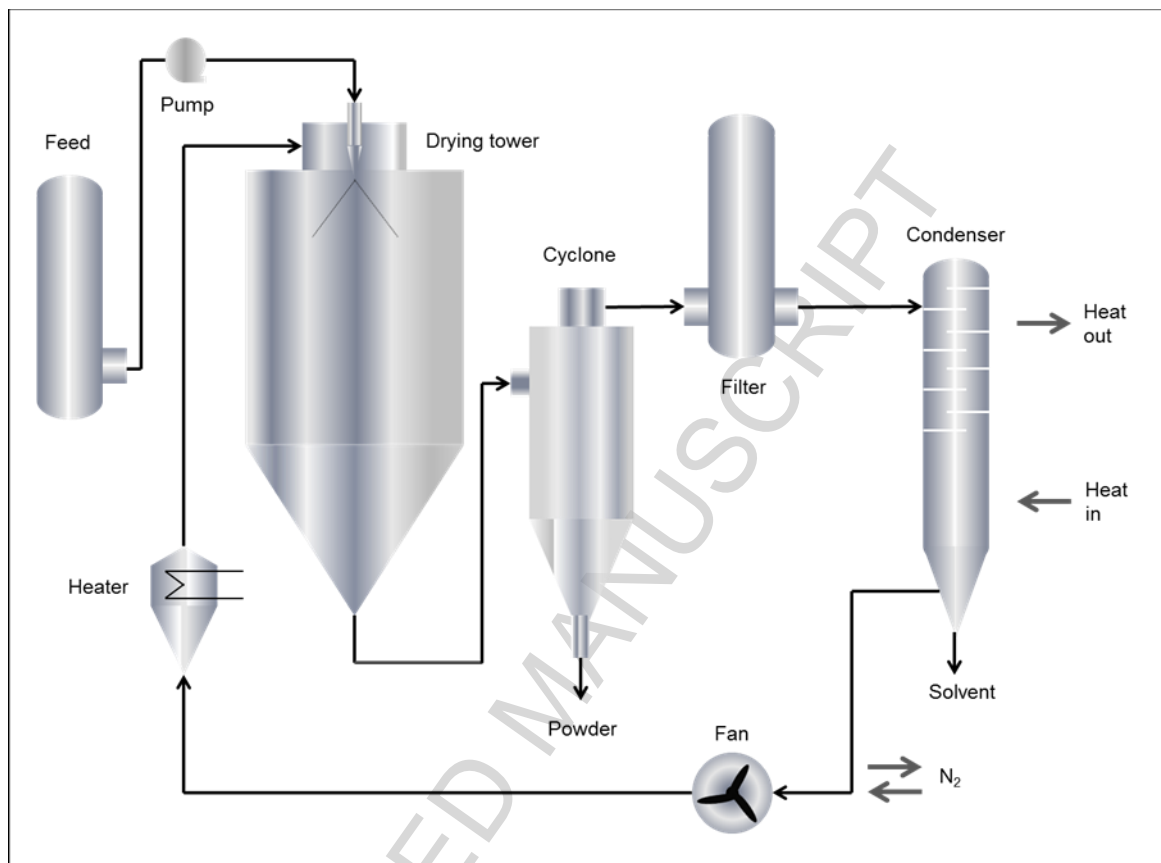
Figure 2. Schematic of a spray drying process in closed mode. The liquid feed is pumped through the nozzle and rapidly dries in the drying chamber before passing through the cyclone and filter to separate the particles from wet gas. A condenser traps the solvent and inert gas nitrogen is recycled back to the top of the drying tower in a closed loop using a fan. This configuration is often employed for spray drying lipophilic drugs.

A novel computerised screening methodology designed for the early development of spray dried amorphous dispersions has been described(Duarte et al., 2015). The model combines thermodynamic, kinetic and manufacturing information in a series of partial differential equations to describe the evolution of drug-polymer microstructure. Itraconazole dispersions were prepared with a variety of polymers and a comparison was made to results obtained from the model. The results from the model were ranked according to miscibility and this compared well with the experimental data. If such *in silico* techniques can be developed to reliably predict the optimal formulation characteristics (e.g. loading) of a drug, they can be of enormous benefit.

FORMULATION

Choosing an appropriate excipient for the spray dried dispersion

Often polymeric excipients are chosen for spray dried dispersions of drugs and HPMC-AS is very popular(Curatolo et al., 2009). Considered a reliable excipient, it has been combined with many drugs and studied in many publications, e.g. Friesen tested 139 drug compounds in combination with this polymer(Friesen et al., 2008). Although HPMC-AS often performs well in spray drying and processing, it should not be regarded as the automatic choice for amorphous dispersions. The diversity of chemical structures in API requires a similar diversity in excipients. Hydrogen bonding may be essential for drug-polymer amorphous stability. If this is the case, then the polymer and API functional groups should be 'tuned' to maximise beneficial intermolecular attractive forces. Choosing the best excipient (or excipient blend) for a given API depends on a series of characteristics and publications reflecting this need are manifold(Patel et al., 2015b). There follows a series of examples of recent publications involving poorly water-soluble API that reflects this need for polymer variety:

Anti-HIV drug efavirenz was formulated into spray dried dispersions with varying quantities of Soluplus® and characterised with multiple spectroscopic techniques(Lavra et al., 2017). Stability studies conducted at accelerated conditions (40 oC/75% RH) confirmed amorphous drug by PXRD and DSC after 12 months. Solubility and dissolution rates were both enhanced in the SDD as a function of polymer concentration.

Dissolution enhancement of celecoxib by spray drying with excipients PVP and Isomalt from hydroalcoholic solution was reported to generate SDD with 20-fold to 30-fold enhanced dissolution(Ghanavati et al., 2017). FTIR studies provided evidence of hydrogen bonding between drug and PVP. Formulations had recrystallized after 1 month of storage at 75% RH, however.

Solid dispersions of nifedipine (20-50%) and PVP were prepared by spray drying and analysed by FTIR, PXRD, DSC, SEM and *in vitro* dissolution(Ikasari et al., 2015). SDD were found to be granulated, yellow and free flowing and SEM showed the particles to be spherical and porous. FTIR spectra revealed no interaction between polymer and drug and all formulations were PXRD amorphous. Thermograms showed broad melting peaks for drug at lower temperature than pure drug, indicating some miscibility of the drug in the carrier. It was concluded that dissolution was related to drug load and that higher polymer levels increased drug dissolution.

Both the solubility and the photosensitivity of amlodipine were improved by spray drying into dispersions comprising dextrin (1:10 w/w) and SLS (0.9% w/w)(Jang et al., 2013). Particles were smooth and spherical with average size of 12.9 μm. Drug was amorphous and storage stability was maintained for 6 months at RT. Dissolution of ASD was much faster than crystalline drug and plasma concentrations in rats were significantly higher, providing a 2.8-fold increase (with SLS) and 2.0 fold increase (without SLS) in AUC value.

Ferulic acid was spray dried at 10% or 20% in binary combination with one of PVP-K30, PEG 6000 or poloxamer-188(Nadal et al., 2016). The relative solubility was improved by increasing the carrier concentration and the formulations were found to be amorphous by PXRD and DSC. FTIR revealed the likelihood of hydrogen bonding in the PVP SDD only. A free-radical scavenging assay confirmed intact antioxidant activity and a statistically relevant increase in anti-platlet effect relative to pure drug.

Structural and thermal properties of microparticles containing methotrexate and PLGA prepared by spray drying were analysed by a series of spectroscopic techniques(De Oliveira

et al., 2013). High levels of encapsulation efficiency (90%) and spherical particle morphology were obtained.

The influence of a variety of excipients, solvent and packaging was studied with the objective of optimising the conditions for spray dried dispersions of fenofibrate (Hugo et al., 2013).

The effect of polymer structure on SDD performance

The influence of the polymer chosen when designing ASD can have a profound influence on the stability and performance of the dispersions. It is well understood that intermolecular attractions such as hydrogen bonding play a key role in the success of certain combinations. More detailed information is required for a deeper understanding and whilst optimisation of formulations by screening various polymers and drug loadings is common, some research groups have probed more deeply, by studying the impact of varying polymer functional group chemistry on SDD performance. Several examples follow:

Ting and co-workers have reported the design and synthesis of a multicomponent polymer platform based on HPMC-AS (Ting et al., 2014). The controlled synthesis of the polymer involved varying the levels of hydroxypropyl, methoxy, acetyl, succinoyl and glucose groups to influence the amphiphilic balance, ionisation point, hydrogen bonding and glass transition temperatures of the resultant polymer analogues. Probucol was then selected as a model BCS class II drug and spray drying was used to form SDD with the various polymer analogues. Dissolution experiments revealed dramatic differences in bioavailability as a function of polymer chemistry. This highlighted the critical importance of chemically driven interactions in facilitating amorphous stability and supersaturation. It was found that increasing carboxylic acid moieties and replacing glucose acetates with hydroxyl groups helped to establish stabilising ionic character and polar connections. This work demonstrated the possibility of a structure-function relationship between drug and polymer in oral delivery.

In a related publication, the deconstruction of HPMC-AS was undertaken in a study of how polymers mechanistically provide storage and supersaturation stability(Ting et al., 2015). A versatile polymeric platform analogous to HPMC-AS was constructed and spray dried with BCS class II drugs probucol, danazol and phenytoin. The polydisperse nature of the polymer was dismantled into well-defined polymeric zones and the performance of the drug-polymer SDD was tested by wide-angle XRD and *in vitro* dissolution tests. Certain functional group zones of the polymer were found to be crucial in drug performance, e.g. polymer containing acetyl and succinoyl groups only in SDD with probucol increased area under curve by 180-, 112-, and 26-fold over pure drug at 10, 25, and 50 % loading (w/w) respectively. Danazol and phenytoin were best protected from *in vitro* recrystallisation using hydroxyl-rich water soluble polymer analogues. These findings provided fundamental insights into how excipient microstructure can affect ASD performance.

Esters of HPMC including five synthetic esters and commercially available HPMC-AS were combined with phenytoin by spray drying(Yin and Hillmyer, 2014). The purpose of the work was to vary the ester groups in the polymer and verify the corresponding impact on drug stability in the formulations. The SDD at 10% drug load had little difference in bulk properties and only minimal amounts of crystalline drug were detected using SEM, PXRD and DSC. In solution, while the HPMC-AS SDD was initially effective at reaching high levels of supersaturation at the beginning, it was not capable of maintaining these levels due to rapid crystallisation of the drug. Contrastingly, SDD with several of the synthesised

HPMC esters achieved high initial supersaturation levels and maintained them over 90 minutes or longer.

Eudragit® RL was tested as a carrier for dispersions of the weakly acidic APIs indomethacin and naproxen, either alone or including PVP K25 (Dereymaker et al., 2017). *In vitro* dissolution performance and phase behaviour of the SDD revealed that inclusion of Eudragit® RL led to prolonged supersaturation and was suitable for higher drug loadings. Unexpectedly, nanocrystals of naproxen and indomethacin were formed in the presence of Eudragit® RL and this was regarded as a consequence of a dissolution-sorption-desorption processes driven by the charged polymer.

A biodegradable polymeric matrix was used in the preparation of ASD microspheres of acetaminophen and ibuprofen by spray drying(Enriquez et al., 2014). The polymeric matrix was formulated using bovine serum albumin (BSA) and glutaraldehyde as crosslinker. Microspheres were about 2 μm and exhibited a zeta potential of -30 mV, indicating stability. Dissolution studies showed a constant release for 16 hours. Spray dried gelatin microspheres containing ganciclovir were also prepared by spray drying after cross linking with glutaraldehyde(Tran et al., 2014). Loading efficiency was 68% and *in vitro* release suggested that drug release was related to the extent of swelling, which was related to drug-to-polymer ratio.

Li *et al* discussed the importance of selecting excipients based on the principles of polymer science(Li et al., 2017).

Formulation optimisation

Different aspects of the spray drying and / or formulation processes can be optimised. If a critical quality attribute (CQA) of the formulation requires optimisation, this can be done through design of experiments (DoE) and response surface methodology (RSM)(Patil et al., 2014; Yousefi et al., 2015). Inlet variables such as temperature or feed concentration are related to critical quality attributes such as particle size distribution, dissolution or stability(O'Hara and Hickey, 2000). Other important outlet variables include yield, flow and moisture levels(Billon et al., 2000). Artificial neural networks (ANN) have also been used to predict particle quality parameters and in the study this compared favourably to RSM (Youssefi et al., 2009).

If the purpose is to optimise a performance aspect of the formulation, such as stability, release, etc., then an optimisation approach based formulation (e.g. drug loading, polymer selection, second polymer etc.) is usually encountered. For instance, during a study to enhance the solubility of repaglinide particles by spray drying with a variety of polymers (Eudragit E100, hydroxyl propyl cellulose and PVP K30), formulations were optimised according to drug solubility, release profile, particle size and angle of repose(Varshosaz et al., 2016). *In vivo* studies in diabetic rats demonstrated that the Eugragit E100 SDD in a 1:3 ratio enhanced drug solubility 100-fold. Furthermore, the SDD was PXRD amorphous and reduced blood glucose levels significantly, relative to untreated drug ($p < 0.05$).

Ternary spray dried dispersions

A successful ASD must have significantly enhanced dissolution relative to the crystalline drug, be resistant to rescrystallisation over 3 to 5 years of storage and maintain supersaturation during dissolution *in vivo*. Manufacturing criteria such as flow and compressibility further limit the number of ASD that can be commercially successful.

Meeting all of these requirements with one single excipient becomes increasingly unlikely and this has resulted in an upsurge of research into ternary systems in recent years.

In a design of experiments approach, BCS class II drug itraconazole was combined with processing polymer Soluplus® and stability polymer HPMCP, generating a range of ternary spray dried dispersions(Davis et al., 2017). Stability was excellent (formulations were PXRD and DSC amorphous for 1 year at 40 °C/75% RH) and further characterisation by solid state NMR and small angle X-ray scattering indicated that the powders were amorphous. Dissolution studies indicated a 50-fold increase in itraconazole concentration levels relative to the crystalline drug in the best case. Furthermore, the inclusion of Soluplus® allowed for comparison with a similar DoE study, prepared through hot melt extrusion(Albadarin et al., 2017). In this way a comparison between the spray dried and melt extruded formulations was made (in a statistically significant way) providing insights into stability, dissolution, thermal and spectroscopic differences between the two preparation techniques.

The synergy between polymers hypromellose and methacrylic acid copolymer in spray dried dispersions was recently investigated(Ohyagi et al., 2017). Dissolution rates of the binary SDD were improved relative to the single polymer dispersions. Intermolecular association was analysed with DSC and solid state NMR and it was suggested that hydrogen bonding reformation was likely improving dissolution rates. Furthermore it was shown that a ternary dispersion with griseofulvin showed significantly higher supersaturation than the equivalent binary SDDs.

The dissolution and precipitation behaviour of ezetimibe from ternary SDD in biorelevant media was described(Alhayali et al., 2017). Ternary dispersions were made by spray drying or melt quenching the drug in combination with PVP-K30 and poloxamer 188 and all were amorphous in nature. Crucially, dissolution at 25 °C lead to supersaturation, but at 37 °C rapid precipitation occurred, showing that results at lower temperatures cannot always be used to predict supersaturation at physiologically relevant temperatures.

Ternary solid dispersions of curcumin (40%) were prepared by spray drying in combination with Gelucire®50 and 13-Aerosil®(Teixeira et al., 2016). The solubility in HCl and phosphate buffer improved up to 3600- and 7.3-fold, respectively. Accelerated stability tests showed the SDD to be stable for 9 months and *in vivo* pharmacokinetic studies showed a 5.5-fold increase in drug in rat blood plasma relative to standard drug. The dispersion was deemed a promising way to enhance curcumin bioavailability, particularly considering the ability to scale up.

Atorvastatin calcium trihydrate (ATC) was converted into novel ternary SDD with HPMC E5 and nicotinamide by rotatable central composite design(Paidi et al., 2015). An optimised formulation was selected following physiochemical, dissolution, stability and pharmacokinetic studies. The optimised ASD was amorphous with spherical morphology and exhibited a 4-fold increase in dissolution rate relative to crystalline ATC and significant oral bioavailability enhancement (134.11%). The stability of the amorphous form even under the stress of high temperature and humidity was attributed to hydrogen bonding between drug, HPMC E5 and nicotinamide. It was concluded that this formulation was a useful tool to enhance the bioavailability of ATC.

The effect of spray drying parameters on the phase behaviour and efficacy of ternary SDD of API in poly (lactic-co-glycolic acid) (PLGA) and PVP was recently reported(Meeus et al., 2015a). Differences were observed in miscibility of components, phase heterogeneity, particle size and morphology. The drug release of the formulations studied was not

influenced by these changes, however. It was considered likely that release was dominated by diffusion from the PVP layer through pores in the PLGA layer.

Gelatin and ethylcellulose microparticles were made by spray drying in a study designed to develop and characterise fluoride delivery systems(De Francisco et al., 2013). Fluoride sources sodium fluoride, sodium monofluorophosphate or aminofluoride were combined with polymers ethylcellulose and surfactant polysorbate 80 or natural polymer gelatin and excipient mannitol and converted to powders by spray drying. Microparticles were found to be <145 μm for ethylcellulose dispersions and <124 μm for gelatin dispersions. Release profile of fluoride from the microparticles was found to be a modified, fitted first order Fickian diffusion. It was concluded that microparticles from spray drying could be used as a platform technology for oral delivery of fluoride.

The release behaviour of cilastazol based on its preparation method and the ratio of HPMC/PVP was studied(G. B. Park et al., 2013). Spray dried dispersions were produced with drug, HPMC and PVP at varying levels in ternary dispersions and dissolution studies were conducted at gastric pH.

Novel ternary SDD of rebamipide with poloxamer 407 and PVP-VA-64 were made by spray drying to improve the bioavailability of the drug(C.-W. Park et al., 2013). Pharmacokinetic and pharmacodynamic testing in rats indicated that the drug bioavailability was 2-fold higher than a reference product and that irritation of the stomach was significantly reduced.

An improvement in the intestinal absorption of probucol by preparation of an SDD with Eudragit was reported(Nishino et al., 2012). Drug was combined with polymer in organic solvent and an aqueous solution of mannitol was prepared separately. Both solutions were concurrently fed to separate feed ports on the nozzle and dried simultaneously. Drug in the matrix was amorphous and the bioavailability in rats was found to be significantly enhanced with respect to the untreated drug.

Tenoxicam dispersions with two molar equivalents of L-arginine and 10-50% (w/w) PVP were prepared by spray drying(Patel et al., 2012). SDD provided a 2-fold increase over equilibrium solubility at the same pH. Solid state NMR studies revealed molecular associations and the formation of a glass solution between the drug and two excipients.

Miscibility of components

Miscibility is important because an amorphous solid dispersion that is intimately mixed is more likely to resist recrystallisation during the stresses of processing, storage and dissolution. Not all drug-polymer combinations or preparation techniques result in a single homogenous layer and a deeper understanding of the factors affecting miscibility is required(Marsac et al., 2009; Qian et al., 2010). Favourable mixing will occur when interactions such as hydrogen bonding and dipole-dipole interactions between drug and polymer outweigh interactions between individual components. Miscibility is further affected by drug loading, heat, humidity, particle morphology, particle size distribution and preparation technique.

The effects of drug and polymer miscibility on the dissolution rates of both drug and polymer were recently reported(Higashi et al., 2015). Dispersions of phenytoin and glibenclamide were prepared with Eudragit® S 100 polymer. Dissolution tests of phenytoin dispersions were highly dependent on the drug loading, but glibenclamide results were independent of drug

loading. Drug-rich and polymer-rich domains were evident in both cases, but with phenytoin these areas were more easily converted into the crystalline form on contact with liquid.

Phase separation in amorphous solid dispersions was characterised by applying isothermal calorimetry at 37 ^{o}C / 100% RH to SDD of BMS-903452 and BMS-986034(McNamara et al., 2017). Although both drugs were individually combined with HPMC-AS at various loadings, BMS-903452 formed a physically robust formulation at 30% that was stable for 6 months, but the chemically analogous BMS-986034 could not be formulated at any load attempted. Isothermal calorimetry as a screening tool (over three days) proved to be very useful in predicting separation, particularly when used along-side orthogonal methods such as PXRD, solid state NMR and FTIR.

An extensive solid-state miscibility study was conducted using model drug ABT-102 and 9 different polymers, followed by analysis using DSC, FTIR and PXRD(Jog et al., 2016). Serial dilution, solvent evaporation and spray drying were used as preparation techniques, with spray drying proving most useful. Melting point depression was used to calculate the interaction parameters and free energy of mixing of the drug-polymer systems. Soluplus$^{®}$ was found to be the best stabiliser, possibly due to hydrogen bonding between C=O in Soluplus and N-H in the drug.

Phase separation processes were recently studied in dispersions of AMG 517 with HPMC-AS using DSC and solid state NMR(Calahan et al., 2015). A weakly asymmetric ($\Delta T_g \approx 13.5$) system with a single glass transition for different blends suggested mixing. Proton spin-lattice relaxation times also suggested that the components were in intimate contact over a 10-20 nm scale. Upon calculating the Flory-Huggins free energy of mixing, however, the thermodynamic values were positive, signifying that drug and polymer will inherently separate over time. These results suggested that the homogeneity observed by DSC and NMR were achieved kinetically and that this accounted for the stability of the ASD.

The miscibility of drug-polymer SDD across a spray dryer was studied using model drugs naproxen and miconazole(Worku et al., 2014). In this work a wide variety of drug-polymer compositions were prepared on assorted laboratory scale spray driers and recovered from various locations. SDD with 30% (w/w) naproxen collected from the transport tube of the Pro-C-epT Microspray dryer showed the finest glass transition width, which seemingly indicates the highest level of drug polymer mixing. Samples with 50% (w/w) naproxen collected from the cyclone of the Büchi mini spray dryer showed a melt endotherm with heat of fusion between 0.7 and 1.8 J/g. The study demonstrated that a disparity in drug polymer miscibility can occur in miscellaneous regions of the spray dryer during small-scale preparation and a mindfulness of such is crucial when scaling up.

Silica as a carrier

Silica offers an inorganic alternative to organic excipient polymers due to its high surface area, porous structure, heat stability and chemical interactions *via* silanol (Si-OH) groups on the surface(Shen et al., 2011; Takeuchi et al., 2005; Watanabe et al., 2003).

The solubility of anti-malaria drug artemisinin was improved by encapsulation with ordered mesoporous silica SBA-15 (Letchmanan et al., 2015). Formulations showed significantly enhanced dissolution rates and supersaturation with respect to the untreated drug. Cytotoxicity studies of the SDD using Caco-2 cells demonstrated promising biocompatibility.

SDD were further tested for storage stability over 6 months and exhibited excellent physical, but poor chemical stability due to a sensitivity of the API towards humidity.

Nano-domains of drug were found in spray dried ibuprofen-silica microspheres with the drug domains found to be 40 nm in diameter from NMR and TEM studies(Fatnassi et al., 2012).

Microparticles of hydrochlorothiazide were prepared by spray drying with PVP and colloidal silicon dioxide using a three-level Box-Behnken design(Martins et al., 2012). Process yields, moisture levels, PSD, flow and solubility of the microparticles were analysed using response surface methodology with analysis of variance. Solubility and dissolution rates were significantly improved relative to pure drug.

Ibuprofen was spray dried with a variety of mesoporous silica materials of different pore and particle sizes (Shen et al., 2011). It was found that the silica pore size affected the physical state and the particle size of the drug. If the pore size was less than 10 nm, amorphous drug was obtained, but if the carrier pore size was greater than 20 nm, nanocrystals were formed. Moreover, drug dissolution was most affected by the physical state of the drug, followed by diffusion kinetics, PSD and finally path length.

Fixed dose combinations prepared by spray drying

Two or more drugs contained in a single dosage form have the advantage of reducing the number of pills a patient need take each day and this can improve both adherence and treatment outcomes. There can also be pharmacokinetic advantages(Connolly et al., 2009; Scagliotti et al., 2008) or disadvantages relative to the single drug. Spray drying is becoming more prevalent as a preparation method.

A fixed dose combination (FDC) of ezetimibe and lovastatin was recently converted into a co-amorphous system or a ternary dispersion by spray drying and quench cooling methods(Riekes et al., 2016). Although co-amorphous systems did not increase the dissolution rate of either drug, ternary SDD (containing Soluplus®) increased dissolution by 18-fold for ezetimibe and 6-fold for lovastatin. This result was seen as promising for the development of more advanced fixed dose combinations.

A fixed dose combination of ritonavir and darunavir in the form of dispersible powders was prepared by spray drying(Nguyen and Van Den Mooter, 2014). An excipient polymer (one of HPMC, PVP or PVPVA-64) was combined with either drug and the influence of the polymers on supersaturation levels was investigated. The concentration of both drugs was found to drop quickly then level out to a plateau and this was considered to equate to the amorphous solubility concentration. Also, the inclusion of darunavir diminished the supersaturation level of ritonavir and vice versa regardless of which polymer was engaged. Furthermore, the rate of drug release was less for both drugs from ternary SD than binary SD powders. NMR studies excluded the presence of intermolecular interactions between the two drugs, implying that the supersaturation level must at least be partially attributed to a solvent mediated process.

Solubility enhancement through nanotechnology

Nanotechnology is widely expected to have a substantial impact on drug delivery strategies and in particular nanoparticles will be pertinent (Parveen et al., 2012). Advantages of nanoparticles include an increase in drug solubility, protection from degradation, targeted delivery and a reduction in toxic side effects. As more and more new chemical entities face

issues with solubility, toxicity or dosage levels, a series of publications preparing nanoparticles through spray drying have appeared.

Natural polymeric coating materials were engaged in the preparation of solid lipid nanoparticles (SLN) and of nanostructure lipid carriers (NLC) by nano spray drying (Wang et al., 2016). Uniform, well-separated, spherical powder particles were attained for NLC, although SLN were aggregated and had irregular shape. Formulation optimisation with 20–30% oleic acid and carrageenan or pectin as coating materials achieved the best result. These results were deemed to represent proof of concept for lipid delivery systems *via* nano spray drying.

In situ analytical techniques (such as NMR) were used to study drug supersaturation nano-sized and amorphous states (Ueda et al., 2015). Ternary formulations of carbamazepine with HPMC and sodium dodecyl sulfate were prepared by spray drying and grinding. Drug was completely amorphous following spray drying, but some crystals remained in the ground mixture. Aqueous dispersions of SDD formed transparent solutions but dispersions of ground mixture formed nanoparticles of around 150 nm. Drug permeation studies showed drug concentration in the bulk water phase rapidly reduced from the spray dried dispersion compared to the ground mixture. The ground mixture may have an advantage of maintaining a supersaturated state due to the presence of nanoparticles.

A DoE study was conducted to investigate the *in vitro* dissolution performance of spray dried nano-crystalline powders of naproxen(Kumar et al., 2015). Wet milling parameters, such as drug concentration, drug-excipient ratio, excipient type (HPMC E15 or Tween 80) and milling intensity were of critical importance. Trehalose and lactose were engaged as auxiliary excipients to lessen particle aggregation. The size of the nano crystals was dependent on drug concentration and milling intensity. A better spray drying yield was found with formulations comprising HPMC E15 relative to Tween 80. Trehalose was selected to reduce aggregation and no polymorphic changes were observed following wet milling or spray drying.

Nanocomposite microparticles (NCMP) were prepared by wet milling and then spray drying griseofulvin and hydroxypropyl cellulose (HPC) in the presence of various dispersants(Azad et al., 2014). The purpose of the work was to compare the effect of various dispersants on drug dissolution, with the overall goal of enhancing the bioavailability of poorly soluble drugs through high drug loaded, surfactant-free NCMPs. The best dissolution enhancement was obtained with formulations of drug-HPC with croscarmellose sodium and sodium starch glycolate and this achieved a rapid release comparable to SDS.

Burgess and co-workers used a DoE approach for the optimisation of spray drying with the purpose of forming crystalline nanosuspensions of BCS class II/IV compounds(Kumar et al., 2014). It was established that glass transition temperature and charge effects had a strong effect on powder yield. Flory-Huggins interaction parameter agreed closely with spray dried nanocrystal formulation stability.

The influence of spray drying parameters on nanocrystal porosity and dispersibility is heavily depend on drying method employed(Khoshkava and Kamal, 2014). In this study, a comparison of spray drying, freeze drying and spray-freeze drying concluded that spray-freeze dried samples performed best.

The dispersibility and bioactivity of curcumin was enhanced by encapsulation in casein nanocapsules through spray drying(Pan et al., 2013). After hydration and centrifugation, 137

µg/mL curcumin was dissolved in the supernatant which was 4 decades higher than the crystalline water solubility.

Solid nanocrystalline dispersions of ziprasidone were prepared by exposing an amorphous spray dried dispersion to a controlled temperature and relative humidity(Thombre et al., 2012). The goal of the work was to enhance oral absorption in the fasted state, thereby reducing the food effect. The formulation was administered orally to beagle dogs and pharmacokinetic studies showed complete fasted-state absorption of drug, attaining the intended enhancement in fed/fasted ratio.

Wet nano-milling was used prior to spray drying to produce a dry nanosuspension of phenytoin(Niwa et al., 2011). SEM analysis revealed 1 µm agglomerates composed of thousands of nano drug crystals. These particles could be spontaneously redispersed in water, in contrast to the equivalent formulation prepared from solution rather than nanosuspensions.

The oral bioavailability of 7 formulations of curcumin were compared using *in vivo* studies in rats(Munjal et al., 2011). Results with nanosuspensions, cyclodextrin complex and ASD were 251%, 567% and 446% increase in AUC respectively.

Preparation of self-emulsifying delivery systems *via* spray drying

Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils, surfactants, solvents and co-solvents used for improving the oral absorption of lipophilic drugs(Gursoy and Benita, 2004). They are generally administered as gelatin capsules and form oil-in-water (o/w) emulsions upon aqueous dilution during their passage through the gastrointestinal fluids. Hansen reported a spray dried emulsion containing a poorly water-soluble drug in 2004(Hansen et al., 2004). In recent years there have been an increasing number of publications involving SEDDS prepared by spray drying(Balakrishnan et al., 2009; Goddeeris and Van den Mooter, 2008).

A solid SEDDS was developed for erlotinib using excipients dextran 40 and Aerosil® 200(Truong et al., 2016). Oil, surfactant and co-surfactant were blended and a ternary phase diagram was created to evaluate the self-emulsifying area. Optimised SEDDS formulations were spray dried and characterised as amorphous. Pharmacokinetic parameters such as C_{max} were significantly improved ($p < 0.05$) relative to unprocessed drug, so it was concluded that SEDDS could be a promising delivery route for erlotinib.

The oral bioavailability and physiochemical properties of clopidrogel napadisilate was explored using solid self-microemulsifying drug delivery system (SMEDDS) prepared by spray drying(Kim et al., 2014). Liquid SMEDDS comprising oil (peceol), a surfactant (Cremophor RH60) and a co-surfactant (Transcutol HP) was optimised using a ternary phase diagram, then spray dried onto silicon dioxide yielding solid SMEDDS. The physiochemical, solubility and pharmacokinetics of the formulations were assessed and compared to clopidogrel napadisilate and clopidrogel bisulfate powders. Although the drug was in the crystalline form in the SMEDDS, solubility was better than in untreated clopidrogel napadisilate. Accelerated stability was enhanced relative to powdered form. Nevertheless, it was also found that a solid dispersion of drug with surfactant and polymer significantly improved bioavailability relative to both SMEDDS and untreated drug powder.

A novel re-dispersible dry emulsion of valsartan in HPMC was reported to be very effective, with enhanced, pH-independent drug release and significantly improved bioavailability(Baek et al., 2014). The system comprised of drug valsartan, polymer HPMC, oil Caprilol 90 and
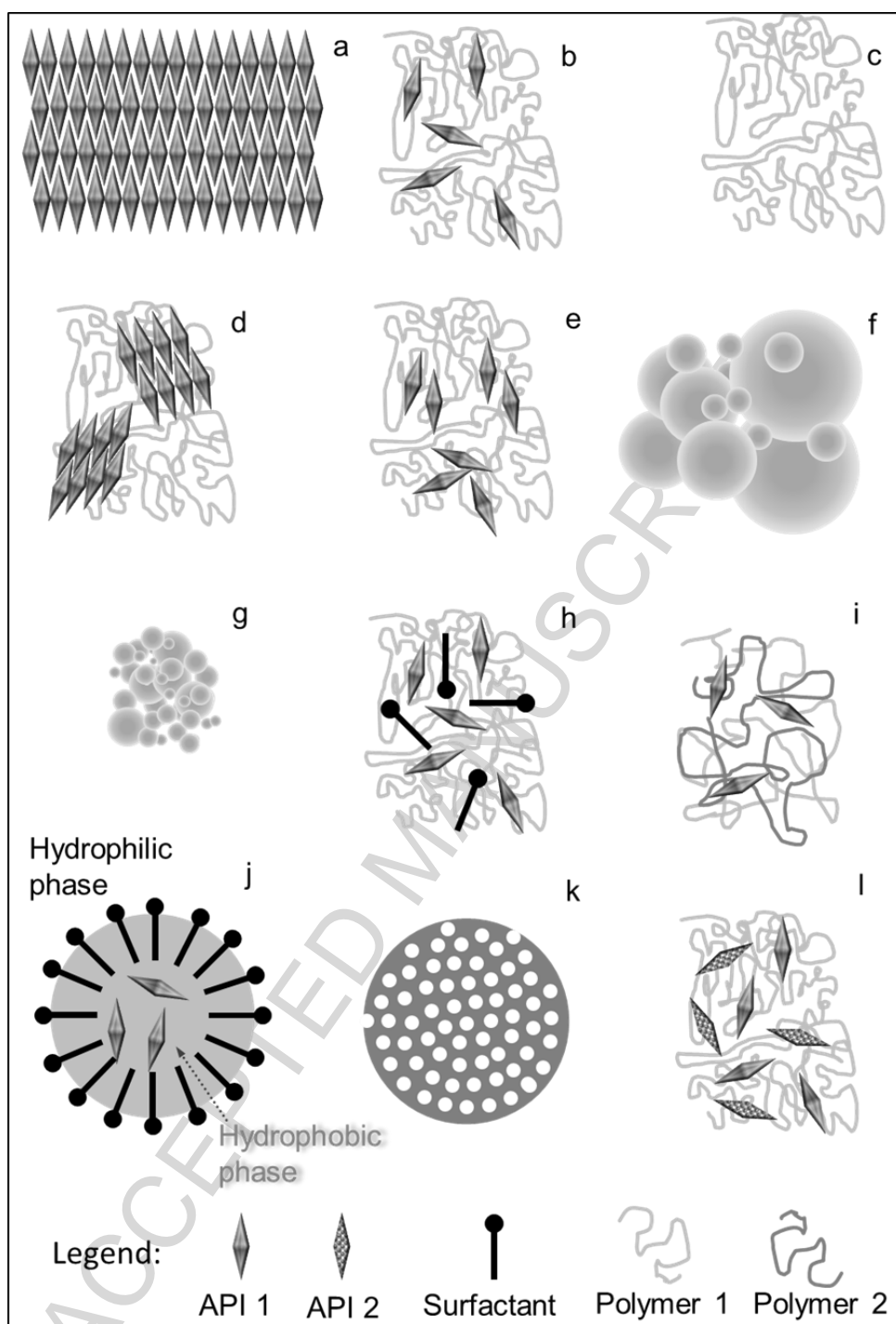
Figure 3: A schematic representation of oral delivery carrier systems prepared via spray drying and their constituent parts; including (a) crystalline drug, (b) amorphous solid dispersion (one phase, solid solution), (c) polymer, (d) crystalline solid dispersion (two phase system), (e) amorphous solid dispersion (two phase system),(f) microparticles (spherical), (g) nanoparticles (spherical), (h) ternary amorphous solid dispersion containing surfactant, (i) ternary amorphous solid dispersion with two polymers, (j) self-emulsifying drug delivery system (SEDDS), (k) silica nanoparticles, (l) fixed-dose combination amorphous solid dispersion.

surfactant poloxamer 407. Mean droplet emulsion size ranged from 133 to 152 nm during dispersion in water.

Stable dry emulsions of itraconazole were designed by full factorial spray drying DoE(Rao and Aghav, 2014) and a 71% increase in C_{max} and 115% improvement in AUC were measured relative to untreated drug.

An overview of popular delivery vehicles prepared by spray drying is given in Figure 3.

Drug release from emulsions for effective dermal and transdermal delivery

Dermal drug delivery involves topical application to the skin to treat local diseases, whereas transdermal drug delivery represents transport through the intact skin into systemic circulation for the treatment of various chronic disorders(Shakeel et al., 2012). In some cases, this route may offer several advantages, such as enhanced bioavailability, reduction in side effects and averting the first pass effect in the liver.

To achieve dermal delivery of drugs by passive transport, formulation optimisation is required. Firstly, the oil/water partition coefficient must be very low, secondly the molar mass of the drug must be >500 $gmol^{-1}$, thirdly the percutaneous absorption should be very low, fourthly the permeation rate through the skin should be low and finally the systemic bioavailability should be low. For transdermal delivery the opposite applies, although active transport may be necessary for adequate delivery. Active transport methods such as iontophoresis, electroporation (electrical energy), abrasion, ablation, perforation (mechanical energy) or ultrasound have improved delivery across the stratum corneum(Brown et al., 2006).

The impact of surfactants on the physical stability of SDD

The higher energy of amorphous forms leads to solubility levels orders of magnitude higher than the crystalline forms, but can also lead to spontaneous recrystallisation. Exposure to heat, moisture and solvent tends to increase recrystallisation rates. The dissolution medium is often a complex multicomponent environment and an understanding of the impact of each component on stability has been limited. Much focus has been directed on the influence of polymers on physical stability, but more recently the effect of surfactants on the performance of spray dried dispersions has been receiving more and more attention.

The impact of surfactants on the crystallisation behaviour of spray dried particles was recently reported by Taylor and co-workers(Chen et al., 2015). Solid dispersions of celecoxib with HPMC-AS were added to acidic media containing various surfactants. Nucleation induction times in the presence and absence of surfactant were measured. Sodium dodecyl sulfate and Polysorbate 80 were found to promote crystallisation while sodium taurocholate and Triton X100 were found to inhibit crystallisation. Crystallisation was found to be related to the effect of the surfactant on nucleation and the tendency of the surfactant to leach the drug from the SDD into the surrounding media. Mindful surfactant selection is therefore critical in order to avoid ASD failure through drug recrystallisation.

Griseofulvin was combined with PVP or PHPMA *via* spray drying or bead milling and the effect of ionic surfactant (sodium dodecyl sulfate) and non-ionic surfactant (Tween-80) on the physiochemical properties was studied(Al-Obaidi et al., 2016). The formulations were found to recrystallise quickly and DVS measurements indicated an increased water uptake.

Slower dissolution rates were observed for ASD containing surfactant. Dispersions prepared by milling showed better stability than SDD.

The effect of plasticisers on the properties of microparticles made by spray drying was reported using theophylline as a model compound(Wan et al., 1992). Formation of pores due to the leaching of plasticisers from SDD particles into dissolution media enhanced drug release. Flow property analysis demonstrated that the plasticisers also affect the cohesiveness of the microparticles.

The role of polymer-surfactant interactions in spray dried dispersions of Ertravirine with HPMC and bile salt or SDS has been studied(Qi et al., 2013). Dissolution experiments and a range of spectroscopic techniques revealed that the maximum increase in apparent solubility of the drug was when both HPMC and surfactant were present.

Selecting an appropriate solvent and monitoring residual solvent levels

Selection of a suitable solvent system is one of the key requirements when formulating an amorphous dispersion by spray drying. Usually the solvent must be capable of dissolving all of the components of the dispersion(Paudel et al., 2013). The viscosity of the feed solution must be appropriate and solvents of low toxicity and high volatility are preferred. ICH guidelines for residual solvents recommend the use of less toxic solvents and set limits for residual organic solvent levels in drug substances(ICHQ(R6)). Several groups have researched methods for detecting trace levels of solvent in spray dried particles or explored replacement solvents with better toxicity profiles.

A strategy to mitigate the risk of ICH Class 1 impurity benzene reaching drug product in spray dried dispersions was reported(Yue et al., 2015). The risk assessment considered the likelihood of residual benzene from primary spray solvents being concentrated in the product. A spiked fate and tolerance study simulating worst case scenario conditions was performed, demonstrating that the mass ratio of spray solution to solid was a critical risk parameter. Slow spray drying kinetics reduced benzene levels by about 700-fold. A secondary drying step was also recommended. Two critical control points were identified: (i) maximum residual benzene levels of 10 ppm and (ii) in-process control of residual solvents in SDD.

Gas chromatography was used to monitor residual acetone levels in spray dried intermediates (Quirk et al., 2014). Due to high levels of polymer, direct liquid injection with gas chromatography (GC) was not a feasible option, so headspace autosampling (GCHS) was utilised instead. Method development involved a number of analytical challenges including application of a conversion factor to correct for reactions occurring between acetone and related impurities (mesityl oxide and diacetone alcohol). After additional optimisation the approach was deemed robust and capable of determining acetone and the impurities over the concentration range 0.008-0.40 μL/mL, with limit of detection of 20 ppm.

SDD of poorly water-soluble drug raloxifene were prepared without using an organic solvent(Tran et al., 2013). Drug, PVP and surfactant Tween 20 were added to water and spray dried yielding particles with a mean size of 180 nm. Formulations showed an enhanced dissolution rate relative to untreated drug at pH 1.2, 4.0, 6.8 and in distilled water. During *in vivo* bioavailability tests in rats, the pharmacokinetic parameters of SDD showed increased AUC and C_{max} of 3.3-fold and 2.3-fold respectively.

The influence of solvent on the miscibility and physical stability of SDD of naproxen with PVP was studied(Paudel and Van Den Mooter, 2012). Dispersions were prepared by spray

drying solutions of drug and polymer using binary blends of methanol, dichloromethane and acetone at varying levels. It was found that SDD prepared from solvent/anti-solvent mixtures showed better miscibility and better physical stability than those from blends of 'good' solvents. Furthermore FTIR spectra indicated differences in drug-polymer interactions in solid dispersions from different solvent blends.
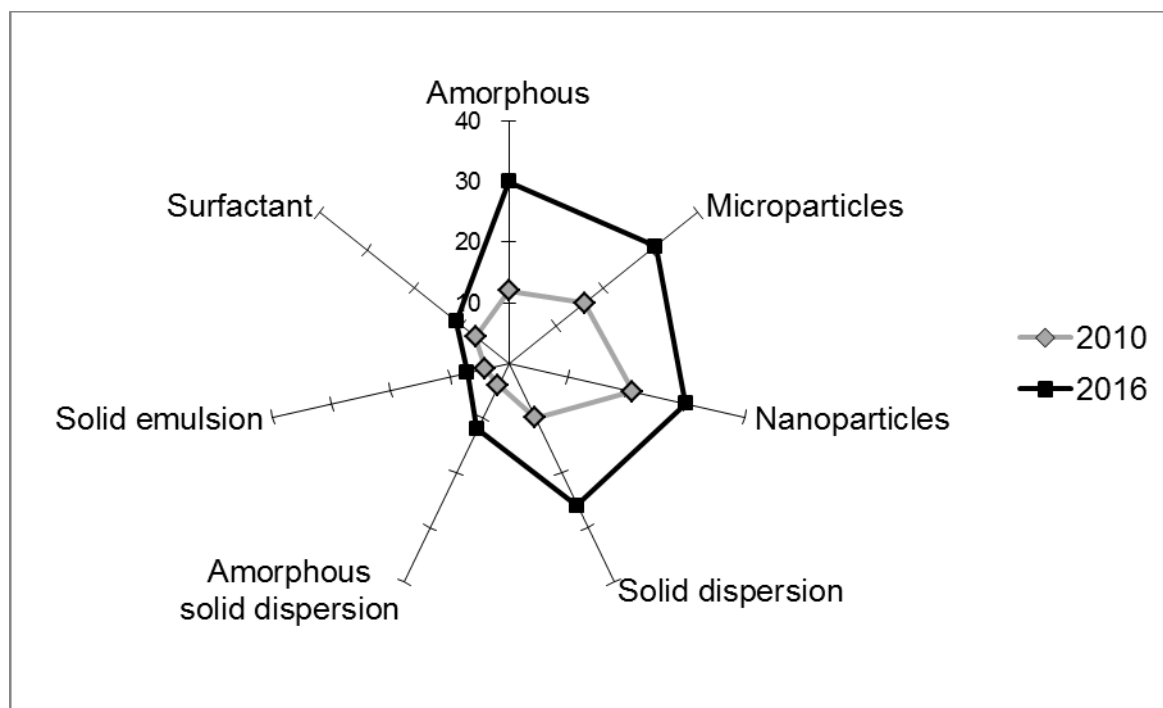

Figure 4. Trend in spray drying publications with specific delivery strategies for years 2010 and 2016, source Scopus®

Recent trends since 2010 have shown an increase in publications in amorphous systems, microparticles, nanoparticles and solid dispersions (Figure 4).

PROCESS OPTIMISATION

A number of mathematical, statistical and *in silico* techniques are utilised in process optimisation, such as design of experiments (DoE), response surface methodology (RSM), analysis of variance (ANOVA) and artificial neural networks (ANN). The trend has been to move away from a trial-and-error (Edisonian) approach(Amis et al., 2002).

A Plackett-Burman design was recently applied to the design of operating and formulation parameters when preparing diclofenac-polymer microspheres by spray drying(Deshmukh and Naik, 2016). Eudragit® RS100 quantity, ethylcellulose quantity and aspirator rate were found to be significant factors. Encapsulation efficiency ranged from 47.55 to 67.99% and the microspheres were discrete, spherical and smooth. *In vitro* drug release was sustained over 12 hours and followed a Korsmeyer–Peppas model with slope (n) ≤ 0.43 indicating a Fickian diffusion.

A DoE approach was taken to optimise the spray drying process on a Büchi B-90 using a central composite design(Gu et al., 2015). Polymer concentration, inlet temperature and air flow rate were taken as input variables with yield, spray rate and drying efficiency as outputs. The model was further tested using a poorly soluble drug, generating a range of formulations

of 2-10 μm that were found to be physically stable (for 3 h) in aqueous methyl cellulose solution (1%).

The solubility of nifedipine was enhanced by spray drying with poly(meth)acrylates following a pre-screening solvent casting method (Patel et al., 2015a). The effect of spray drying process parameters was examined in a 2^3, full factorial, DoE approach. Dissolution studies revealed a significant enhancement of 90% drug release in 20 min relative to 12% from crystalline drug. SEM images indicated uniform, spherical particles and DSC and PXRD showed samples to be amorphous after 3 months storage. Feed rate had a significant effect on *in vitro* dissolution, whereas solid content had the highest effect on process yield.

An optimisation of the process variables of spray drying using different statistical techniques was made by Patel(Patel et al., 2014). Response surface model and ensemble artificial neural network methods were employed. Pearson correlation analysis, self-organising maps, contour plots and response surface plots were used to illustrate the effect of input variables on quality attributes.

The Büchi B-90 spray drying process was optimised using a central composite design focusing on the effects of polymer concentration, inlet temperature and air flow rate on yield, spray rate and drying efficiency(Gu et al., 2015).

A study was conducted to ascertain the critical processing parameters of a laboratory-scale spray drier affecting solubility behaviour and physical stability of solid dispersions(Kojima et al., 2013). Nitrogen flow rate, sample concentration and pump speed were varied and the powders were characterised by spectroscopic techniques, dissolution tests and physical stability testing. It was found that low nitrogen flow rate and high sample concentration gave the most favourable solubility behaviour and physical stability results.

A model for predicting the quality attributes of binary solid dispersions of drug-polymer from spray drying using response surface model and ensemble artificial neural network was reported(Patel et al., 2013).

The effects of changing spray drying temperature and atomising airflow rate were studied by Paudel *et al*(A Paudel et al., 2013). Taking a naproxen-PVP system, they monitored the phase structure, physical stability and performance of the resultant ASD. Higher inlet temperatures produced phase-separated dispersions whilst lower inlet temperatures produced more homogenous dispersions. Higher inlet temperature ASD retained more amorphous drug content during a three week stability trial at 75% RH. The rate and extent of drug dissolution from the highest atomised ASD was higher.

Nozzle modifications

Traditionally, the two-fluid nozzle has been the most popular choice for preparing amorphous spray dried dispersions of pharmaceuticals, but this is changing. Alternative nozzle types, such as the pressure nozzle(Beyerinck et al., 2010) or vibrational nozzle can produce larger particles with better flow properties.

Sildenafil has been incorporated into poly(lactide-co-glycolide) microparticles by vibrational spray drying(Beck-Broichsitter et al., 2016). Microparticles were optimised to a size range of 4-8 μm with a sildenafil encapsulation rate of >90%. A scaled-up preparation process did not cause significant changes to physiochemical properties or *in vitro* drug release.

A 4-fluid nozzle was used to prepare matrix particles of acetaminophen with chitosan (ratio 1:5) to achieve sustained release(Chen et al., 2006).

COMPARISONS WITH OTHER PREPARATION TECHNIQUES

Comparisons between manufacturing techniques can reveal information on the impact of processing on the critical quality attributes of an ASD. Comparisons with hot melt extrusion, freeze drying, milling, electro spinning, electrospraying, precipitation, film casting, rotary evaporation and other techniques are frequently reported. Formulation and process optimisation using DoE and analysis of variance or RSM interpretation of results is an increasing trend in such publications.

An improvement on the dissolution of albendazole by amorphous solid dispersions was studied comparing spray drying and hot melt extrusion (Hengsawas Surasarang et al., 2017). Flory-Huggins theory was used to construct phase diagrams of the binary dispersions of drug with polymer to assess miscibility and processability. Despite the precaution of forced chemical and thermal degradation studies, it was found that albendazole was not stable during hot melt extrusion, with degradation up to 97.4%. It was possible to make amorphous drug by spray drying, however. SDD containing drug with acids and polymers were prepared and found to have up to 8-fold improved non-sink dissolution in acidic media and good shelf life stability (intact up to 6 months or 5% degradation after 1 year). It was concluded that amorphous albendazole solid dispersions in combination with acid and polymer could be prepared by spray drying, but were degraded by hot melt extrusion.

In a recent publication, the authors hypothesised that hot melt extrusion was a better manufacturing technique than spray drying when the API in question had a high crystallisation tendency(Haser et al., 2017). To examine this, systems of naproxen with povidone K25 at 30% and 60% drug loadings were prepared and analysed using PXRD, DSC, FTIR and solid state NMR. At 30% drug loading, hydrogen bonding sites of povidone were unsaturated and the glass transition area was higher, so both spray dried and melt extruded materials were amorphous and remained so at 40 °C. At 60% drug load, H-bond sites were saturated and the glass transition area was lower. It was not possible to prepare fully amorphous materials and the quantity of crystalline material increased to 2.7% ± 0.3% and 21.6% ± 1.0% for hot melt extruded and spray dried materials respectively. It was rationalised that the spray dried formulation was more susceptible to recrystallisation due to higher drug diffusivity in the dispersion, a lack of kinetic stabilisation from the polymer solution, a greater number of nucleation sites and a higher surface area relative to the melt extruded dispersion. It was concluded that there were unique advantages to formulating high drug levels of naproxen by hot melt extrusion, although no mention was made of dissolution studies.

Indomethacin was spray dried in combination with PVP and the resultant ASD was compared to similar formulations made by co-milling and supercritical anti-solvent processes(Lim et al., 2017). Samples were characterised by SEM, TGA, PXRD, physical stability testing, FTIR and Raman spectroscopy. It was found that PXRD amorphous formulations could be prepared with up to 80% drug load by spray drying and up to 60% drug load by the other techniques. Furthermore the samples made by SD and supercritical antisolvent techniques were stable for 6 months at 40 °C/75% RH.

A spray drying method has recently been reported as an improvement on freeze drying for the production of ASD of docetaxel or paclitaxel for phase 1 clinical trials(Sawicki et al., 2016). Both saturation solubility (S_{max}) and precipitation onset time (T_{precip}) were equal or better to the freeze-dried results for both drugs. Furthermore, the process was more suited to scaling up and SDD were fully amorphous with a mean batch yield of 84%. Flow properties were poor and this was not improved by changing settings, but by employing lactose at 75% as diluent. Drug product tablets were stable for 24 months and spray drying was deemed suitable for producing ASD for phase 1 clinical trials.

In order to improve the oral absorption of flubendazole, three drug delivery technologies were evaluated: spray drying, modified spray drying (using a flash nozzle) and formulation with ordered mesoporous silica(Vialpando et al., 2016). The formulations were tested for physiochemical stability and *in vitro* release and only the modified spray dried and ordered mesoporous formulations did not crystallise following 2 weeks at 40 °C/75% RH. *In vivo* testing revealed that the highest area under the curve and C_{max} values were achieved by the ordered mesoporous formulation.

Celecoxib was combined with Phospholipoid E80 and trehalose to create solid phospholipid nanoparticles *via* spray drying or freeze drying(Fong et al., 2015). An optimal ratio of 1:10:16 produced amorphous spherical particles by spray drying and amorphous matrix-like structures by freeze drying. Although both formulations increased the dissolution rates and apparent solubility of drug in phosphate buffer, the spray dried dispersions achieved the larger enhancement in apparent solubility (29- to 132-fold) and molecular solubility (18-fold) at equilibrium.

Slow release caffeine was combined with polymers PLGA and PLA using spray drying or electrospinning technology(Sóti et al., 2015). Both dispersion types were characterised by SEM, PXRD, DSC, at-line Raman mapping and *in vitro* dissolution. The ultrafine fibres from electrospinning were easier to handle than the microspheres from spray drying and also had slightly better dissolution performance.

High speed electrospinning (HSES) was compared with single needle electrospinning, spray drying and film casting as preparation methods for ASD that are compatible with the pharmaceutical industry(Nagy et al., 2015). Itraconazole with PVPVA64 was the model drug-polymer system and this was shown to be amorphous by PXRD and DSC in all cases except for film casting. The dissolution rate of itraconazole was vastly improved compared to crystalline: >90% within 10 min for the electrospun fibres, although the improvement for spray dried microspheres was lower.

Solid dispersions of BCS class IV drug tolvaptan were prepared by hot melt extrusion and spray drying with a variety of polymers such as Soluplus®, copovidone, PVP and hypromellose in order to improve aqueous solubility(Ramesh et al., 2015). Higher drug release levels were found in dispersions from HME relative to SDD. There was a 7-fold increase in solubility in dispersions from both methods compared to the crystalline drug. Physical characterisation of both formulations by FTIR, DSC, PXRD and SEM revealed a change in crystal structure towards an amorphous form.

ASD of celecoxib with Soluplus® have been prepared by spray drying, solvent evaporation and melt methods at a range of drug loadings(Homayouni et al., 2015). Particles were characterised by particle sizing, optical microscopy, SEM, PXRD, DSC and FTIR. Experimental values of T_g were compared to those predicted by the Gordon-Taylor equation.

Solubility and dissolution rates were studied. Stability testing at ambient conditions for 12 months revealed the formulations to be PXRD and DSC amorphous. The 1:2 spray dried ASD had the optimal dissolution rate although very high drug loadings (2:1 and 1:1) surprisingly had slower dissolution than crystalline drug. Stability studies showed no decrease in dissolution rate after 12 months ambient storage. Overall it was concluded that Soluplus® was a suitable carrier to enhance dissolution of celecoxib.

A comparison was made between hot melt extrusion and felodipine as preparation techniques for creating ASD of felodipine(Mahmah et al., 2014). The purpose of the work was to compare the properties of the solid dispersions from the two techniques. Two different polymers PVP and HPMC-AS were chosen and used at several different ratios. Characterisation of ASD was performed using DSC, PXRD, SEM and *in vitro* dissolution. Stability of ASD was studied over accelerated conditions of 40 °C/75% RH over 8 weeks. Key findings were that spray dried formulae released felodipine faster than melt extruded felodipine for both polymer matrices. SD with HPMC-AS had higher drug release rates and better wettability than PVP SD. No significant difference was noted in stability except for HPMC-AS at 1:1 ratio, where crystallisation was detected in the spray dried formulation.

The use of Flory-Huggins phase diagrams as a pre-formulation tool for the preparation of ASD by HME and spray drying was investigated by Tian(Tian et al., 2014). The method was used to forecast drug solubility and miscibility in polymer candidates and the data was used to predict outcomes based on manufacturing method. Solid dispersions were prepared by both techniques and characterised using a combination of thermogravimetric analysis, DSC, FTIR and PXRD. Key findings were that spray drying allowed generation of ASD over a wider range of drug loads than HME. Melt extrusion provided enough energy for more efficient mixing between drug and polymer, which may improve stability. It was also established that stronger drug-polymer interactions could be generated through melt extrusion. Remixing and dissolution of recrystallized felodipine into polymer occurred during DSC, but the complimentary information from FTIR confirmed that freshly prepared spray dried samples were amorphous with the existence of amorphous drug domains in highly loaded samples.

A comparison of the properties of binary ASD of felodipine with polymers PVP and HPMC-AS prepared by hot melt extrusion and spray drying was published by Paradkar and co-workers(Mahmah et al., 2014). The key findings were that spray dried formulations released felodipine faster than melt extruded formulations for both polymer matrices. ASD comprising HPMC-AS released higher drug rates and better wettability than those comprising PVP. No significant differences in stability were noted except with HPMC-AS at high drug loading where crystallisation was detected in spray dried dispersions.

The influence of preparation method on the surface/bulk structural relaxation and glass fragility of ASD of indomethacin with PVP was reported(Ke et al., 2012). Melt quenching, ball milling and spray drying were employed as preparation techniques and values in bulk and at surface were reported. All samples had higher molecular mobility at the surface than in the bulk. The glass fragility was affected by the preparation method with the most fragile systems showing the best stability.

A comparison between spray drying and freeze drying for producing ASD of hydrocortisone with PVP was reported(Dontireddy and Crean, 2011). Freeze dried dispersions had faster dissolution rates than SDD and this was still the case after samples had been put on stability at 40 °C and 75% RH.

A comparison of spray drying and milling as preparation methods for producing ASD of sulfathiazole or sulfadimidine with PVP was reported(Caron et al., 2011). DSC studies revealed a single glass transition temperature for sulfathiazole with weight loadings of 0% - 95% for spray drying and 0% - 40% for milling. Similarly, sulfadimidine weight loadings of 0 - 100% for spray drying and 0 - 30% for milling produced homogenous glassy solutions. The value of T_g did not depend on the production technique. A good overlap was found between experimental observations and both Gordon-Taylor equation and Flory-Huggins theory. Dissolution was found to increase for co-processed materials relative to physical mixtures and results from milling were comparable to spray dried materials.

NOVEL ANALYTICAL TECHNIQUES

Powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC) and polarised light microscopy (PLM) have become the gold standard techniques for characterising amorphous solid dispersions. However there is a limit to the type of information that can be interpreted from these methods and work has been ongoing to develop complimentary means for analysing such materials.

The phase separation of an itraconazole-HPMC amorphous dispersion was recently examined using fluorescence at nano and micron levels(Purohit et al., 2017). It was found that the rate of solvent evaporation played a key role in the size of the phase separated domains, with smaller domains (<10 nm) observed in spray dried dispersions and larger domains (>30 nm) in ASD from slower evaporation techniques. Confocal imaging provided visual confirmation of the phases while solid state NMR confirmed fluorescence results and was used to quantify the size of the domains.

X-ray microtomography has been assessed as a tool to measure powder characteristics such as wall thickness and solid volume fraction for hollow, polymer-stabilised spray dried dispersions(Gamble et al., 2016). SDD of various shell wall thickness and degree of particle collapse were studied and the morphology was discussed in terms of performance characteristics and processing of the bulk powder. Quantitative measurement of wall thickness, void volume and solid volume was performed and the impact of drying rate on morphology was examined. A deeper knowledge of particle characteristics may lead to a better understanding of their impact in downstream processing and final dosage performance.

Crystallisation behaviour of a ternary SDD of probucol with HPMC and sodium dodecyl sulfate was recently studied using atomic force microscopy (AFM)(Egami et al., 2015). The ASD was prepared by spray drying and examination by PXRD and solid state NMR showed that the dispersion were amorphous. The SDD was then added to water, whereupon nanocrystals of 25 nm were observed and this gradually increased to 94 nm upon storage for 7 days. AFM was employed to directly observe morphology and agglomeration behaviour of the nanoparticles in water. Depending on the storage period involved the AFM force-distance curves varied from complete indentation at 1 nN through to almost no indentation at 5 nN. Stiffness increase in the particles was rationalised by changes from the amorphous to crystalline states and these findings were supported by solid-state NMR measurements.

Transmission electron microscopy (TEM) was utilised as a technique to evaluate the crystallinity of SDD comprising griseofulvin and HPMC-AS(Ricarte et al., 2015). The advantages of the technique included real-space images, electron diffraction patterns (for unambiguous assignment) and ability to detect drug crystals at levels of around 3 % (v/v).

Both TEM and wide-angle X-ray scattering (WAXS) detected no crystals present in the SDDs, with drug loadings of 5, 10 and 50 % (w/w). However a 5 % annealed sample was detected by TEM but not WAXS or DSC, thereby demonstrating the superior sensitivity of TEM for detecting crystals.

Modulated DSC has been combined with surface analysis techniques to study the phase behaviour and drug distribution of ternary SDD(Meeus et al., 2015b). For ternary systems, DSC alone is insufficient for rigorous analysis of phase behaviour or determination of drug distribution within a two-phased matrix. Combination of DSC with time-of-flight mass spectrometry and atomic force microscopy provided insights into drug distribution in three spray dried formulations with varying API/PLGA/PVP ratios.

Fluorine-Carbon heteronuclear NMR has been reported as a simple and robust method for measuring fluorine-carbon proximities in solid state nuclear magnetic resonance (ssNMR) experiments using magic angle spinning (MAS). The method was applied to crystalline drug avagacestat, containing two types of fluorine atoms and also to the API-polymer dispersion(Abraham and Crull, 2014). Results provided insights into molecular structure, aided in assignment of carbon resonances and explored the API-polymer proximities in the formulation. The method has an advantage over proton-carbon HETCOR due to the large chemical shift dispersion in the fluorine dimension. Fluorine-carbon distances of up to 8 Å were probed, providing data on API structure, crystal packing and assignment. The main benefit of the method was the information on the close molecular level contact between amorphous API and the polymer in the SDD, giving insights into the molecular association and the role of the polymer in stability.

Novel approaches to the use of imaging based tools for characterisation of hollow spray dried amorphous particles have been reported by Gamble *et al*(Gamble et al., 2014). Cryo-SEM is a form of electron microscopy where hydrated samples can be prepared using fewer preparation steps to standard SEM and is regularly used for biological samples. It was used to measure the solid volume fraction and particle density of the powders. Static image analysis using the Morphologi G3 characterisation system was conducted to explain both the extent of attrition within a series of SDD samples and to measure relative particle wall thickness. The rich information from imaging based systems can be used concurrently with other powder measurements such as bulk density to better understand their impact on downstream processing and final dosage form acceptability.

NOVEL DISSOLUTION TECHNIQUES

Permeability and solubility remain the key elements deciding the oral bioavailability of a drug(Leuner and Dressman, 2000). The mutual advantage of a solid dispersion approach lies in a local increase in the solubility and maximising the surface area of the compound that comes into contact with the dissolution medium. Because the drug has no crystal structure in an amorphous dispersion, no energy is required to break the lattice prior to dissolution. Once the solid solution has dissolved, the drug exists as a supersaturated solution. Furthermore, the carrier may act to reduce recrystallisation from the supersaturated solution.

Spray dried rifaximin (BCS class IV) dispersions were prepared in combination with hydrophilic polymers and their supersaturation performance was assessed(Beig et al., 2017). During parallel artificial membrane permeability assay (PAMPA) and single-pass rat intestinal perfusion (SPIP) models, it was found that the results were highly dependent on the

polymer selected. Copovidone/HPC-SL formulations performed best, with supersaturation of 200 times that of crystalline drug over 20 h. *In vivo* studies measuring absorption rate coefficient (ka) also demonstrated an increase in permeability, so an increase in both solubility and permeability was achieved.

BCS class II drug glipizide was spray dried with excipients HPMC-AS and copovidone S-630(Lu et al., 2016). These occurred as a single amorphous phase up to 60% drug loading according to analysis by PXRD, DSC and SEM. Prolonged supersaturation (up to 180 min) and solubility increases (5.2–13.9 fold) were reported relative to crystalline drug. Formulations containing HPMC-AS-M and HPMC-AS-H achieved the highest stable supersaturation levels. Controlled release tablets comprising SDD also provided sustained release over 24 h and combination of HPMC-AS and HPMC in the hydrating matrix showed strong suppression of drug recrystallisation.

Binary spray dried dispersions of nifedipine in carriers HPMC-AS, copovidone and PVP were prepared to study their supersaturation efficiency and solubility-permeability interplay(Dahan et al., 2013). Parallel artificial membrane permeability assays and single pass rat intestinal perfusion models were selected. It was found that maintaining drug supersaturation was highly polymer dependent, with HPMC-AS being 20-fold, copovidone 10-fold and PVP 5-fold higher than crystalline nifedipine. Drug flux from supersaturated solutions across the intestine was increased and this was independent of the polymer used. The twin advantages of increased apparent solubility and increased drug flux was deemed more advantageous than competing solubility approaches (e.g. combination with surfactants, cyclodextrins or cosolvents).

Dahan and co-workers have described a trade-off between the increase in solubility and a decrease in permeability when formulating with solubilising excipients to increase the solubility of lipophilic drugs(Miller et al., 2012). In order to evade this problem, a spray-dried ASD of progesterone and HPMC-AS was prepared and tested. Supersaturation was found to be 4-fold higher than untreated drug. Furthermore, apparent permeability did not decrease and overall flux was markedly increased when measured in PAMPA or rat models. The work demonstrated that amorphous dispersions may have a significant advantage over other solubility enhancing approaches.

Special dissolution techniques

Microcentrifuge dissolution has been studied as a technique to rapidly assess the performance of SDD(Wu et al., 2016). The aim was to provide a better understanding of the supernatant after centrifugation. Dispersions comprised of indomethacin and ketoconazole with polymers PVP and HPMC-AS. Centrifugation was completed at various speeds and supernatant was passed through a series of filters to examine particulate properties. It was found that the indomethacin dispersions were more suited to this method than ketoconazole dispersions and therefore the use of microcentrifuge dissolution should be selected on a case-by-case basis.

An *in vitro* dissolution method that could discriminate for crystalline drug content using tablets comprising spray dried evacetrapib was reported by Aburub and co-workers (Pack et al., 2017). Dissolution media, paddle speed and surfactant parameters were varied during optimisation. Selectivity was tested by spiking tablets with 10, 20 and 30% crystalline drug substance, leading to a 13%, 22% and 32% drop in dissolution end point, relative to unspiked SDD tablets. Also, tablets were tested in a relative bioavailability study where the dissolution

end point of SDD tablets was found to be 4-fold higher than that of tablets with crystalline drug.

Improvements on commercial dosage forms

There have been several recent publications with direct comparisons to commercial products where prototype SDD dosage forms have displayed significantly better dissolution. It should be mentioned that relatively few commercial examples of amorphous solid dispersions exist. As more and more publications elucidate a deeper knowledge of spray dried dispersions and with more than 70% of NCE are classed as poorly soluble, there are likely to be more commercial dosage forms in the future.

Immediate release spray dried formulations of valsartan and Eudragit® E PO were developed to enhance delivery in the gastric environment(Pradhan et al., 2016). Significant improvements in dissolution rate at pH 1.2 and pH 4.0, compared to both the free drug and the commercial product were observed. The amorphous state of the drug was confirmed using SEM, DSC and PXRD analysis.

A spray dried dispersion of ziprasidone and poloxamer 188 was recently incorporated into osmotic pump tablets to develop a controlled release strategy with no food effects(Yanfei et al., 2015). Various weight ratios were prepared and converted to tablets using wet granulation. PXRD and DSC studies showed the SDD to be amorphous and solubility was significantly enhanced relative to both non-processed drug and physical mix. Drug release profiles in various media showed typical osmotically controlled release and fitted zero-order kinetics. Pharmacokinetics during *in vivo* trials with fasted and fed beagle dogs showed prolonged action and no food effect compared to commercial Zeldox®. It was concluded that the osmotic pump tablet approach might be suitable to enhance ziprasidone bioavailability in the fasted state and also showed sustained release with prolonged actions.

Commercial new chemical entity (NCE) BMS-B was converted to an amorphous SDD by spray drying at 10-25 % (w/w) drug with HPMC-AS(Chen et al., 2014). The SDD were used to improve aqueous solubility and study oral toxicology in rats and monkeys. The SDD approach was considered possible although challenging due to limitations on wetting and dissolution.

Cui and co-workers have reported the use of spray drying to prepare ASD to improve the bioavailability of a B-Raf inhibitor compound G-F(Cui et al., 2013). G-F has poor aqueous solubility and is interesting for the treatment of late stage melanoma. Solubility studies of the novel ASD indicated an advantage over the crystalline drug form. Both *in vitro* dissolution and *in vivo* absorption were found to be in good agreement with theoretical solubility predictions.

The solution behaviour of SDD of BMS-A in PVP-VA and HPMC-AS was studied(Qian et al., 2012). Both dispersions performed similarly *in vitro* but the HPMC-AS dispersion was significantly better *in vivo*. This was an excellent example of how polymer selection can have a significant *in vivo* impact that is unrelated to ASD physical stability.

DOWNSTREAM PROCESSING

During manufacturing, smooth downstream processing is critically important (Demuth et al., 2015). Flow into a die or from a hopper can face issues such as bridging, arching or rat-

holing, leading to production interruptions and incorrect tablet weight. A trade off may be required between bioavailability demands of a drug (where smaller PSD is advantageous) and flow demands (where larger, spherical particles are more desirable). Granulation with water seems like an unnecessary risk, as recrystallisation rates are greatly increased in the presence of moisture(Oksanen and Zografi, 1990). Compressibility of some ASD can also be challenging, leading to poor tablet quality. Research into win-win solutions is ongoing.

The physiochemical properties of direct compression tablets from spray dried and ball milled solid dispersions of tadalafil in vinylpyrrolidone and vinyl acetate block copolymer (PVP-VA) was studied(Wlodarski et al., 2016). ASD were demonstrated to be amorphous by PXRD, DSC and FTIR. All formulations and the crystalline drugs were successfully made into directly compressible tablets at doses of 2.5 mg, 10 mg and 20 mg and each lot met the requirements of Ph.Eur. The immediate release tablets comprising solid dispersions (IRSDTs) had significantly better dissolution profiles to equivalent tablets containing crystalline drug or the marketed formulation.

An unexpected result was recently noted following the post-processing treatment of spray dried dispersions of poorly soluble drugs(Chan et al., 2016). Two drugs were spray dried into solid dispersions with polyvinyl alcohol then the SD were post-processing treated by exposure to 75% RH at room temperature. As expected the percent of crystallinity was increased in the post-processing drugs, however, unexpectedly the dissolution efficiencies of the post-treated SD systems was higher and more consistent.

Gliclazide is listed on the WHO list of essential medicines and is also a BCS class II drug. A hydrophilic oral controlled release system was developed for this drug by spray drying with HPMC-AS or copovidone. Supersaturated dissolution testing indicated prolonged supersaturation state and solubility increase of 1.5- to 4.0-fold. Optimised SDD were included in matrix tablets with HPMC blends using a compaction simulator. Dissolution profiles from matrix tablets were linear with varied dissolution rates. After six month storage stability dissolution profiles were stable with similarity factor (f2 = 85). The formulations were homogenous (single phase) and HPMC-AS was deemed to be promising for the development of matrix systems with HPMC.

Piroxicam was spray dried both neat and with D-glucosamine HCl in order to enhance the dissolution rate(Adebisi et al., 2016). Drug only SDD contained the form II polymorph and showed no improvement in solubility but drug-glucosamine (2:1) SDD showed the most improved dissolution rate. Electrostatic charges were also studied and it was found that piroxicam had a higher tendency to accumulate charge than glucosamine at −7.5 versus 3.1 nC/g for spray dried components. A negligible charge density of 0.1−0.3 nC/g was recorded for spray dried dispersions, thereby improving handling and dissolution behaviour of the drug.

Compression effects were studied in ASD of miconazole with PVPVA64 made by spray drying and hot melt extrusion(Singh et al., 2015). SDD from spray drying initially showed two glass transition temperatures, whereas extruded ASD showed a single T_g indicating better mixing. Compression led to mixing of SDD at higher pressures and higher dwell times. Extruded samples showed no statistical difference on compression, but physical mixtures of extruded samples underwent mixing. Coincidence Doppler measurements on the pure polymer revealed a small but significant difference dependant on manufacturing technique. Plastic deformation and flow induced by compression increases molecular mobility leading to

domains in solid dispersions. Different manufacturing methods may lead to products with similar free volume and therefore similar molecular mobility.

Solid dispersions of nifedipine have been prepared and characterised in a Würster coater using porous spherical silicate microbeads (100 μm) and polymer PVPVA(Nagane et al., 2015). Supersaturation was superior to previous studies using microbeads only. Powder characteristics were preferable to conventional spray dried dispersions of nifedipine and PVPVA, thereby easing downstream manufacturing.

Nifedipine was spray dried in various weight ratio combination with Soluplus®, an excipient polymer usually processed by hot melt extrusion(Soulairol et al., 2015). Powders were compacted in tablet form. Addition of the polymer improved the smoothness of the particles and reduced crystallinity of the drug in the resultant powder, although phase separation was observed at high drug loadings. Compaction with polymer improved cohesiveness of SDD and this was confirmed by Heckel modelling. Dissolution kinetics of all spray dried samples was improved relative to crystalline drug.

Compression induced mixing of phase-separated SDD was studied using miconazole-PVPVA64 as a model system(Singh et al., 2014). At several drug loadings two T_g values were observed prior to compression, but one T_g value was seen post compression. This was attributed to polymer flow.

The effect of aqueous or organic solutions of Eudragit RS for the production of sustained release microparticles of theophylline using spray drying has been reported(Garekani et al., 2013). The SD samples were compacted and crushing strengths and release profiles of the tablets were determined. Yields were higher for SDaqueous, but SDorganic samples had higher crushing strength and better release profiles.

The effect of different excipients and processing conditions on the stability of SDD of ibipinabant was investigated(Leane et al., 2013). The physical stability of tablets with different excipients was significant and the best results were obtained using microcrystalline cellulose (MCC). Minimising the number of compression steps improved formulation stability, with direct compression performing best. Levels of crystallinity were higher in coated tablets, probably caused by exposure to moisture and heat.

Although wet granulation of amorphous systems is risky(Oksanen and Zografi, 1990), wet granulation is a standard unit operation in the pharmaceutical industry and most drug product plants use this process. The effects of wet granulation on the properties of solid dispersions was recently reported by Kinoshita(Kinoshita et al., 2017) with emphasis on physical stability and dissolution. Nilvadipine was combined with hypromellose and spray dried before wet granulation and drying under variable conditions. Drug concentration at 4 h from dissolution tests was used to assess solubility. PXRD patterns were recorded on granules to test physical stability during storage at 60 °C over 3 months. Statistical analysis revealed that the amount of granulation liquid and the ratio of water to ethanol in the liquid significantly affected dissolution properties and that drying temperature significantly affected physical stability. It was concluded that the risk of including water in the granulation of an SD could be mitigated by selection of lower proportions of liquid, higher ratios of ethanol in the liquid and higher drying temperature.

MECHANISTIC STUDIES OF SUPERSATURATION OR RECRYSTALLISATION

By deepening insight into the mechanistic processes involved in supersaturation, dissolution and recrystallisation, it will become possible to formulate dosage forms with better pharmacokinetic properties. Spectroscopy, *in silico* studies, mathematical modelling, imaging techniques and spectrometry are utilised to gain information at an intimate molecular level.

Spray dried dispersions of anti-malaria drug artemether were prepared in combination with a variety of polymers and physiochemical, dissolution and *in silico* studies ensued(Pawar et al., 2016). A reduced crystallinity of SDD relative to neat drug was detected by DSC and PXRD. Drug-polymer interactions were studied by docking and molecular dynamics and a van der Waals stabilisation was suggested. The best formulation released 82% drug after 60 min and all SDD were reported to be stable over ICH timelines and free of crystalline drug.

The influence of solution-state polymer assemblies on amorphous SDD performance of drugs phenytoin and probucol was studied using four model polymer excipients(Dalsin et al., 2014). Selective and non-selective solvents for the hydrophilic block of the polymers were used to induce or repress solution state assemblies prior to spray drying and this was monitored using dynamic light scattering (DLS). DLS revealed differences in solution assembly, size and structure. Crystallisation temperatures and enthalpies indicated that the drugs interacted mostly with the N,N-dimethylacrylamide (DMA) portions of the polymers studied. *In vitro* dissolution tests indicated an excellent performance for one of the systems containing probucol. Dissolution studies involving DLS were performed to better understand the drug-polymer aggregates. Forced aggregation of polymer into regular micelles was found to be a critical factor in increasing both the dissolution rate and the supersaturation maintenance.

An investigation into the mechanisim of crystallisation of spray dried drugs indapamide, metolazone and glibenclamide was recently reported(Edueng et al., 2017). A step-by-step experimental protocol employing DSC, DVS, PLM and a small scale dissolution apparatus (µDISS Profiler) to investigate the mechanism by which crystallisation occurred in solution. An addition of 0.001% - 0.01% (w/v) HPMCP to the dissolution medium successfully prevented drug crystallisation from supersaturation in some samples. Molecular dynamic simulations of drugs with HPMC suggested that hydrogen bonding could play a greater stabilising role in indapamide, compared to glibenclamide.

The dissolution mechanism of spray dried ASD of felodipine-copovidone was investigated using a combination of spectrophotometric, magnetic resonance imaging and mathematical modelling techniques(Langham et al., 2012). Both compacted and powdered materials were studied revealing that compaction resulted in a strong decrease in both rate and extent of release. Lower drug-loadings (5% and 15%) eroded with linear kinetics suggesting matrix control, but higher loadings (30%) experienced dissolution dominated by the drug with swelling rather than erosion.

An excellent study on the factors influencing drug release from ASD has recently been reported by Chen and co-workers(Chen et al., 2016). Ketoconazole dispersions were prepared by spray drying with a range of polymers and these SDD were compared with physical mix and polymer-only equivalents by NMR and FTIR techniques. Flory-Huggins interaction parameter (χ) showed the drug to be miscible with PVP, PVP-VA and HPMC-AS, but poorly miscible with HPMC and this was confirmed by spectral data. Overall it was concluded that initial drug release from dispersions was controlled by (a) polymer release rate, (b) the strength of the drug-polymer interaction, including effects from both inherent chemistry and ratio and (c) the level of mixing homogeneity.

OTHER ORAL DELIVERY TECHNOLOGIES

Cubosome precursor microparticles prepared by spray drying and converting to cubosomes *in situ* (on exposure to aqueous media) have recently been reported(Mei et al., 2017). This approach may be a solution to storage stability issues frequently encountered using cubosome delivery strategies. Docetaxel was chosen as a model drug for dissolution studies and the cumulative release was found to be 96% after 120 minutes compared with 75% for the physical mix. Drug entrapment efficiency was >95%.

Spray drying has also been used to produce ASD of metformin hydrochloride for use in bioadhesive drug delivery systems for the oral cavity(Sander et al., 2013).

FUTURE PROSPECTS

Spray drying is enjoying great popularity in research as a tool for creating particles with enhanced bioavailability. Given the high number of drugs experiencing poor solubility it is likely that research, development and commercial use of spray drying will continue to increase.

Commercial technology is improving. Advanced rotary atomisers are now available that are no longer prone to high maintenance costs(Lonergan, n.d.). A direct drive magnetic spray machine (MSM) is now in production(Khatri et al., 2015). Bend research have patented the use of a pressure nozzle and diffuser plate for producing pharmaceutical particles with larger particle size distribution(Beyerinck et al., 2014). As mentioned in the section on downstream processing, this is important for flow, die fill, compression and tablet uniformity. Hovione have filed a patent concerning continuous production of particles(Fonseca et al., 2016). High-temperature spray drying using a flash nozzle has also been patented by Bend research(Friesen et al., 2016). Process analytical technologies such as FBRM, turbidimetry, viscosimetry, laser diffraction, NIR and mass spectroscopy can reduce timescales for production quality control(Burggraeve et al., 2013; Chan et al., 2008).

Regulatory pressures are likely to drive a move away from toxic solvents, over time. Supercritical CO_2 technology represents a move away from toxicity, but several issues such as solubility need to be addressed for this to become more mainstream. Even ppm levels of dichloromethane are undesirable, so ethanol and isopropyl alcohol are more likely to be used if they fully solubilise all components(Paudel et al., 2013). An information age consumer is also more likely to buy a medicine that can be marketed as 'greener' than the consumers of yesterday. Such information is becoming increasingly readily available with the continued rise in information technology and can be exploited as a marketing tool.

Future innovations are likely to come from within industrial pharmaceutical research groups, but also from parallel industries. Food and cosmetic sectors are fast-paced dynamic environments with differing regulatory requirements to pharma. Academia-industry collaborations are particularly useful sources of new ideas and academic research is not nearly as hampered by regulatory constraints.

Due to the population of lipophilic drugs populating the pharmaceutical pipeline and the preference for oral solid dosage, further breakthroughs are very likely. Future publications are likely to focus on many of the areas addressed by this review, particularly in the areas of understanding stability, manufacturing, dissolution, pharmacokinetics and downstream processing.

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REFERENCES

Abraham, A., Crull, G., 2014. Understanding API-polymer proximities in amorphous stabilized composite drug products using fluorine-carbon 2d hetcor solid-state NMR. Mol. Pharm. 11, 3754–3759. doi:10.1021/mp400629j

Adebisi, A.O., Kaialy, W., Hussain, T., Al-Hamidi, H., Nokhodchi, A., Conway, B.R., Asare-Addo, K., 2016. Solid-state, triboelectrostatic and dissolution characteristics of spray-dried piroxicam-glucosamine solid dispersions. Colloids Surfaces B Biointerfaces 146, 841–851. doi:10.1016/j.colsurfb.2016.07.032

Al-Obaidi, H., Lawrence, M.J., Buckton, G., 2016. Atypical effects of incorporated surfactants on stability and dissolution properties of amorphous polymeric dispersions. J. Pharm. Pharmacol. 68, 1373–1383. doi:10.1111/jphp.12645

Albadarin, A.B., Potter, C.B., Davis, M.T., Iqbal, J., Korde, S., Pagire, S., Paradkar, A., Walker, G., 2017. Development of stability-enhanced ternary solid dispersions via combinations of HPMCP and Soluplus® processed by hot melt extrusion. Int. J. Pharm. 532, 603–611. doi:10.1016/j.ijpharm.2017.09.035

Alhayali, A., Tavellin, S., Velaga, S., 2017. Dissolution and precipitation behavior of ternary solid dispersions of ezetimibe in biorelevant media. Drug Dev. Ind. Pharm. 43, 79–88. doi:10.1080/03639045.2016.1220566

Amidon, G.L., Lennernäs, H., Shah, V.P., Crison, J.R., 1995. A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of in Vitro Drug Product Dissolution and in Vivo Bioavailability. Pharm. Res. An Off. J. Am. Assoc. Pharm. Sci. 12, 413–420. doi:10.1023/A:1016212804288

Amis, E.J., Xiang, X.-D., Zhao, J.-C., 2002. Combinatorial materials science: What's new since Edison? MRS Bull. 27, 295–300. doi:10.1557/mrs2002.96

Azad, M., Arteaga, C., Abdelmalek, B., Davé, R., Bilgili, E., 2014. Spray drying of drug-swellable dispersant suspensions for preparation of fast-dissolving, high drug-loaded, surfactant-free nanocomposites. Drug Dev. Ind. Pharm. 41, 1617–1631. doi:10.3109/03639045.2014.976574

Balakrishnan, P., Lee, B.-J., Oh, D.H., Kim, J.O., Hong, M.J., Jee, J.-P., Kim, J.A., Yoo, B.K., Woo, J.S., Yong, C.S., Choi, H.-G., 2009. Enhanced oral bioavailability of dexibuprofen by a novel solid Self-emulsifying drug delivery system (SEDDS). Eur. J. Pharm. Biopharm. 72, 539–545. doi:10.1016/j.ejpb.2009.03.001

Beck-Broichsitter, M., Bohr, A., Aragão-Santiago, L., Klingl, A., Kissel, T., 2016. Formulation and process considerations for the design of sildenafil-loaded polymeric microparticles by vibrational spray-drying. Pharm. Dev. Technol. doi:10.3109/10837450.2015.1098661

Beig, A., Fine-Shamir, N., Lindley, D., Miller, J.M., Dahan, A., 2017. Advantageous Solubility-Permeability Interplay When Using Amorphous Solid Dispersion (ASD) Formulation for the BCS Class IV P-gp Substrate Rifaximin: Simultaneous Increase of Both the Solubility and the Permeability. AAPS J. 19, 806–813. doi:10.1208/s12248-017-0052-1

Beyerinck, R.A., Diebele, H.L.M., Dobry, D.E., Ray, R.J., Settell, D.M., Spence, K.R., 2014. Method for making homogeneous spray-dried solid amorphous drug dispersions utilizing modified spray-drying apparatus.

Beyerinck, R.A., Ray, R.J., Dobry, D.E., Settell, D.M., 2010. Method for making homogeneous spray-dried solid amorphous drug dispersions using pressure nozzles.

Billon, A., Bataille, B., Cassanas, G., Jacob, M., 2000. Development of spray-dried acetaminophen microparticles using experimental designs. Int. J. Pharm. 203, 159–168. doi:10.1016/S0378-5173(00)00448-8

Blagden, N., de Matas, M., Gavan, P.T., York, P., 2007. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv. Drug Deliv. Rev. 59, 617–630. doi:10.1016/j.addr.2007.05.011

Brouwers, J., Brewster, M.E., Augustijns, P., 2009. Supersaturating Drug Delivery Systems: The Answer to Solubility-Limited Oral Bioavailability? . J. Pharm. Sci. . doi:10.1002/jps.21650

Brown, M.B., Martin, G.P., Jones, S.A., Akomeah, F.K., 2006. Dermal and transdermal drug delivery systems: Current and future prospects. Drug Deliv. J. Deliv. Target. Ther. Agents 13, 175–187. doi:10.1080/10717540500455975

Burggraeve, A., Van Den Kerkhof, T., Geens, J., Bijnens, L., Hellings, M., 2013. PAT for pharmaceutical spray drying. Eur. Pharm. Rev. 18, 27–29.

Cal, K., Sollohub, K., 2010. Spray drying technique. I: Hardware and process parameters. J. Pharm. Sci. 99, 575–586. doi:10.1002/jps.21886

Calahan, J.L., Azali, S.C., Munson, E.J., Nagapudi, K., 2015. Investigation of Phase Mixing in Amorphous Solid Dispersions of AMG 517 in HPMC-AS Using DSC, Solid-State NMR, and Solution Calorimetry. Mol. Pharm. 12, 4115–4123. doi:10.1021/acs.molpharmaceut.5b00556

Caron, V., Tajber, L., Corrigan, O.I., Healy, A.M., 2011. A comparison of spray drying and milling in the production of amorphous dispersions of sulfathiazole/polyvinylpyrrolidone and sulfadimidine/ polyvinylpyrrolidone. Mol. Pharm. 8, 532–542. doi:10.1021/mp1003674

Chan, L.W., Tan, L.H., Heng, P.W.S., 2008. Process analytical technology: Application to particle sizing in spray drying. AAPS PharmSciTech 9, 259–266. doi:10.1208/s12249-007-9011-y

Chan, S.-Y., Toh, S.-M., Khan, N.H., Chung, Y.-Y., Cheah, X.-Z., 2016. The improved dissolution performance of a post processing treated spray-dried crystalline solid dispersion of poorly soluble drugs. Drug Dev. Ind. Pharm. 42, 1800–1812.

doi:10.3109/03639045.2016.1173054

Chatterjee, K., Dollimore, D., Alexander, K., 2001. A new application for the Antoine equation in formulation development. Int. J. Pharm. 213, 31–44. doi:10.1016/S0378-5173(00)00644-X

Chen, J., Ormes, J.D., Higgins, J.D., Taylor, L.S., 2015. Impact of surfactants on the crystallization of aqueous suspensions of celecoxib amorphous solid dispersion spray dried particles. Mol. Pharm. 12, 533–541. doi:10.1021/mp5006245

Chen, R., Okamoto, H., Danjo, K., 2006. Particle design using a 4-fluid-nozzle spray-drying technique for sustained release of acetaminophen. Chem. Pharm. Bull. 54, 948–953. doi:10.1248/cpb.54.948

Chen, X.-Q., Stefanski, K., Shen, H., Huang, C., Caporuscio, C., Yang, W., Lam, P., Su, C., Gudmundsson, O., Hageman, M., 2014. Oral delivery of highly lipophilic poorly water-soluble drugs: Spray-dried dispersions to improve oral absorption and enable high-dose toxicology studies of a P2Y1 antagonist. J. Pharm. Sci. 103, 3924–3931. doi:10.1002/jps.24199

Chen, Y., Wang, S., Wang, S., Liu, C., Su, C., Hageman, M., Hussain, M., Haskell, R., Stefanski, K., Qian, F., 2016. Initial Drug Dissolution from Amorphous Solid Dispersions Controlled by Polymer Dissolution and Drug-Polymer Interaction. Pharm. Res. 33, 2445–2458. doi:10.1007/s11095-016-1969-2

Chieng, N., Aaltonen, J., Saville, D., Rades, T., 2009. Physical characterization and stability of amorphous indomethacin and ranitidine hydrochloride binary systems prepared by mechanical activation. Eur. J. Pharm. Biopharm. 71, 47–54. doi:10.1016/j.ejpb.2008.06.022

Connolly, S.J., Ezekowitz, M.D., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., Pogue, J., Reilly, P.A., Themeles, E., Varrone, J., Wang, S., Alings, M., Xavier, D., Zhu, J., Diaz, R., Lewis, B.S., Darius, H., Diener, H.-C., Joyner, C.D., Wallentin, L., Alings, A.M.W., Amerena, J. V, Avezum, A., Baumgartner, I., Brugada, J., Budaj, A., Caicedo, V., Ceremuzynski, L., Chen, J.H., Commerford, P.J., Connolly, S.J., Dans, A.L., Darius, H., Di Pasquale, G., Diaz, R., Erol, C., Ezekowitz, M.D., Ferreira, J., Flaker, G.C., Flather, M.D., Franzosi, M.G., Gamboa, R., Golitsyn, S.P., Gonzalez Hermosillo, J.A., Halon, D., Heidbuchel, H., Hohnloser, S.H., Hori, M., Huber, K., Jansky, P., Kamensky, G., Keltai, M., Kim, S., Lau, C.P., Le Heuzey, J.Y.F., Lewis, B.S., Liu, L.S., Nanas, J., Oldgren, J., Pais, P.S., Parkhomenko, A.N., Pedersen, K.E., Piegas, L.S., Raev, D., Razali, O., Simmers, T.A., Smith, P.J., Talajic, M., Tan, R.S., Tanomsup, S., Toivonen, L., Vinereanu, D., Wallentin, L., Xavier, D., Yusuf, S., Zhu, J., 2009. Dabigatran versus warfarin in patients with atrial fibrillation. N. Engl. J. Med. 361, 1139–1151. doi:10.1056/NEJMoa0905561

Crowley, M.M., Zhang, F., Repka, M.A., Thumma, S., Upadhye, S.B., Battu, S.K., McGinity, J.W., Martin, C., 2007. Pharmaceutical applications of hot-melt extrusion: Part I. Drug Dev. Ind. Pharm. 33, 909–926. doi:10.1080/03639040701498759

Cui, Y., Chiang, P.-C., Choo, E.F., Boggs, J., Rudolph, J., Grina, J., Wenglowsky, S., Rana, Y., 2013. Systemic in vitro and in vivo evaluation for determining the feasibility of

making an amorphous solid dispersion of a B-Raf (rapidly accelerated fibrosarcoma) inhibitor. Int. J. Pharm. 454, 241–248. doi:10.1016/j.ijpharm.2013.06.064

Curatolo, W., Nightingale, J.A., Herbig, S.M., 2009. Utility of hydroxypropylmethylcellulose acetate succinate (HPMCAS) for initiation and maintenance of drug supersaturation in the GI milieu. Pharm. Res. 26, 1419–1431. doi:10.1007/s11095-009-9852-z

Dahan, A., Beig, A., Ioffe-Dahan, V., Agbaria, R., Miller, J.M., 2013. The twofold advantage of the amorphous form as an oral drug delivery practice for lipophilic compounds: Increased apparent solubility and drug flux through the intestinal membrane. AAPS J. 15, 347–353. doi:10.1208/s12248-012-9445-3

Dalsin, M.C., Tale, S., Reineke, T.M., 2014. Solution-state polymer assemblies influence BCS class II drug dissolution and supersaturation maintenance. Biomacromolecules 15, 500–511. doi:10.1021/bm401431t

Davis, M.T., Egan, D.P., Kuhs, M., Albadarin, A.B., Griffin, C.S., Collins, J.A., Walker, G.M., 2015. Amorphous solid dispersions of BCS class II drugs: A rational approach to solvent and polymer selection. Chem. Eng. Res. Des. doi:10.1016/j.cherd.2016.04.008

Davis, M.T., Potter, C.B., Mohammadpour, M., Albadarin, A.B., Walker, G.M., 2017. Design of spray dried ternary solid dispersions comprising itraconazole, soluplus and HPMCP: Effect of constituent compositions. Int. J. Pharm. 519, 365–372. doi:http://dx.doi.org/10.1016/j.ijpharm.2017.01.043

De Francisco, L.M.B., Cerquetani, J.A., Bruschi, M.L., 2013. Development and characterization of gelatin and ethylcellulose microparticles designed as platforms to delivery fluoride. Drug Dev. Ind. Pharm. 39, 1644–1650. doi:10.3109/03639045.2012.728610

De Oliveira, A.R., Molina, E.F., De Castro Mesquita, P., Fonseca, J.L.C., Rossanezi, G., De Freitas Fernandes-Pedrosa, M., De Oliveira, A.G., Da Silva-Júnior, A.A., 2013. Structural and thermal properties of spray-dried methotrexate-loaded biodegradable microparticles. J. Therm. Anal. Calorim. 112, 555–565. doi:10.1007/s10973-012-2580-3

Demuth, B., Nagy, Z.K., Balogh, A., Vigh, T., Marosi, G., Verreck, G., Van Assche, I., Brewster, M.E., 2015. Downstream processing of polymer-based amorphous solid dispersions to generate tablet formulations . Int. J. Pharm. . doi:10.1016/j.ijpharm.2015.03.053

Dereymaker, A., Cinghia, G., Van den Mooter, G., 2017. Eudragit® RL as a stabilizer for supersaturation and a substrate for nanocrystal formation. Eur. J. Pharm. Biopharm. 114, 250–262. doi:10.1016/j.ejpb.2017.02.002

Deshmukh, R.K., Naik, J.B., 2016. Optimization of spray-dried diclofenac sodium-loaded microspheres by screening design. Dry. Technol. 34, 1593–1603. doi:10.1080/07373937.2016.1138121

Dontireddy, R., Crean, A.M., 2011. A comparative study of spray-dried and freeze-dried hydrocortisone/ polyvinyl pyrrolidone solid dispersions. Drug Dev. Ind. Pharm. 37, 1141–1149. doi:10.3109/03639045.2011.562213

Duarte, I., Santos, J.L., Pinto, J.F., Temtem, M., 2015. Screening methodologies for the development of spray-dried amorphous solid dispersions. Pharm. Res. 32, 222–237. doi:10.1007/s11095-014-1457-5

Edueng, K., Mahlin, D., Larsson, P., Bergström, C.A.S., 2017. Mechanism-based selection of stabilization strategy for amorphous formulations: Insights into crystallization pathways. J. Control. Release 256, 193–202. doi:10.1016/j.jconrel.2017.04.015

Egami, K., Higashi, K., Yamamoto, K., Moribe, K., 2015. Crystallization of Probucol in Nanoparticles Revealed by AFM Analysis in Aqueous Solution. Mol. Pharm. 12, 2972–2980. doi:10.1021/acs.molpharmaceut.5b00236

Enriquez, G.G., Orawiec, B.A., Rizvi, S.A.A., Do, D.P., 2014. Formulation development and in vitro evaluation of oral extended-release capsules containing biodegradable microspheres. J. Nanomedicine Nanotechnol. 5. doi:10.4172/2157-7439.1000208

Fahr, A., Liu, X., 2007. Drug delivery strategies for poorly water-soluble drugs. Expert Opin. Drug Deliv. 4, 403–416. doi:10.1517/17425247.4.4.403

Fatnassi, M., Tourné-Péteilh, C., Mineva, T., Devoisselle, J.-M., Gaveau, P., Fayon, F., Alonso, B., 2012. Drug nano-domains in spray-dried ibuprofen-silica microspheres. Phys. Chem. Chem. Phys. 14, 12285–12294. doi:10.1039/c2cp42092a

Fong, S.Y.K., Ibisogly, A., Bauer-Brandl, A., 2015. Solubility enhancement of BCS Class II drug by solid phospholipid dispersions: Spray drying versus freeze-drying. Int. J. Pharm. 496, 382–391. doi:10.1016/j.ijpharm.2015.10.029

Fonseca, T., Duarte, I., Temtem, M., Vicente, J., 2016. Continuous production of particles.

Friesen, D.T., Newbold, D.D., Baumann, J.M., Dubose, D.B., Millard, D.L., 2016. High-temperature spray drying process and apparatus.

Friesen, D.T., Shanker, R., Crew, M., Smithey, D.T., Curatolo, W.J., Nightingale, J.A.S., 2008. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: An overview. Mol. Pharm. 5, 1003–1019. doi:10.1021/mp8000793

Gamble, J.F., Ferreira, A.P., Tobyn, M., DiMemmo, L., Martin, K., Mathias, N., Schild, R., Vig, B., Baumann, J.M., Parks, S., Ashton, M., 2014. Application of imaging based tools for the characterisation of hollow spray dried amorphous dispersion particles. Int. J. Pharm. 465, 210–217. doi:10.1016/j.ijpharm.2014.02.002

Gamble, J.F., Terada, M., Holzner, C., Lavery, L., Nicholson, S.J., Timmins, P., Tobyn, M., 2016. Application of X-ray microtomography for the characterisation of hollow polymer-stabilised spray dried amorphous dispersion particles. Int. J. Pharm. 510, 1–8. doi:10.1016/j.ijpharm.2016.05.051

Garekani, H.A., Moghaddam, Z.F., Sadeghi, F., 2013. Organic solution versus aqueous dispersion of Eudragit RS in preparation of sustained release microparticles of theophylline using spray drying. Colloids Surfaces B Biointerfaces 108, 374–379. doi:10.1016/j.colsurfb.2013.03.012

Ghanavati, R., Taheri, A., Homayouni, A., 2017. Anomalous dissolution behavior of

celecoxib in PVP/Isomalt solid dispersions prepared using spray drier. Mater. Sci. Eng. C 72, 501–511. doi:10.1016/j.msec.2016.11.042

Goddeeris, C., Van den Mooter, G., 2008. Free flowing solid dispersions of the anti-HIV drug UC 781 with Poloxamer 407 and a maximum amount of TPGS 1000: Investigating the relationship between physicochemical characteristics and dissolution behaviour. Eur. J. Pharm. Sci. 35, 104–113. doi:10.1016/j.ejps.2008.06.010

Gu, B., Linehan, B., Tseng, Y.-C., 2015. Optimization of the Büchi B-90 spray drying process using central composite design for preparation of solid dispersions. Int. J. Pharm. 491, 208–217. doi:10.1016/j.ijpharm.2015.06.006

Gursoy, R.N., Benita, S., 2004. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed. Pharmacother. 58, 173–182. doi:10.1016/j.biopha.2004.02.001

Hansen, T., Holm, P., Schultz, K., 2004. Process characteristics and compaction of spray-dried emulsions containing a drug dissolved in lipid. Int. J. Pharm. 287, 55–66. doi:10.1016/j.ijpharm.2004.08.014

Haser, A., Cao, T., Lubach, J., Listro, T., Acquarulo, L., Zhang, F., 2017. Melt extrusion vs. spray drying: The effect of processing methods on crystalline content of naproxen-povidone formulations. Eur. J. Pharm. Sci. 102, 115–125. doi:10.1016/j.ejps.2017.02.038

Hengsawas Surasarang, S., Keen, J.M., Huang, S., Zhang, F., McGinity, J.W., Williams, R.O., 2017. Hot melt extrusion versus spray drying: hot melt extrusion degrades albendazole. Drug Dev. Ind. Pharm. 43, 797–811. doi:10.1080/03639045.2016.1220577

Higashi, K., Hayashi, H., Yamamoto, K., Moribe, K., 2015. The effect of drug and EUDRAGIT<sup>®</sup> S 100 miscibility in solid dispersions on the drug and polymer dissolution rate. Int. J. Pharm. 494, 9–16. doi:10.1016/j.ijpharm.2015.08.007

Homayouni, A., Sadeghi, F., Nokhodchi, A., Varshosaz, J., Garekani, H.A., 2015. Preparation and characterization of celecoxib dispersions in soluplus®: Comparison of spray drying and conventional methods. Iran. J. Pharm. Res. 14, 35–50.

Hugo, M., Kunath, K., Dressman, J., 2013. Selection of excipient, solvent and packaging to optimize the performance of spray-dried formulations: Case example fenofibrate. Drug Dev. Ind. Pharm. 39, 402–412. doi:10.3109/03639045.2012.685176

Ikasari, E.D., Fudholi, A., Martono, S., Marchaban, 2015. Investigation of nifedipine solid dispersion with solvent PVP K-30. Int. J. Pharm. Pharm. Sci. 7, 389–392.

Impurities: Guideline for Residual Solvents, 2016. . European Medicines Agency, Budapest.

Jang, D.-J., Sim, T., Oh, E., 2013. Formulation and optimization of spray-dried amlodipine solid dispersion for enhanced oral absorption. Drug Dev. Ind. Pharm. 39, 1133–1141. doi:10.3109/03639045.2012.723218

Jog, R., Gokhale, R., Burgess, D.J., 2016. Solid state drug-polymer miscibility studies using

the model drug ABT-102. Int. J. Pharm. 509, 285–295. doi:10.1016/j.ijpharm.2016.05.068

Ke, P., Hasegawa, S., Al-Obaidi, H., Buckton, G., 2012. Investigation of preparation methods on surface/bulk structural relaxation and glass fragility of amorphous solid dispersions. Int. J. Pharm. 422, 170–178. doi:10.1016/j.ijpharm.2011.10.047

Kenawy, E.-R., Abdel-Hay, F.I., El-Newehy, M.H., Wnek, G.E., 2009. Processing of polymer nanofibers through electrospinning as drug delivery systems. Mater. Chem. Phys. 113, 296–302. doi:10.1016/j.matchemphys.2008.07.081

Khatri, R.K., Hawkins, L.A., Bazergui, C., 2015. Demonstrated operability and reliability improvements for a prototype high-speed rotary-disc atomizer supported on active magnetic bearings, in: Proceedings of the ASME Turbo Expo. doi:10.1115/GT2015-43803

Khoshkava, V., Kamal, M.R., 2014. Effect of drying conditions on cellulose nanocrystal (CNC) agglomerate porosity and dispersibility in polymer nanocomposites. Powder Technol. 261, 288–298. doi:10.1016/j.powtec.2014.04.016

Kinoshita, R., Ohta, T., Shiraki, K., Higashi, K., Moribe, K., 2017. Effects of wet-granulation process parameters on the dissolution and physical stability of a solid dispersion. Int. J. Pharm. 524, 304–311. doi:10.1016/j.ijpharm.2017.04.007

Kojima, Y., Ohta, T., Shiraki, K., Takano, R., Maeda, H., Ogawa, Y., 2013. Effects of spray drying process parameters on the solubility behavior and physical stability of solid dispersions prepared using a laboratory-scale spray dryer. Drug Dev. Ind. Pharm. 39, 1484–1493. doi:10.3109/03639045.2012.692378

Kumar, S., Shen, J., Zolnik, B., Sadrieh, N., Burgess, D.J., 2015. Optimization and dissolution performance of spray-dried naproxen nano-crystals. Int. J. Pharm. 486, 159–166. doi:10.1016/j.ijpharm.2015.03.047

Kumar, S., Xu, X., Gokhale, R., Burgess, D.J., 2014. Formulation parameters of crystalline nanosuspensions on spray drying processing: a DoE approach. Int. J. Pharm. 464, 34–45.

Langham, Z.A., Booth, J., Hughes, L.P., Reynolds, G.K., Wren, S.A.C., 2012. Mechanistic insights into the dissolution of spray-dried amorphous solid dispersions. J. Pharm. Sci. 101, 2798–2810. doi:10.1002/jps.23192

Law, D., Wang, W., Schmitt, E.A., Qiu, Y., Krill, S.L., Fort, J.J., 2003. Properties of rapidly dissolving eutectic mixtures of poly(ethylene glycol) and fenofibrate: The eutectic microstructure. J. Pharm. Sci. 92, 505–515. doi:10.1002/jps.10324

Leane, M.M., Sinclair, W., Qian, F., Haddadin, R., Brown, A., Tobyn, M., Dennis, A.B., 2013. Formulation and process design for a solid dosage form containing a spray-dried amorphous dispersion of ibipinabant. Pharm. Dev. Technol. 18, 359–366. doi:10.3109/10837450.2011.619544

Letchmanan, K., Shen, S.-C., Ng, W.K., Tan, R.B.H., 2015. Enhanced dissolution and stability of artemisinin by nano-confinement in ordered mesoporous SBA-15 particles. J. Microencapsul. 32, 390–400. doi:10.3109/02652048.2015.1035684

Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 50, 47–60. doi:http://dx.doi.org/10.1016/S0939-6411(00)00076-X

Li, J., Patel, D., Wang, G., 2017. Use of Spray-Dried Dispersions in Early Pharmaceutical Development: Theoretical and Practical Challenges. AAPS J. 19, 321–333. doi:10.1208/s12248-016-0017-9

Lim, R.T.Y., Ong, C.K., Cheng, S., Ng, W.K., 2017. Amorphization of crystalline active pharmaceutical ingredients via formulation technologies. Powder Technol. 311, 175–184. doi:10.1016/j.powtec.2017.01.004

Lonergan, G., n.d. The Future of Spray Drying [WWW Document]. URL http://www.powderbulksolids.com/article/future-spray-drying (accessed 7.13.17).

Lu, Z., Yang, Y., Covington, R.-A., Bi, Y. V, Dürig, T., Ilies, M.A., Fassihi, R., 2016. Supersaturated controlled release matrix using amorphous dispersions of glipizide. Int. J. Pharm. 511, 957–968. doi:10.1016/j.ijpharm.2016.07.072

Mahmah, O., Tabbakh, R., Kelly, A., Paradkar, A., 2014. A comparative study of the effect of spray drying and hot-melt extrusion on the properties of amorphous solid dispersions containing felodipine. J. Pharm. Pharmacol. 66, 275–284. doi:10.1111/jphp.12099

Marsac, P.J., Li, T., Taylor, L.S., 2009. Estimation of drug-polymer miscibility and solubility in amorphous solid dispersions using experimentally determined interaction parameters. Pharm. Res. 26, 139–151. doi:10.1007/s11095-008-9721-1

Martins, R.M., Machado, M.O., Pereira, S. V, Nosari, A.B.F.L., Tacon, L.A., Freitas, L.A.P., 2012. Microparticulated Hydrochlorothiazide Solid Dispersion: Enhancing Dissolution Properties via Spray Drying. Dry. Technol. 30, 959–967. doi:10.1080/07373937.2011.652268

McNamara, D., Yin, S., Pan, D., Crull, G., Timmins, P., Vig, B., 2017. Characterization of phase separation propensity for amorphous spray dried dispersions. Mol. Pharm. 14, 377–385. doi:10.1021/acs.molpharmaceut.6b00722

Meeus, J., Lenaerts, M., Scurr, D.J., Amssoms, K., Davies, M.C., Roberts, C.J., Van Den Mooter, G., 2015a. The Influence of Spray-Drying Parameters on Phase Behavior, Drug Distribution, and in Vitro Release of Injectable Microspheres for Sustained Release. J. Pharm. Sci. 104, 1451–1460. doi:10.1002/jps.24361

Meeus, J., Scurr, D.J., Chen, X., Amssoms, K., Davies, M.C., Roberts, C.J., Van Den Mooter, G., 2015b. Combination of (M)DSC and surface analysis to study the phase behaviour and drug distribution of ternary solid dispersions. Pharm. Res. 32, 1407–1416. doi:10.1007/s11095-014-1543-8

Mei, L., Xie, Y., Jing, H., Huang, Y., Chen, J., Ran, H., Pan, X., Wu, C., 2017. A novel design for stable self-assembly cubosome precursor-microparticles enhancing dissolution of insoluble drugs. Drug Dev. Ind. Pharm. doi:10.1080/03639045.2017.1304958

Miller, J.M., Beig, A., Carr, R.A., Spence, J.K., Dahan, A., 2012. A win-win solution in oral

delivery of lipophilic drugs: Supersaturation via amorphous solid dispersions increases apparent solubility without sacrifice of intestinal membrane permeability. Mol. Pharm. 9, 2009–2016. doi:10.1021/mp300104s

Mosharraf, M., Nyström, C., 1995. The effect of particle size and shape on the surface specific dissolution rate of microsized practically insoluble drugs. Int. J. Pharm. 122, 35–47. doi:10.1016/0378-5173(95)00033-F

Munjal, B., Pawar, Y.B., Patel, S.B., Bansal, A.K., 2011. Comparative oral bioavailability advantage from curcumin formulations. Drug Deliv. Transl. Res. 1, 322–331. doi:10.1007/s13346-011-0033-3

Nagabandi, V., Chandragiri, A.K., Thota, S., Katakam, P., 2014. Enhancement of dissolution rate of naproxen by lipid based solid dispersions. J. Pharm. Sci. Res. 6, 78–82.

Nagane, K., Kimura, S., Ukai, K., Takahashi, C., Ogawa, N., Yamamoto, H., 2015. Application of spherical silicate to prepare solid dispersion dosage forms with aqueous polymers. Int. J. Pharm. 493, 55–62. doi:10.1016/j.ijpharm.2015.07.037

Nagy, Z.K., Balogh, A., Démuth, B., Pataki, H., Vigh, T., Szabó, B., Molnár, K., Schmidt, B.T., Horák, P., Marosi, G., Verreck, G., Van Assche, I., Brewster, M.E., 2015. High speed electrospinning for scaled-up production of amorphous solid dispersion of itraconazole . Int. J. Pharm. . doi:10.1016/j.ijpharm.2015.01.025

Nguyen, D.N., Van Den Mooter, G., 2014. The fate of ritonavir in the presence of darunavir. Int. J. Pharm. 475, 214–226. doi:10.1016/j.ijpharm.2014.08.062

Nishino, Y., Kubota, A., Kanazawa, T., Takashima, Y., Ozeki, T., Okada, H., 2012. Improved intestinal absorption of a poorly water-soluble oral drug using mannitol microparticles containing a nanosolid drug dispersion. J. Pharm. Sci. 101, 4191–4200. doi:10.1002/jps.23278

Niwa, T., Miura, S., Danjo, K., 2011. Design of dry nanosuspension with highly spontaneous dispersible characteristics to develop solubilized formulation for poorly water-soluble drugs. Pharm. Res. 28, 2339–2349. doi:10.1007/s11095-011-0465-y

Ohyagi, N., Ueda, K., Higashi, K., Yamamoto, K., Kawakami, K., Moribe, K., 2017. Synergetic Role of Hypromellose and Methacrylic Acid Copolymer in the Dissolution Improvement of Amorphous Solid Dispersions. J. Pharm. Sci. 106, 1042–1050. doi:10.1016/j.xphs.2016.12.005

Oksanen, C.A., Zografi, G., 1990. The Relationship Between the Glass Transition Temperature and Water Vapor Absorption by Poly(vinylpyrrolidone). Pharm. Res. An Off. J. Am. Assoc. Pharm. Sci. 7, 654–657. doi:10.1023/A:1015834715152

Pack, B.W., Babayan, Y., Schrad, M.A., Stroud, P.A., Sperry, D.C., White, K.C., Aburub, A., 2017. Development of an in vivo-relevant drug product performance method for an amorphous solid dispersion. J. Pharm. Biomed. Anal. 142, 307–314. doi:10.1016/j.jpba.2017.05.029

Paidi, S.K., Jena, S.K., Ahuja, B.K., Devasari, N., Suresh, S., 2015. Preparation, in-vitro and in-vivo evaluation of spray-dried ternary solid dispersion of biopharmaceutics

classification system class II model drug. J. Pharm. Pharmacol. 67, 616–629. doi:10.1111/jphp.12358

Pan, K., Zhong, Q., Baek, S.J., 2013. Enhanced dispersibility and bioactivity of curcumin by encapsulation in casein nanocapsules. J. Agric. Food Chem. 61, 6036–6043. doi:10.1021/jf400752a

Park, C.-W., Tung, N.-T., Rhee, Y.-S., Kim, J.-Y., Oh, T.-O., Ha, J.-M., Chi, S.-C., Park, E.-S., 2013. Physicochemical, pharmacokinetic and pharmacodynamic evaluations of novel ternary solid dispersion of rebamipide with poloxamer 407. Drug Dev. Ind. Pharm. 39, 836–844. doi:10.3109/03639045.2012.674138

Park, G.B., Yoon, H., Bae, J.W., Kim, Y.U., Jeon, D.Y., Song, J.E., Lee, D., Khang, G., 2013. Release behavior of cilostazol according to the fabrication methods and ratio of HPMC/PVP. Macromol. Res. 21, 971–976. doi:10.1007/s13233-013-1126-2

Parveen, S., Misra, R., Sahoo, S.K., 2012. Nanoparticles: A boon to drug delivery, therapeutics, diagnostics and imaging. Nanomedicine Nanotechnology, Biol. Med. 8, 147–166. doi:10.1016/j.nano.2011.05.016

Patel, A.D., Agrawal, A., Dave, R.H., 2014. Investigation of the effects of process variables on derived properties of spray dried solid-dispersions using polymer based response surface model and ensemble artificial neural network models. Eur. J. Pharm. Biopharm. 86, 404–417. doi:10.1016/j.ejpb.2013.10.014

Patel, A.D., Agrawal, A., Dave, R.H., 2013. Development of polyvinylpyrrolidone-based spray-dried solid dispersions using response surface model and ensemble artificial neural network. J. Pharm. Sci. 102, 1847–1858. doi:10.1002/jps.23526

Patel, B.B., Patel, J.K., Chakraborty, S., 2015a. Solubility enhancement using poly(meth)acrylate based solid dispersions. Powder Technol. 27–38. doi:10.1016/j.powtec.2014.10.006

Patel, B.B., Patel, J.K., Chakraborty, S., Shukla, D., 2015b. Revealing facts behind spray dried solid dispersion technology used for solubility enhancement. Saudi Pharm. J. 23, 352–365. doi:10.1016/j.jsps.2013.12.013

Patel, J.R., Carlton, R.A., Yuniatine, F., Needham, T.E., Wu, L., Vogt, F.G., 2012. Preparation and structural characterization of amorphous spray-dried dispersions of tenoxicam with enhanced dissolution. J. Pharm. Sci. 101, 641–663. doi:10.1002/jps.22800

Patil, V., Chauhan, A.K., Singh, R.P., 2014. Optimization of the spray-drying process for developing guava powder using response surface methodology. Powder Technol. 253, 230–236. doi:10.1016/j.powtec.2013.11.033

Patterson, A., Ferreira, A.P., Banks, E., Skeene, K., Clarke, G., Nicholson, S., Rawlinson-Malone, C., 2015. Modelling drug degradation in a spray dried polymer dispersion using a modified Arrhenius equation. Int. J. Pharm. 478, 348–360. doi:10.1016/j.ijpharm.2014.11.063

Paudel, A., Loyson, Y., Van den Mooter, G., 2013. An investigation into the effect of spray

drying temperature and atomizing conditions on miscibility, physical stability, and performance of naproxen-PVP K 25 solid dispersions. J. Pharm. Sci. 102, 1249–1267. doi:10.1002/jps.23459

Paudel, A., Van Den Mooter, G., 2012. Influence of solvent composition on the miscibility and physical stability of naproxen/PVP K 25 solid dispersions prepared by cosolvent spray-drying. Pharm. Res. 29, 251–270. doi:10.1007/s11095-011-0539-x

Paudel, A., Worku, Z.A., Meeus, J., Guns, S., Van den Mooter, G., 2013. Manufacturing of solid dispersions of poorly water soluble drugs by spray drying: formulation and process considerations. Int. J. Pharm. doi:10.1016/j.ijpharm.2012.07.015

Paudel, A., Worku, Z.A., Meeus, J., Guns, S., Van Den Mooter, G., 2013. Manufacturing of solid dispersions of poorly water soluble drugs by spray drying: Formulation and process considerations. Int. J. Pharm. 453. doi:10.1016/j.ijpharm.2012.07.015

Pawar, J.N., Shete, R.T., Gangurde, A.B., Moravkar, K.K., Javeer, S.D., Jaiswar, D.R., Amin, P.D., 2016. Development of amorphous dispersions of artemether with hydrophilic polymers via spray drying: Physicochemical and in silico studies. Asian J. Pharm. Sci. 11, 385–395. doi:10.1016/j.ajps.2015.08.012

Pradhan, R., Kim, S.Y., Yong, C.S., Kim, J.O., 2016. Preparation and characterization of spray-dried valsartan-loaded Eudragit® E PO solid dispersion microparticles. Asian J. Pharm. Sci. 11, 744–750. doi:10.1016/j.ajps.2016.05.002

Purohit, H.S., Ormes, J.D., Saboo, S., Su, Y., Lamm, M.S., Mann, A.K.P., Taylor, L.S., 2017. Insights into Nano- and Micron-Scale Phase Separation in Amorphous Solid Dispersions Using Fluorescence-Based Techniques in Combination with Solid State Nuclear Magnetic Resonance Spectroscopy. Pharm. Res. doi:10.1007/s11095-017-2145-z

Qi, S., Roser, S., Edler, K.J., Pigliacelli, C., Rogerson, M., Weuts, I., Van Dycke, F., Stokbroekx, S., 2013. Insights into the role of polymer-surfactant complexes in drug solubilisation/stabilisation during drug release from solid dispersions. Pharm. Res. 30, 290–302.

Qian, F., Huang, J., Hussain, M.A., 2010. Drug-polymer solubility and miscibility: Stability consideration and practical challenges in amorphous solid dispersion development. J. Pharm. Sci. 99, 2941–2947. doi:10.1002/jps.22074

Qian, F., Wang, J., Hartley, R., Tao, J., Haddadin, R., Mathias, N., Hussain, M., 2012. Solution behavior of PVP-VA and HPMC-AS-Based amorphous solid dispersions and their bioavailability implications. Pharm. Res. 29, 2766–2776. doi:10.1007/s11095-012-0695-7

Quirk, E., Doggett, A., Bretnall, A., 2014. Determination of residual acetone and acetone related impurities in drug product intermediates prepared as Spray Dried Dispersions (SDD) using gas chromatography with headspace autosampling (GCHS). J. Pharm. Biomed. Anal. 96, 37–44. doi:10.1016/j.jpba.2014.03.027

Ramesh, K., Chandra Shekar, B., Khadgapathi, P., Bhikshapathi, D.V.R.N., 2015. Design and evaluation of tolvaptan solid dispersions using hot-melt extrusion and spray drying technique - A comparative study. Der Pharm. Lett. 7, 218–231.

Rao, M.R.P., Aghav, S.S., 2014. Spray-Dried Redispersible Emulsion to Improve Oral Bioavailability of Itraconazole . J. Surfactants Deterg. . doi:10.1007/s11743-013-1538-1

Ricarte, R.G., Lodge, T.P., Hillmyer, M.A., 2015. Detection of pharmaceutical drug crystallites in solid dispersions by transmission electron microscopy. Mol. Pharm. 12, 983–990. doi:10.1021/mp500682x

Riekes, M.K., Engelen, A., Appeltans, B., Rombaut, P., Stulzer, H.K., Van Den Mooter, G., 2016. New Perspectives for Fixed Dose Combinations of Poorly Water-Soluble Compounds: A Case Study with Ezetimibe and Lovastatin. Pharm. Res. 33, 1259–1275. doi:10.1007/s11095-016-1870-z

Sander, C., Madsen, K.D., Hyrup, B., Nielsen, H.M., Rantanen, J., Jacobsen, J., 2013. Characterization of spray dried bioadhesive metformin microparticles for oromucosal administration. Eur. J. Pharm. Biopharm. 85, 682–688. doi:10.1016/j.ejpb.2013.05.017

Savjani, K.T., Gajjar, A.K., Savjani, J.K., 2012. Drug Solubility: Importance and Enhancement Techniques. ISRN Pharm. 2012, 195727. doi:10.5402/2012/195727

Sawicki, E., Beijnen, J.H., Schellens, J.H.M., Nuijen, B., 2016. Pharmaceutical development of an oral tablet formulation containing a spray dried amorphous solid dispersion of docetaxel or paclitaxel. Int. J. Pharm. 511, 765–773. doi:10.1016/j.ijpharm.2016.07.068

Scagliotti, G. V, Parikh, P., Von Pawel, J., Biesma, B., Vansteenkiste, J., Manegold, C., Serwatowski, P., Gatzemeier, U., Digumarti, R., Zukin, M., Lee, J.S., Mellemgaard, A., Park, K., Patil, S., Rolski, J., Goksel, T., De Marinis, F., Simms, L., Sugarman, K.P., Gandara, D., 2008. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J. Clin. Oncol. 26, 3543–3551. doi:10.1200/JCO.2007.15.0375

Serajuddin, A.T.M., 2007. Salt formation to improve drug solubility. Adv. Drug Deliv. Rev. 59, 603–616. doi:10.1016/j.addr.2007.05.010

Shakeel, F., Shafiq, S., Haq, N., Alanazi, F.K., Alsarra, I.A., 2012. Nanoemulsions as potential vehicles for transdermal and dermal delivery of hydrophobic compounds: An overview. Expert Opin. Drug Deliv. 9, 953–974. doi:10.1517/17425247.2012.696605

Shen, S.-C., Ng, W.K., Chia, L., Hu, J., Tan, R.B.H., 2011. Physical state and dissolution of ibuprofen formulated by co-spray drying with mesoporous silica: Effect of pore and particle size. Int. J. Pharm. 410, 188–195. doi:10.1016/j.ijpharm.2011.03.018

Singh, A., De Bisschop, C., Schut, H., Van Humbeeck, J., Van Den Mooter, G., 2015. Compression Effects on the Phase Behaviour of Miconazole-Poly (1-Vinylpyrrolidone-Co-Vinyl Acetate) Solid Dispersions - Role of Pressure, Dwell Time, and Preparation Method. J. Pharm. Sci. 104, 3366–3376. doi:10.1002/jps.24540

Singh, A., Van den Mooter, G., 2016. Spray drying formulation of amorphous solid dispersions. Adv. Drug Deliv. Rev. 100, 27–50. doi:http://dx.doi.org/10.1016/j.addr.2015.12.010

Singh, A., Van Humbeeck, J., Van Den Mooter, G., 2014. A new twist in the old story-can compression induce mixing of phase separated solid dispersions? A case study of spray-

dried Miconazole-PVP VA64 solid dispersions. Pharm. Res. 31, 3191–3200. doi:10.1007/s11095-014-1411-6

Sollohub, K., Cal, K., 2010. Spray drying technique: II. Current applications in pharmaceutical technology. J. Pharm. Sci. 99, 587–597. doi:10.1002/jps.21963

Sóti, P.L., Nagy, Z.K., Serneels, G., Vajna, B., Farkas, A., Van Der Gucht, F., Fekete, P., Vigh, T., Wagner, I., Balogh, A., Pataki, H., Mezo, G., Marosi, G., 2015. Preparation and comparison of spray dried and electrospun bioresorbable drug delivery systems. Eur. Polym. J. 68, 671–679. doi:10.1016/j.eurpolymj.2015.03.035

Soulairol, I., Tarlier, N., Bataille, B., Cacciaguerra, T., Sharkawi, T., 2015. Spray-dried solid dispersions of nifedipine and vinylcaprolactam/vinylacetate/PEG<inf>6000</inf> for compacted oral formulations. Int. J. Pharm. 481, 140–147. doi:10.1016/j.ijpharm.2015.01.012

Takeuchi, H., Nagira, S., Yamamoto, H., Kawashima, Y., 2005. Solid dispersion particles of amorphous indomethacin with fine porous silica particles by using spray-drying method. Int. J. Pharm. 293, 155–164. doi:10.1016/j.ijpharm.2004.12.019

Teixeira, C.C.C., Mendonça, L.M., Bergamaschi, M.M., Queiroz, R.H.C., Souza, G.E.P., Antunes, L.M.G., Freitas, L.A.P., 2016. Microparticles Containing Curcumin Solid Dispersion: Stability, Bioavailability and Anti-Inflammatory Activity. AAPS PharmSciTech 17, 252–261. doi:10.1208/s12249-015-0337-6

Thombre, A.G., Caldwell, W.B., Friesen, D.T., McCray, S.B., Sutton, S.C., 2012. Solid nanocrystalline dispersions of ziprasidone with enhanced bioavailability in the fasted state. Mol. Pharm. 9, 3526–3534. doi:10.1021/mp3003607

Tian, Y., Caron, V., Jones, D.S., Healy, A.-M., Andrews, G.P., 2014. Using Flory-Huggins phase diagrams as a pre-formulation tool for the production of amorphous solid dispersions: A comparison between hot-melt extrusion and spray drying. J. Pharm. Pharmacol. 66, 256–274. doi:10.1111/jphp.12141

Ting, J.M., Navale, T.S., Bates, F.S., Reineke, T.M., 2014. Design of Tunable Multicomponent Polymers As Modular Vehicles to Solubilize Highly Lipophilic Drugs. Macromolecules 47, 6554–6565. doi:10.1021/ma501839s

Ting, J.M., Navale, T.S., Jones, S.D., Bates, F.S., Reineke, T.M., 2015. Deconstructing HPMCAS: Excipient Design to Tailor Polymer-Drug Interactions for Oral Drug Delivery. ACS Biomater. Sci. Eng. 1, 978–990. doi:10.1021/acsbiomaterials.5b00234

Tran, T.H., Poudel, B.K., Marasini, N., Chi, S.-C., Choi, H.-G., Yong, C.S., Kim, J.O., 2013. Preparation and evaluation of raloxifene-loaded solid dispersion nanoparticle by spray-drying technique without an organic solvent. Int. J. Pharm. 443, 50–57. doi:10.1016/j.ijpharm.2013.01.013

Tran, T.H., Ramasamy, T., Poudel, B.K., Marasini, N., Moon, B.K., Cho, H.J., Choi, H.-G., Yong, C.S., Kim, J.O., 2014. Preparation and characterization of spray-dried gelatin microspheres encapsulating ganciclovir. Macromol. Res. 22, 124–130. doi:10.1007/s13233-014-2018-9

Truong, D.H., Tran, T.H., Ramasamy, T., Choi, J.Y., Lee, H.H., Moon, C., Choi, H.-G., Yong, C.S., Kim, J.O., 2016. Development of Solid Self-Emulsifying Formulation for Improving the Oral Bioavailability of Erlotinib. AAPS PharmSciTech 17, 466–473. doi:10.1208/s12249-015-0370-5

Ueda, K., Higashi, K., Yamamoto, K., Moribe, K., 2015. In situ molecular elucidation of drug supersaturation achieved by nano-sizing and amorphization of poorly water-soluble drug. Eur. J. Pharm. Sci. 77, 79–89. doi:10.1016/j.ejps.2015.05.027

Van Eerdenbrugh, B., Taylor, L.S., 2010. Small scale screening to determine the ability of different polymers to inhibit drug crystallization upon rapid solvent evaporation. Mol. Pharm. 7, 1328–1337. doi:10.1021/mp1001153

Vehring, R., 2008. Pharmaceutical particle engineering via spray drying. Pharm. Res. 25, 999–1022. doi:10.1007/s11095-007-9475-1

Vialpando, M., Smulders, S., Bone, S., Jager, C., Vodak, D., Van Speybroeck, M., Verheyen, L., Backx, K., Boeykens, P., Brewster, M.E., Ceulemans, J., Novoa de Armas, H., Van Geel, K., Kesselaers, E., Hillewaert, V., Lachau-Durand, S., Meurs, G., Psathas, P., Van Hove, B., Verreck, G., Voets, M., Weuts, I., Mackie, C., 2016. Evaluation of Three Amorphous Drug Delivery Technologies to Improve the Oral Absorption of Flubendazole. J. Pharm. Sci. 105, 2782–2793. doi:10.1016/j.xphs.2016.03.003

Wan, L.S.C., Heng, P.W.S., Chia, C.G.H., 1992. Plasticizers and their effects on microencapsulation process by spray-drying in an aqueous system. J. Microencapsul. 9, 53–62. doi:10.3109/02652049209021222

Wang, T., Hu, Q., Zhou, M., Xue, J., Luo, Y., 2016. Preparation of ultra-fine powders from polysaccharide-coated solid lipid nanoparticles and nanostructured lipid carriers by innovative nano spray drying technology. Int. J. Pharm. 511, 219–222. doi:10.1016/j.ijpharm.2016.07.005

Watanabe, T., Hasegawa, S., Wakiyama, N., Kusai, A., Senna, M., 2003. Comparison between polyvinylpyrrolidone and silica nanoparticles as carriers for indomethacin in a solid state dispersion. Int. J. Pharm. 250, 283–286. doi:10.1016/S0378-5173(02)00549-5

Whiteside, P.T., Zhang, J., Parker, A.P., Madden-Smith, C.E., Patel, N., Jensen, J., Sloth, J., Roberts, C.J., 2013. A physical and chemical comparison of material from a conventional spray-dried system and a single particle spray-dried system. Int. J. Pharm. 455, 306–311. doi:10.1016/j.ijpharm.2013.07.013

Williams, H.D., Trevaskis, N.L., Charman, S.A., Shanker, R.M., Charman, W.N., Pouton, C.W., Porter, C.J.H., 2013. Strategies to address low drug solubility in discovery and development. Pharmacol. Rev. 65, 315–499. doi:10.1124/pr.112.005660

Wlodarski, K., Tajber, L., Sawicki, W., 2016. Physicochemical properties of direct compression tablets with spray dried and ball milled solid dispersions of tadalafil in PVP-VA. Eur. J. Pharm. Biopharm. 109, 14–23. doi:10.1016/j.ejpb.2016.09.011

Worku, Z.A., Aarts, J., Singh, A., Van Den Mooter, G., 2014. Drug-polymer miscibility across a spray dryer: A case study of naproxen and miconazole solid dispersions. Mol. Pharm. 11, 1094–1101. doi:10.1021/mp4003943

Wu, B., Li, J., Wang, Y., 2016. Evaluation of the Microcentrifuge Dissolution Method as a Tool for Spray-Dried Dispersion. AAPS J. 18, 346–353. doi:10.1208/s12248-016-9872-7

Yanfei, M., Guoguang, C., Lili, R., Pingkai, O., 2015. Controlled release of ziprasidone solid dispersion systems from osmotic pump tablets with enhanced bioavailability in the fasted state. Drug Dev. Ind. Pharm. 41, 1353–1362. doi:10.3109/03639045.2014.950273

Yin, L., Hillmyer, M.A., 2014. Preparation and performance of hydroxypropyl methylcellulose esters of substituted succinates for in vitro supersaturation of a crystalline hydrophobic drug. Mol. Pharm. 11, 175–185. doi:10.1021/mp4003656

Yoshioka, M., Hancock, B.C., Zografi, G., 1994. Crystallization of indomethacin from the amorphous state below and above its glass transition temperature. J. Pharm. Sci. 83, 1700–1705. doi:10.1002/jps.2600831211

Yousefi, S., Emam-Djomeh, Z., Mousavi, M., Kobarfard, F., Zbicinski, I., 2015. Developing spray-dried powders containing anthocyanins of black raspberry juice encapsulated based on fenugreek gum. Adv. Powder Technol. 26, 462–469. doi:10.1016/j.apt.2014.11.019

Youssefi, S., Emam-Djomeh, Z., Mousavi, S.M., 2009. Comparison of artificial neural network (ANN) and response surface methodology (RSM) in the prediction of quality parameters of spray-dried pomegranate juice. Dry. Technol. 27, 910–917. doi:10.1080/07373930902988247

Yue, H., Nicholson, S.J., Young, J.D., Hsieh, D., Ketner, R.J., Hall, R.G., Sackett, J., Banks, E.C., Castoro, J.A., Randazzo, M.E., 2015. Development of a control strategy for benzene impurity in hpmcas-stabilized spray-dried dispersion drug products using a science-based and risk-based approach. Pharm. Res. 32, 2636–2648. doi:10.1007/s11095-015-1649-7

Graphical abstract
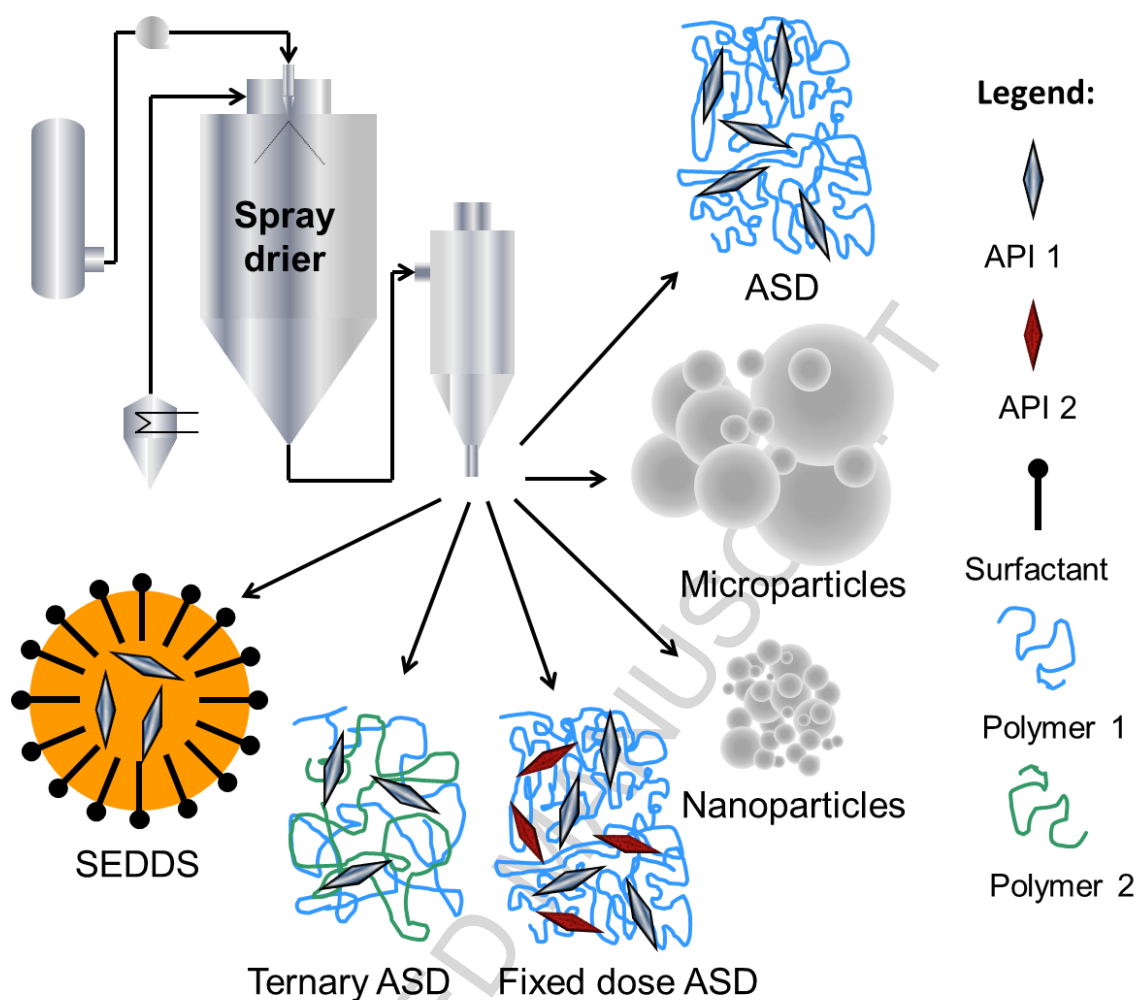
Schematic representation of amorphous solid dispersions (ASD), microparticles, nanoparticles, Fixed dose (ASD), Ternary ASD and Self-emulsifying drug delivery systems (SEDDS) prepared by spray drying. Active pharmaceutical ingredient (API) 1 and 2, surfactant and polymers 1 and 2 are illustrated in the legend.

List of abbreviations

AFM: Atomic force microscopy

ANN: Artificial neural networks

ANOVA: Analysis of variance

API: Active pharmaceutical ingredient

ASD: Amorphous solid dispersion

ATC: Atorvastatin calcium trihydrate

AUC: Area under curve

BCS: Biopharmaceutics classification system

BSA: Bovine serum albumin

DLS: Dynamic light scattering

DoE: Design of Experiments

DSC: Differential scanning calorimetry

DVS: Dynamic vapour sorption

FBRM: Focused beam reflectance measurement

FDC: Fixed dose combination

FTIR: Fourier transform infrared spectroscopy

GC: Gas chromatograpy

GCHS: Gas chromatography headspace autosampling

HETCOR: Heteronuclear correlation

HIV: Human immunodeficiency virus

HME: hot melt extrusion

HPC: Hydroxypropyl cellulose

HPLC: High performance liquid chromatography

HPMC: Hydroxypropyl methylcellulose

HPMC-AS: Hydroxypropyl methylcellulose acetate succinate

HPMCP: Hydroxypropyl methylcellulose phthalate

HSES: High speed electrospinning

IBC: Intermediate bulk container

ICH: International conference on harmonisation

LOD: Loss on drying

MAS: Magic angle spinning

MCC: Microcrystalline cellulose

MSM: Magnetic spray machine

NCE: New chemical entity

NCMP: Nanocomposite microparticles

NIR: Near infrared

NLC: Nanostructure lipid carriers

NMR: Nuclear magnetic resonance

PAMPA: Parallel artificial membrane permeability assay

PEG: Poly ethylene glycol

PHPMA: Poly(N-(2-hydroxypropyl)methacrylamide)

PLA: Polylactic acid

PLGA: poly(lactic-co-glycolic acid)

PSD: Particle size distribution

PVP: Poly vinylpyrrolidone

PVP-VA-64: Vinylpyrrolidone-vinyl acetate

PXRD: Powder X-ray diffraction

RH: Relative humidity

RSM: Response surface methodology

RSM: Response surface methodology

SD: Spray drying

SDD: Spray dried dispersion

SDS: Sodium dodecyl sulfate

SEDDS: Self-emulsifying drug delivery system

SEM: Scanning electron microscopy

SEM: Scanning electron microscopy

SLN: Solid lipid nanoparticles

SLS: Sodium lauryl sulfate

SMEDDS: Solid self-microemulsifying drug delivery system

SPIP: Single-pass rat intestinal perfusion

TEM: Transition electron microscopy

TGA: Thermal gravimetric analysis

USP: United States pharmacopeia

UV: Ultraviolet

WAXS: Wide-angle X-ray scattering

WHO: World health organisation

XRD: X-ray diffraction