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Particle design via spherical agglomeration: A critical review of controlling parameters, rate processes and modelling

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Abstract

Particle design via spherical agglomeration is a size enlargement technique used in various bulk and fine chemical industries, with recent interest extending into pharmaceuticals, in which an immiscible bridging liquid is added to agglomerate crystals prior to deliquoring. Spherical agglomeration has the potential to dramatically simplify downstream processing, and improves the handling of difficult, needle-shaped crystals. This review consolidates the understanding of the controlling process parameters, identifies the rate processes that control agglomerate attributes, and examines the modelling approaches taken in the literature to optimise the design of such systems. The most important controlling parameters are solvent system composition (requiring knowledge of the ternary phase diagram) and bridging liquid to solid ratio (BSR). Agglomerate size is a highly non-linear function of BSR with many literature systems showing qualitatively similar behaviour. However, there is no method to predict the optimum BSR. Other important process parameters are temperature, constituent particle properties, agitation rate and batch/residence time. Each parameter can have significant effects on the final agglomerate properties including agglomerate size, porosity, strength and dissolution profile.

The rate processes in spherical agglomeration are analogous to those in wet granulation. A general classification of rate processes is proposed in this review including nucleation by distribution or

immersion, consolidation, coalescence, layered growth and breakage. While many papers give proof of concept examples of spherical agglomeration for specific systems, only a few have focused explicitly on mechanistic understanding. There is significant scope for further work to quantify the effect of both process parameters and formulation properties on these rate processes. Recent developments in on-line monitoring using process analytical technologies (PAT) should enable these studies.

Using the mechanistic understanding, population balance models can be developed to include kernels for each of the relevant rate processes. Such models should be powerful tools of process optimisation and model driven design with reduced experiments at all scales.

Keywords

Spherical agglomeration; spherical crystallisation; agglomeration in suspension; spherical agglomeration mechanisms; modelling spherical agglomeration; continuous spherical agglomeration

1. Introduction

In this paper, we present a review of spherical agglomeration. Spherical agglomeration is one method of spherical crystallisation; a particle design technique where crystallisation and agglomeration occur simultaneously yielding agglomerated crystals in a compacted, spherical form. This route offers many advantages such as ease of active pharmaceutical ingredient (API) handling and improved tabletability, thus reducing the need for further downstream processing during pharmaceutical manufacture. Other spherical crystallisation methods exist such as quasi-emulsion solvent diffusion and ammonia diffusion. However, these methods are beyond the scope of this review.

Crystallisation is a widely-used process for the synthesis and purification of products and is used in many industries such as pharmaceuticals, food, chemicals, cosmetics and catalysis. The manufacture of most solid products involves at least one crystallisation step. As crystallisation is usually the first step during synthesis where pure solid is separated from liquid, it offers an opportunity to beneficially tailor the micromeritic properties (e.g. size, size distribution, surface area, morphology, polymorphic form) and the subsequent functional properties (e.g. strength, flowability, reactivity, solubility and dissolution profile) of crystals. The combination of micromeritic and functional properties will have an impact on the quality of the final product. Furthermore, the efficiencies of downstream processes (e.g. filtering, drying) will also be influenced by crystal properties. Therefore, the proper design and control of the crystallisation process is imperative for the manufacture of products with superior, tailor-made properties.

In many industries, the manufacture of the desired product usually involves multiple processing steps after initial crystallisation. For example, in the pharmaceutical industry, where tablets are the preferred dosage form, tablets are eventually produced after a series of unit operations: crystallisation; filtration; washing and drying; granulation and drying; and finally, tableting [1]. The properties of the crystals ultimately affect the efficiencies of each stage. For example, larger sized crystals often facilitate filtering, drying and handling whilst smaller sized crystals have superior biopharmaceutical properties. Crystals with low sphericity, such as needles, also present difficulties for downstream handling and processing. Larger sized, free flowing particles are also required for efficient tableting. Size enlargement is usually carried out by granulation, where fine particles are agglomerated together into larger entities [2]. This gives the particles improved mechanical properties such as compressibility and flowability; both of which are essential for effective tableting. However, the granulation stage, including a second drying step, results in increased manufacturing costs, as well as being time-consuming. Consequently, if the crystallised particles already possess these mechanical attributes, they can be directly tableted without the need for

further unit operations such as granulation, decreasing associated costs and time to market. Such process intensification is a strong focus of modern pharmaceutical engineering.

One avenue of research used to produce agglomerates with improved properties is spherical agglomeration. The process can consist of simultaneous precipitation and agglomeration or agglomeration in suspension (post-crystallisation) of primary crystals to form spherical particles with increased size. The concept of spherical agglomeration originated from studies performed in the 1960's and 1970's involving the selective agglomeration of a variety of materials including barium sulphate [3], calcium carbonate [4], graphite [5], coal [6] and sand [7]. More recently, the notion of spherical agglomeration has expanded into pharmaceuticals research [8]. Spherical agglomeration has several key benefits which are directly related to improving micromeritic and functional properties [9]. In the case of pharmaceutical products, there is no requirement for the addition of subsequent unit operations such as granulation, as crystallisation and agglomeration occur in the same process [10]. In this sense, the process is applicable to industries other than pharmaceuticals, such as agrochemicals and detergents, where granulation may be used [1]. The method has also been exploited in the food industry [11], in the selective recovery of fine mineral particles [12] and the de-inking of toner on printed paper for fibre recycling [13].

Many authors have reported improved properties of spherically agglomerated crystals over conventionally formed crystals. Zhang et al. [9] reported the improved properties of cefotaxime sodium agglomerates produced via spherical agglomeration compared to single crystals, including bulk density, flowability and compactibility. Similar improvements in properties using spherically agglomerated particles over conventional crystals have also been reported for salicylic acid [8,14], tolbutamide [15], buccillamine [16] and aceclofenac [17]. Maghsoodi [18] has suggested that stronger bonds are formed from agglomerated carbamazepine crystals under compression leading to increased tensile strength compared to single crystals. The higher tensile strength was a result of

agglomerate structure. Agglomerates consist of small particles giving a relatively large volume change under compression as a result of fragmentation; leading to an increased number of contact points giving enhanced inter-particle bonding and, therefore, increased strength. It has also been suggested by Jbilou et al. [19] that improved compressibility of agglomerates of ibuprofen compared to single crystals is associated with the isotropic texture of the agglomerates. In addition to their physico-mechanical properties, spherical agglomerates are also desirable for drug delivery as they can be designed to consist of small crystals with a high specific surface area. Consequently, they can demonstrate high dissolution rates and bioavailability. Improvements in the dissolution profiles for many drugs have been reported, including tolbutamide [15], aceclofenac [17], ketoprofen [20] and simvastatin [21]. Although spherical agglomeration offers many beneficial product qualities over conventional crystallisation, there are some disadvantages of the spherical agglomeration process over conventional methods. The selection of appropriate liquids for both precipitation and agglomeration can be quite complex for certain materials [22]. The optimisation of processing parameters can also be difficult and time consuming [23]. The removal of subsequent residual solvents in the final agglomerate particles may also be a concern, although studies in the literature have demonstrated that successful solvent removal through washing and drying is possible [9,24]. As such, it can be a tedious process to find suitable solvent combinations and operating conditions for successful spherical agglomeration.

1.1. The spherical agglomeration method

There are three common ways in which spherical crystallisation can be achieved; spherical agglomeration, ammonia diffusion (AD) and quasi-emulsion solvent diffusion (QESD) [25]. In all these methods, the initial crystallisation is carried out by dissolving the material of interest in a solvent and subsequently mixing with an anti-solvent. In the AD [26] and QESD [27] methods, quasi-emulsion droplets are formed where the solvent diffuses out of the droplets into the anti-solvent.

Simultaneously, the anti-solvent diffuses into the droplets, leading to crystallisation within the droplets. The residual solvent in the droplets acts as an agglomerating agent.

The spherical agglomeration method also employs 'good' solvents and anti-solvents for the direct crystallisation of the solid in solution. This is often referred to as either 'drowning out' or 'solvent change' where a miscible anti-solvent is added to reduce the solubility of the material to be crystallised, which is pre-dissolved in a solvent. However, in contrast to AD and QESD, the spherical agglomeration method involves the addition of a third liquid, the bridging liquid, which is immiscible with the anti-solvent and has a high affinity for the solid, to agglomerate the precipitated crystals. The bridging liquid is often added directly into the precipitating mixture, or can be present initially in one of the solvents. In agglomeration in suspension, it is subsequently added to the system after precipitation is complete. In such cases, precipitation may be carried out through any number of traditional techniques (e.g. cooling, evaporation, melting) [28]. The resultant product consists of compact, crystalline agglomerates. Fig. 1 shows images of primary crystals of salicylic acid (Fig. 1b) which have been spherically agglomerated using chloroform as the bridging liquid (Fig. 1a) [8].

Fig. 1. Spherical agglomeration of salicylic acid using chloroform as bridging liquid: (a) spherically agglomerated crystals (scale bar = 10mm), and (b) primary crystals without spherical agglomeration (scale bar = 200 μ m). Source: Kawashima et al. [8].

It should be noted that a further type of spherical agglomeration known as 'neutralisation' is often classed as a separate technique in the literature [29,30]. This technique is similar to spherical agglomeration in the sense that a bridging liquid is added to agglomerate the particles. However, in this method the primary crystals are produced by neutralisation of a basic solution containing the dissolved solid with acid, rather than solvent change. Primary crystals may also be initially produced from 'salting out' precipitation [31].

The choice of bridging liquid is important and depends upon the ability to wet the crystals of interest. There are some general rules suggested for solvent and bridging liquid selection [32,33] which are essentially dependent upon the miscibility of the good solvent, anti-solvent and bridging liquid and the contact angle between the bridging liquid and crystals. In addition to the choice of the solvent-bridging liquid system, there are many other operational parameters that must be considered which affect the precipitation and agglomeration rate and resultant particle properties. These include the solvent addition method, bridging liquid amount and addition method, agitation rate, temperature and residence time. A review of the effect of these formulation and process parameters is given in Section 3.

1.2. Structure of this review

This review explores spherical agglomeration, including a discussion of parameters which influence the product properties (Section 3), the rate processes identified in the literature (Section 4) and the current state of the modelling of the process (Section 5). The use of spherical agglomeration with excipients/additives (co-agglomeration) is reviewed in Section 6. We also compare the spherical agglomeration method with quasi-emulsion solvent diffusion, another method of spherical crystallisation, with regard to methodology and product properties (Section 7). Furthermore, a move from batch to continuously operating systems is addressed in Section 8.

Specifically, a critical review of the literature on spherical agglomeration will be given, with a strong emphasis on the rate processes that control the final agglomerate properties. A structure for defining these processes is proposed (Section 2), and recommendations for further studies to quantify the processes are given.

2. Rate processes

An understanding of the mechanisms involved in spherical agglomeration is paramount to being able to control and predict the properties of spherical agglomerates. The rate processes taking place have been proposed in early spherical agglomeration literature [34]. More recently, analogies have been made with the rate processes occurring during wet granulation [2]; from the initial wetting of particles to agglomerate growth and breakage [35–37]. Fig. 2 depicts our view of how these rate processes may be defined for spherical agglomeration.

Fig. 2. Rate processes and possible mechanisms occurring during spherical agglomeration.

As with granule nucleation, initial wetting of the crystals by the bridging liquid and agglomerate nuclei formation may follow one of two mechanisms [38]. When the bridging liquid droplets are smaller than the crystals, a distribution mechanism occurs where the droplets initially coat the crystals, followed by the formation of agglomerate nuclei. When the bridging liquid droplets are larger than the crystals, wetting follows an immersion mechanism where crystals cover the droplets and subsequently penetrate and fill the droplets giving agglomerate nuclei. Under further agitation, consolidation/compaction of these agglomerates occurs due to agglomerate-agglomerate/agglomerate-equipment collisions. This results in a decrease in agglomerate size and porosity. Here, no growth occurs due to the absence of readily available bridging liquid following agglomerate nuclei formation, and this may be referred to as the zero-growth regime [34]. However, eventually the bridging liquid will be squeezed out to the agglomerate surface allowing growth of the agglomerates by coalescence with other agglomerates or un-agglomerated primary crystals. Layering of agglomerates may also occur, where primary crystals adhere to the agglomerate surface [39]. Breakage and attrition of agglomerates may also take place simultaneously to growth due to shear forces and agglomerate-agglomerate / agglomerate-equipment impacts. Fragments and fines

resulting from breakage and attrition may also contribute to the growth mechanism, where they incorporate into the agglomerate via coalescence or layering [37]. Eventually, an equilibrium will be reached where the mean particle size remains unchanged, or may even reduce slightly due to further consolidation or attrition/breakage of the agglomerates.

These rate processes have been reported in the spherical agglomeration literature (Table 1), and will be reviewed in Sections 4 and 5. However, no prior studies have captured all the potentially relevant rate processes in their mechanistic map. It is important to correctly identify these processes in order that the most important phenomena are studied experimentally and modelled.

Table 1

Summary of experimental (E) and modelling (M) studies which specifically focus on identifying the rate processes occurring during spherical agglomeration.

Authors	Rate Process					Ref
	Agglomerate nuclei formation	Consolidation	Growth		Breakage	
			Coalescence	Layering		
Morishima et al. (1993)		√(E)	√(E)			[40]
Müller & Löffler (1996)	√(E)	√(E)				[41]
Blandin et al. (2003)		√(E)	√(E)	√(E)		[39]
Blandin et al. (2005)		√(E & M)	√(E & M)			[10]
Subero-Couroyer et al. (2006)	√(E)					[36]
Thati & Rasmuson (2011)		√(E)	√(E)	√(E)	√(E)	[37]

3. Parameters affecting the spherical agglomeration process

There is an abundance of spherical agglomeration literature which explores how formulation and operational parameters affect both precipitation and agglomeration and, therefore, the resultant agglomerate properties. A review of these parameters will be given in this section. However, these studies do not take a mechanistic approach to understanding the governing rate processes, specifically those which govern agglomeration behaviour. Rather, correlations between experimental conditions and product properties are discussed. However, their findings are important to further our understanding of the mechanisms and rate processes involved.

3.1. Effect of solvent system and addition methods

Spherical agglomeration of a specific material can only succeed by using certain combinations of solvents. Therefore, the solvent system for spherical agglomeration must be carefully selected to maximise the degree of crystallisation and agglomeration. It is imperative to spherical agglomeration to use solvents which have the required miscibility as stated in Section 1.1, as the technique is directly reliant upon miscibility. The relative concentration of the solvents is also important. The ternary phase diagram for the solvent/anti-solvent/bridging liquid system is a useful tool for selecting the appropriate compositions of solvents. For example, Zhang et al. [9] comprehensively assessed the solubility of the isopropanol-water-chloroform system for the spherical agglomeration of cefotaxime sodium through the construction of a phase diagram which provided a graphical representation of the relative solubility of both the solvents and bridging liquid (chloroform) used (Fig. 3). Ternary phase diagrams have also been constructed to aid studies of the spherical agglomeration of salicylic acid [8], tolbutamide [42], acebutolol hydrochloride [43], fenbufen [44], ketoprofen [20], benzoic acid [37], simvastation [21], and etodolac [24].

Fig. 3. Ternary phase diagram showing the solubility of chloroform in a 2-propanol/water mixture. Chloroform is miscible (M) in the region above the line and immiscible (I) below the line. The shaded region represents where spherical agglomeration occurs. Source: Zhang et al. [9].

Amaro-Gonzalez and Biscans [45] investigated a variety of different solvents as the bridging liquid for the crystallisation of lobenzarit disodium. The authors evaluated the wettability of lobenzarit particles with different solvents through a capillary rise technique (Washburn's test). Out of the potential bridging liquids investigated, it was proposed that n-hexane would be the most suitable wetting agent due to its lower contact angle with lobenzarit disodium. This selection of the bridging liquid was subsequently validated using spherical agglomeration experiments. Indeed, experiments using n-hexane produced larger, denser, well-shaped spherical agglomerates with a narrower size distribution suggesting that wettability via Washburn's method could be a good indicator for the choice of bridging liquid. A similar study by Thati and Rasmuson [46] investigated the effect of different bridging liquids on the spherical agglomeration of benzoic acid. It was found that yield, sphericity, strength, size and size distribution all varied depending on the bridging liquid used. The authors suggested that as well as low solubility of the bridging liquid in the anti-solvent, good wettability between the bridging liquid and benzoic acid was critical. Furthermore, the interfacial tension between the bridging liquid and the anti-solvent should be high.

There are various possibilities in which the components can be mixed together. For example, Kawashima et al. [14], in their study of the spherical agglomeration of salicylic acid, used two different procedures. Method one involved the addition of water to an ethanolic salicylic acid solution to initially precipitate the solid. After precipitation was complete, chloroform as bridging liquid was added to agglomerate the crystals. For method two, the ethanolic salicylic acid solution was added to a mixture of water and chloroform. Agglomerated crystals formed from method two were found to be more compact and spherical compared to those prepared from method one. Katta and Rasmuson [47], in their studies of the spherical agglomeration of benzoic acid, reported a larger fraction of spherical agglomerates when the bridging liquid is initially mixed into the precipitating

solvent system compared to when it is added after precipitation. Similar results were also reported by Wu et al. [48] where agglomerates of atorvastatin calcium agglomerated immediately when the bridging liquid was initially mixed into the drug solution, and the product evidenced improved flowability and compressibility compared to when it was added after precipitation.

In the same study using atorvastatin calcium, Wu et al. [48] also explored polymorphic transformation during the spherical agglomeration process using focused beam reflectance measurement (FBRM) and X-ray diffraction. It was concluded that the addition mode of the bridging liquid is important for the desired polymorph to be obtained. Sano et al. [42] suggested that the resulting polymorphic form of tolbutamide was dependent upon the solvent composition at the time of nuclei formation. In their study of the spherical agglomeration of tranilast, Kawashima et al. [49] also reported the effect of solvent composition on the polymorph formed.

Some studies have investigated how the feed rate of a suspension alters crystallisation behaviour and the resulting spherical agglomerates. For example, in their study of the spherical agglomeration of benzoic acid, Thati and Rasmuson [37] studied the effect of the addition rate of an ethanolic benzoic acid solution containing the bridging liquid, toluene, into the anti-solvent (water). They found that agglomerate size decreases with increasing feed rate. The same observations were also noted by Kawashima et al. [50] during a continuously operated system for the agglomeration of sulfamethoxale. The smaller size was attributed to the increased supersaturation achieved by the higher feed rate. Subero-Couroyer et al. [36] also observed a decrease in agglomerate size with faster injection times of chloroform bridging liquid into a suspension of pre-formed salicylic acid crystals. In combination with high stirring rates, the faster injection time favoured an increase in the dispersion of the bridging liquid into small droplets. This led to an increased number of smaller agglomerate nuclei, ultimately leading to small final agglomerates.

3.2. Effect of temperature

It is well known that temperature has a significant effect on the nucleation and growth of crystals [51] as it dictates the level of supersaturation in the crystallising system. Consequently, the temperature will influence the initial crystallisation and subsequent properties of the primary particles during the spherical agglomeration process. Furthermore, the temperature will also affect the relative solubility of different components in the spherical agglomeration system and, therefore, their availability in the system. Thus, temperature changes can influence the agglomeration process.

Kawashima et al. [35] carried out a study into the effect of temperature on the spherical agglomeration of salicylic acid using an ethanol–water–chloroform solvent system. It was found that the temperature had a significant effect on the agglomerate size. With an initial increase in temperature there was a decrease in agglomerate size. Then, with further increases in temperature, the size of the agglomerates increased, along with the size variation. These changes were attributed to both changes in the solid and bridging liquid solubility in the system. As the temperature increased, the solubility of chloroform decreased slightly. However, the amount of product precipitated significantly decreased. Therefore, the amount of chloroform available for agglomeration apparently increased, resulting in larger agglomerates at higher temperature. The constituent particle size within the agglomerates was seen to increase with increasing temperature. It was suggested that smaller particles require less bridging liquid for agglomeration than larger particles, and it was thought that the relatively smaller amount of chloroform available at the lower temperature would still be sufficient to efficiently agglomerate these smaller particles, leading to the increase in agglomerate size at lower temperature. This theory has also been used to describe the increase in the size of carbamazepine agglomerates at lower temperatures reported in a more recent study by Maghsoodi [52]. Both authors also noted a decrease in agglomerate bulk density and sphericity with an increase in temperature.

Thati and Rasmuson [46] found that increasing the temperature also caused a reduction in the yield of benzoic acid agglomerates due to the increased solute solubility. Over the temperature range studied, they noted a decrease in final agglomerate size with increasing temperature. Similar observations in cefotaxime sodium agglomerate size and yield with changes in temperature were also reported by Zhang et al [9]. As reported in the study by Kawashima et al [35], Thati and Rasmuson [46] also observed an increase in constituent crystal size with increasing temperature. They suggested that this was a result of lower solute solubility at lower temperature. Thus, a higher supersaturation promotes nucleation yielding smaller crystals at lower temperatures, whilst high temperatures result in lower supersaturation favouring crystal growth.

3.3. Effect of the amount of bridging liquid

The amount of bridging liquid added to the spherical agglomeration system can have a significant impact on the process, and it has often been stated as being the most influential parameter affecting the final product [9,36,39,47,48]. Indeed, the importance of the amount of bridging liquid was specifically highlighted in a study by Blandin et al. [39] during an investigation into the effect of operating parameters on final agglomerate mean size. It was found that the coefficient of variation of the final agglomerate size distribution could be summarised through empirical equations relating to solids concentration, bridging liquid to solid ratio and agitation rate. From these equations, it was possible to adequately predict the final agglomerate size regardless of the operating conditions. Moreover, the equations suggest that the bridging liquid to solid ratio is the most significant parameter of the agglomeration process.

During early studies by Kawashima et al. on the spherical agglomeration of lactose [53], salicylic acid [8] and sodium theophylline [31,54], the authors observed an increase in agglomerate size with increasing bridging liquid fraction. This is thought to be due to the increased probability of cohesion of particles leading to larger agglomerates. This finding has also been reported more recently by

many authors [36,39,45,46,48]. In these studies, the bridging liquid content is usually quantified as the volume of bridging liquid to volume of solid ratio (BSR). The BSR range is highly dependent on the system of study, and is found empirically. It has been shown that there is a critical range for the BSR. Below this range, there is no significant agglomeration, and above this range a paste-like product is produced [55,56]. Only within this range is the agglomeration process efficient. Fig. 4 shows a schematic of the evolution of agglomerates as the BSR is increased. When the BSR is significantly below the critical ratio (BSR_{crit}) agglomerates will start to form, although there will still be single crystals present in suspension (Fig. 4a). As the BSR approaches the BSR_{crit} , the agglomerates are more firmly held together and further particles adhere to the agglomerates with the disappearance of the single crystals (Fig. 4b). At a BSR above the BSR_{crit} (Fig. 4c) a bridging liquid layer forms around the agglomerates. At a higher BSR (Fig. 4d) the bridging liquid layer reaches a maximum. At BSRs higher than this, excess bridging liquid will be present and individual droplets will form in the suspension (Fig. 4e). Finally, at extremely high BSRs, agglomerates will behave in a soft, paste-like manner (Fig. 4f).

Fig. 4. The formation of agglomerates as the bridging liquid to solid ratio (BSR) is increased. Source: Peña and Nagy [56].

Within the critical BSR range, Blandin et al. [39] reported that the size of the final agglomerates of salicylic acid significantly increased with increasing BSR. This finding has also been observed in studies by Subero-Couroyer et al. [36], Thati and Rasmuson [37,46] and Bos and Zuiderweg [57]. It was found that increasing the BSR leads to higher agglomerate deformability. This results in more energy dissipation during collisions and an increase in agglomeration efficiency, ultimately yielding larger agglomerates [36]. Furthermore, Thati and Rasmuson [37] noted an improvement in agglomerate morphology as the BSR increases, yielding highly spherical agglomerates. They also

reported an increase in agglomerate strength with increasing BSR. Subero-Couroyer et al. [36] found that increasing the chloroform fraction within the critical range produces a narrower size distribution of salicylic acid agglomerates. This agrees with earlier results obtained by Kawashima et al. [31] when increasing the bridging liquid fraction of the system above a certain concentration.

The influence of the BSR may also be likened to the effect of binder to solid ratio in granulation. If insufficient binder is present, little or no granulation will occur. However, if too much binder is present, a slurry will result. As with the critical BSR range in spherical agglomeration, in a critical range of binder-solid ratio it has been shown that the mean granule size increases rapidly with increasing binder content. In wet granulation, it has been shown that pore saturation is the critical factor [58]; i.e. the degree of intra-granular voids filled with the binder phase. Fig. 5a shows calcium hydrogen phosphate growth curves using a range of different binders; all of which collapse onto one curve regardless of the binder used. This may also be the case for the effect of BSR in spherical agglomeration. Fig. 5b shows that similar trends in the increase in agglomerate size as a function of BSR within the critical range are observed for the systems studied here. However, they are quantitatively different and, consequently, a barrier to prediction design. Therefore, an interesting avenue of future research could be to further explore and compare the relationship between agglomerate pore saturation and agglomerate size for different bridging liquid – crystal systems.

Fig. 5. (a) Granule growth as a function of pore saturation for calcium hydrogen phosphate using a range of different binders. Source: Iveson et al. [2]. (b) Agglomerate size as a function of bridging liquid to solid ratio for different spherical agglomeration systems: o CaCO_3 /kerosene [57]; Δ salicylic acid/chloroform [39]; x benzoic acid/toluene [37]; - lozbenzarit disodium/hexane [45]; + atorvastatin calcium/dichloromethane [48].

3.4. Effect of the initial precipitated particles on agglomeration

The effect of initial particle concentration on spherical agglomeration has been studied by Blandin et al. [39] for their salicylic acid system. Below a certain concentration of solid (C_s), the higher the C_s , the faster the agglomeration process, with an increase in final agglomerate size. Above this, there appeared to be no change in the final agglomerate size. This finding was also reported in a study by Katta and Rasmuson [47]. Furthermore, the porosity of the final product decreased with increasing solids concentration. The authors, therefore, implied that increased agglomerate collisions contribute to the agglomerate compaction process. Peña et al. [59] found that a high concentration of solids did not yield efficient agglomeration, or operation, for their benzoic acid system using a continuous oscillatory flow baffled crystalliser; requiring operating conditions that significantly differed from previous benzoic acid studies in various systems to achieve spherical agglomeration [37,46,56].

Other studies have investigated the influence of the initial size and morphology of crystals and their influence on the final size of spherical agglomerates. Subero-Couroyer et al. [36] conducted a study comparing commercially available salicylic acid particles with precipitated particles. As well as being significantly larger than the precipitated particles, the commercial particles also exhibited more of an acicular morphology compared to the precipitated crystals. The agglomeration process was not as efficient for the commercial particles, where the agglomerates produced were smaller and less spherical. This was attributed to the fact that acicular particles are more difficult to pack together than isotropic particles. Furthermore, a larger initial particle size results in a lower surface area which increases agglomerate deformability and reduces coalescence efficiency during the agglomerate growth stage. The effect of initial particle size has also been conducted by Kawashima et al. [53] for lactose agglomeration and similar conclusions were drawn. Kawashima and Capes [7] also reported that smaller particles required a lower amount of bridging liquid for agglomeration leading to larger agglomerates. It was suggested that the adhesive force between the bridging liquid

and small particles is stronger compared to that of larger particles. These studies highlight how product properties can be significantly influenced through the initial crystal size and morphology.

3.5. Effect of agitation rate and residence time

The agitation rate of the system during spherical agglomeration can directly influence the agglomerates formed through the level of hydrodynamic forces produced. The agitation speed must be sufficient to allow adequate mixing of the system. Furthermore, increasing the speed of agitation promotes agglomerate collisions which could significantly increase agglomerate growth. However, too much agitation can also lead to the disruption of coalescence and the breakage of agglomerates. Consequently, studies which investigate the effect of agitation rate often report an increase in agglomerate size up to a certain agitation rate, followed by a decrease in size after this point [47,60]. Therefore, an optimum agitation rate is often sought to give the desired agglomerate size, and this is largely conducted through trial and error.

The initial mixing in the spherical agglomeration process is an important step. Subero-Couroyer et al. [36] reported that agitation rate influences the bridging liquid droplet dispersion and size, with an increase in agitation rate giving smaller droplet sizes. Higher agitation rates may also affect the dispersion of initially formed particles and agglomerates. Too low an agitation rate could lead to flocculation in the absence of a bridging liquid. Amaro-Gonzalez and Biscans [45] reported that the probability of collisions between crystal particles and bridging liquid droplets is promoted at higher agitation rates. However, very high agitation rates can lead to very short contact times. Furthermore, in a study conducted by Wu et al. [48] it was observed that the minimum bridging liquid to solid ratio decreased with increasing agitation speed, suggesting that less bridging liquid is required to obtain agglomerates at higher agitation rates. This was due to a more homogeneous dispersion of the bridging liquid in the suspension at higher agitation rate, increasing the chance of a particle being wetted by a bridging liquid droplet.

Agglomerate evolution and growth is significantly influenced by the agitation rate. Up to a certain rate, an increase in agitation rate is reported to increase the chances of agglomerate-single particle and agglomerate-agglomerate collisions and, therefore, coalescence. Thus, an increase in agglomerate size is observed within this relatively low range of agitation rate [47,60]. After this point the agglomeration process becomes less efficient due to increasing disruptive shear forces; this increases the likelihood of colliding agglomerates being sheared before coalescence is complete, and can even induce breakage to agglomerates that have already formed. Therefore, a decrease in agglomerate size with agitation rate is observed at relatively high ranges of agitation rates [8,9,17,39,52,60,61]. Zhang et al. [9] also reported broader agglomerate size distributions with increasing agitation speed for their cefotaxime sodium system. This was attributed to the additional presence of smaller agglomerates, unable to grow due to high agitation.

The agitation rate has also been reported to influence agglomerate porosity and compressive strength. Blandin et al. [39] reported that an increase in stirrer speed led to a decrease in agglomerate porosity, giving denser agglomerates with greater compressive strength. The decrease in porosity of agglomerates with increasing agitation speed has been attributed to higher shear forces aiding compaction of the agglomerates [52]. Compaction and consolidation will also lead to a reduction in agglomerate size [9]. Improved sphericity and, therefore, flowability with increasing shear rate has also been reported [17].

In addition to agglomeration, the agitation rate will also affect the crystallisation conditions, influencing the nucleation and growth rate of the primary crystals to be precipitated; higher agitation rates encourage nucleation and lead to formation of smaller primary crystals [51].

Another important parameter affecting spherical agglomeration product properties is the residence time of the agglomerates, i.e. duration under agitation. Kawashima et al. [62] reported that the size of agglomerated crystals of aminophylline increased gradually with residence time and, after a certain time, an equilibrium state was attained. A similar observation was noted by Morishima et al. [40] with an increase in agglomerate size with increasing agitation time due to continued coalescence. Blandin et al. [39] described changes in the porosity in salicylic acid agglomerates as the residence time increased. As the agglomerates grew, their porosity decreased and they became more spherical. This was attributed to compaction via agglomerate-agglomerate collisions or agglomerate-vessel collisions, due to the continued agitation of the system. The compaction process also gives the agglomerates increased compressive strength. Similar observations regarding agglomerate size, sphericity and strength with continued agitation after the completion of feeding were also reported by Thati and Rasmuson [46] in their study on the spherical agglomeration of benzoic acid. An increase in buccillamine agglomerate density with agitation time was also noted by Morishima et al. [40].

4. Kinetics and Mechanisms

As discussed previously, much of the spherical agglomeration literature focuses on how formulation and operational parameters affect the properties of the agglomerates formed (e.g. size, size distribution, sphericity, porosity) and their subsequent strength, flowability, tabletability and solubility. These studies, while highlighting the improved properties of products formed by spherical agglomeration, have generally been carried out on an experimental 'trial and error' basis to achieve the desired product, and there are limited attempts to specifically elucidate the actual mechanisms of the process. However, there have been several studies which have offered insights into the mechanisms of spherical agglomeration. An understanding of the rate processes is imperative to control and predict the properties of the product.

Possible rate processes occurring during agglomeration were proposed in an early study by Bemer [34] when agglomerating glass in carbon tetrachloride using water-glycerol mixtures as the bridging liquid. Bemer suggested four main regimes which contribute to the agglomeration process; flocculation, zero growth, fast growth and the equilibrium regime. The flocculation regime refers to the formation of loose flocs of particles initially created by the addition of bridging liquid. During the zero growth regime, immediately following the flocculation regime, the particle mean size remains unchanged largely due to the reduced availability of bridging liquid following flocculation. The zero growth regime can vary depending on the agglomeration system (compound, solvents) and the operating conditions. The zero growth regime is followed by a fast growth regime, where loose flocs are transformed into closely packed pellets by consolidation and further agglomeration occurs via coalescence due to bridging liquid moving to the surface of the flocs (as proposed in granulation). Finally, an equilibrium is reached in which the mean size remains unchanged or reduces slightly due to further consolidation.

Some early studies conducted by Kawashima et al. have attempted to quantitatively study the process by which agglomerates are formed, particularly the kinetics. Kawashima and Capes [63] explored the kinetics of the spherical agglomeration of sands dispersed in carbon tetrachloride using calcium chloride as the bridging liquid. It was found that agglomerate growth could be described by first order kinetics. This indicates that particles are limited in movement during their growth; a consequence of aggregation due to the bridging liquid and a relatively high solids concentration. Thus, it has been postulated that growth proceeds via a layering mechanism. Other studies have also concluded similar kinetics [7,31,35,64] with the rate constant being a function of the agitation rate, primary particle size and concentration of bridging liquid, for example. A further study by Kawashima et al. [53] agglomerated lactose dispersed in chloroform using saturated aqueous lactose solution as the bridging liquid. A quantitative correlation between agglomerate size and the physico-chemical properties of the bridging liquid (contact angle with particles and interfacial tension with the

dispersing medium) was obtained, which could account for the effect of bridging liquid quantity and primary particle size.

More recent studies of spherical agglomeration have involved specifically designed experiments to probe the process in more detail and propose mechanistic theories. An important aspect of the mechanism of spherical agglomeration is the wetting phase; this being the first stage of agglomeration where particles interact with the bridging liquid. As previously mentioned in Section 3, selection of an appropriate bridging liquid is important. In a study by Amaro-Gonzalez and Biscans [45], bridging liquid wettability was measured using the capillary rise method. This was found to be a good indicator for bridging liquid selection. Furthermore, the authors proposed two possible mechanisms for particle-bridging liquid interaction and subsequent agglomerate formation, depending on the relative size of the droplets and the crystals: (i) when droplets are smaller than the particles, a distribution mechanism occurs where the liquid droplets coat the particles leading to formation of agglomerates, and (ii) when the liquid droplets are larger than the particles, an immersion mechanism occurs in which the particles enter the droplet to form agglomerates (Fig. 2). These observations were also noted by Muller and Loffler [41] when agglomerating limestone with kerosene. These mechanisms are analogous to the proposed nucleation mechanisms taking place during granulation [2] where the immersion mechanism leads to formation of more spherical and denser agglomerates with a narrower particle size distribution compared to those formed by the distribution mechanism.

The above rate processes have also been proposed by Subero-Couroyer et al. [36]. In their studies, the wetting period was investigated using image analysis techniques. Initial experiments employed a specifically designed visualisation flow cell located under an optical microscope to observe interactions between a bridging liquid drop (chloroform) and particles (salicylic acid); with the size of the droplets considerably larger than the particles. Particles were observed to enter the bridging

liquid droplets; due to the high particle-droplet affinity and the impact energy between the particles and the droplet in the flow cell. This is characteristic of the immersion mechanism (Fig. 2), agreeing with the observations reported by Muller and Löffler [41]. Further experiments were also carried out using the same materials in a stirred vessel and the wetting phase was observed using an image acquisition probe. When visualising droplets alone at various agitation rates, as expected, the droplet size decreased with increasing agitation rate; potentially providing a larger surface of bridging liquid available for contact with particles. However, all agitation rates evidenced wide size distributions. Prior to agglomeration, particles were also characterised and, although the mean size of the mono-particles was approximately $5\mu\text{m}$, there was a strong tendency for the particles to aggregate and form flocs. Subsequent analyses attempted to visualise interactions between the bridging liquid droplets and particles/particle flocs. There was some evidence of bridging liquid droplets present among flocs, giving a loose network of flocs/droplets, and penetration of particles/flocs into bridging liquid droplets. However, distinguishing between drops and particles was reported by the authors to be difficult. There was also a tendency for the bridging liquid to stick to the analysis probe, making visualisation further problematic and, therefore, making it impossible to draw conclusions. The authors suggest further work using the visualisation cell to investigate interactions between flocs and droplets. Agglomerates were collected after the experiments, dried and visualised by optical microscopy off-line. It was found that agglomerate size increases with the square of the bridging liquid to solid volume ratio. Furthermore, a well-dispersed bridging liquid, which can be attained through increased agitation, favoured smaller agglomerates and a faster rate of agglomeration.

Formation of bridging liquid bridges between particles could play an important role on agglomeration rate processes. Rossetti and Simons [65] and Rossetti et al. [66] adopted a microscale approach to study liquid bridge geometry and strength between particles using a novel device (micro force balance). In their work, the behaviour of liquid bridges (silicone oil) formed between pairs of

particles (glass ballotini; 80-130 μm) submerged in water was investigated and compared with predicted theory. The geometry and force exerted by the liquid bridge can be theoretically predicted by calculation of the pressure variation across the liquid bridge interface. This agreed well with experimental results. This type of study could prove to be useful when investigating the effect of particle and bridging liquid properties on the spherical agglomeration process for different systems. Despite the demonstrated importance of this wetting and 'nucleation' stage of the agglomeration process, few papers on spherical agglomeration measure or record the initial drop size of the bridging liquid, or the contact angle and interfacial energies between the solid and two liquid phases. While the mechanisms for wetting are well described qualitatively, in contrast to wet granulation, quantitative, generalisable recommendations for design in terms of dimensionless groups and regime maps are not available [2,67,68].

After the initial wetting period and the formation of agglomerate nuclei, spherical agglomerate evolution is thought to occur via compaction and coalescence mechanisms. Blandin et al. [10,39] used a novel image analysis technique, combined with off-line characterisation techniques, to monitor the spherical agglomeration process in-situ. In their study, they used chloroform to agglomerate salicylic acid particles. During the wetting period, the bridging liquid agglomerated all the particles to form nuclei or flocs. A decrease in particle size was subsequently observed due to compaction of flocs. During their work on the spherical agglomeration of calcium carbonate with kerosene, Muller and Loffler [41] observed that branched flocs, formed initially via a distribution mechanism, break down into smaller compact flocs which subsequently grow to produce spherical agglomerates (Fig. 6). In the study by Blandin et al. [39] it was noted that the mean size quickly reached a minimum and subsequently agglomerates grew via coalescence. Growth of agglomerates was rapid initially before the mean size plateaued and the distribution became narrower. It was also noted that fine particles present at the start of the process disappeared completely indicating that the agglomeration kinetics of fines are higher than that of larger particles. Although not discussed by

the authors, this could be a result of their very high surface area to volume ratio making it easy for them to be incorporated into the droplets via an immersion mechanism. Thati and Rasmuson [37] suggested that agglomerate breakage may also contribute to the process at high agitation rates and fragments may be incorporated into agglomerates. However, there are conflicting views on whether breakage phenomena exist for spherical agglomeration processes. Due to the deformable nature of the agglomerates upon initial wetting, disruptive forces during coalescence due to shear are more likely than breakage of agglomerates [10]. Furthermore, Blandin et al. [39] demonstrated that the compressive strength of dried agglomerates was significantly higher than that of agglomerates in liquid suspension. Due to the volatility and slight solubility of the compound in the bridging liquid, liquid bridges which bind the wet agglomerates are replaced by solid crystalline bridges during the drying process due to evaporation of the bridging liquid [69].

Fig. 6. Images of flocs formed at different stages of the agglomeration process. Source: Muller and Loffler [41].

Blandin et al. [39] also conducted structural analysis of the agglomerates using optical microscopy. Images showed that agglomerates consisted of tightly piled up primary particles. It was proposed that the structure could be due to either a 'compaction and rearrangement' mechanism or an 'adhesion' mechanism. With the compaction and rearrangement process, agglomerates will be deformed and compacted where primary particles can be organised in a compacted manner producing highly spherical agglomerates with a decrease in porosity. In contrast, if the adhesion mechanism is dominant, layers should be present in the structure delimited by porous/breakable areas. Indeed, this was seen to be the case in their studies as successive layers of smaller agglomerates were observed using SEM cryomicroscopy. Furthermore, the agglomerates fractured easily.

In addition to initial wetting, analogies to the wet granulation rate processes [2] have also been made for the growth and evolution of agglomerates during spherical agglomeration. Thati and Rasmuson [37], in their study of the spherical agglomeration of benzoic acid, describe how bridging liquid rich agglomerates collect and bind particles via capillary forces. Agitation results in the consolidation of the agglomerates leading to a reduction in size and porosity. The bridging liquid is forced out to the agglomerate surface, resulting in further agglomerate growth via coalescence. The similarities between spherical agglomeration and granulation rate processes have also been reported in studies involving the spherical agglomeration of salicylic acid [35,36]. A comparable mechanism has also been reported by Morishima et al. [40] who suggest that microcrystals initially form loose agglomerates held together in the funicular state and can coalesce with small agglomerates or single crystals. With further agitation, the ratio of bridging liquid in the agglomerates increases under shear force, allowing the agglomerates to achieve the capillary state. Larger agglomerates are subsequently formed via coalescence with a slight increase in density. In a further comparison to granulation, Thati and Rasmuson [37] also propose the possibility of a 'layering' mechanism involving the attachment of fines and single crystals to the agglomerate surface. A layering-type mechanism had also been suggested earlier by Kawashima et al. [31,64].

In traditional wet granulation processes, a regime map approach has been taken to describe and predict granulation mechanisms. For example, the regime map for the immersion nucleation process (Fig. 7) uses two dimensionless groups to describe granule nuclei formation [2,67]. On the y-axis, the dimensionless drop penetration time (τ_p) is used (Eq. (1)). This parameter gives the ratio of the estimated penetration time (t_p) of a droplet into a bed of powder to the expected time for this powder to pass back through the wetting zone (the circulation time, t_c):

$$\tau_p = \frac{t_p}{t_c} \quad (1)$$

$$t_p = 1.35 \frac{V_o^{2/3}}{\epsilon^2 R_{pore}} \frac{\mu}{\gamma_{LV} \cos \theta_d} \quad (2)$$

where V_o is the drop volume, ϵ is the porosity of the powder bed, R_{pore} is the radii of the pores, μ is liquid viscosity, γ_{LV} is the surface tension of the liquid and θ_d is the dynamic contact angle of liquid in the solid capillary. On the x-axis, the dimensionless spray flux (Ψ_a) is used (Eq. (3)). This parameter quantifies important processes variables in the nucleation zone, and is a measure of the area wetted by droplets compared to renewal flux of powder traversing the spray zone;

$$\Psi_a = \frac{3\dot{V}}{2\dot{A}d_d} \quad (3)$$

where \dot{V} is the volumetric spray rate, d_d is the droplet diameter and \dot{A} is the area flux of powder across the spray zone. In this way, the regime map can be used to predict nuclei properties as a function of formulation and operating variables. For example, drop controlled nucleation (when one drop of binder produces one granule nucleus) is expected to occur when the dimensionless spray flux is low and the droplet penetration time is fast. This leads to a narrow nuclei size distribution. If either of these conditions is not met, a broader size distribution will result, and good mechanical mixing is required for good binder dispersion. In contrast to immersion, the distribution mechanism for granule nucleation is less well understood. Recent work has validated a parameter which estimates the fractional coating of particles passing through a liquid spray, through the use of the particle coating number [68]. The particle coating number (Φ_p) and the fractional particle coating (F) are described in Eq. (4) and Eq. (5) respectively;

$$F = 1 - \exp(-\Phi_p) \quad (4)$$

$$\Phi_p \equiv \frac{Na_d}{A_p} = Nf \quad (5)$$

where, N is the number of droplets, a_d is the footprint area of a droplet, A_p is surface area of the particle and f is the fractional coverage of the particle. This is one step towards quantifying the distribution rate process. However, more work is required in this area. Furthermore, there are several papers that have been published which study the granule growth mechanism in isolation (for example, [70-74]). It has been shown that the Stokes deformation number (St_{def}) is an important

dimensionless group for predicting granule coalescence [70]. St_{def} is a descriptor for the expected deformation of particles in a granulator, and defined in Eq. (6);

$$St_{def} = \frac{\rho U^2}{2Y} \quad (6)$$

where ρ is the granule density, U is the average relative granule collision velocity and Y is the granule dynamic yield strength. St_{def} has also been shown to be a reasonable indicator for granule breakage [75]. However, literature on breakage in flocculation processes, e.g. [76-78], may be a better starting point for understanding breakage during spherical agglomeration.

The method of using dimensionless groups and regime maps has proved to be a valuable tool in describing and predicting the granulation process. Accordingly, there is enormous potential to apply this approach to develop the understanding and prediction of the spherical agglomeration process.

Fig 7. An example of a regime map used to predict granulation; in this case, granule nucleation. Source: Iveson et al. [2].

The relatively small group of mechanistic studies relating to spherical agglomeration described in this review have largely focused on a single model system (Table 2) and investigated the effect of operating variables on the rate processes. A complete mechanistic picture needs to consider both formulation properties and process conditions to be useful for predictive process and product design.

Table 2

Examples of systems used for studying rate processes.

System (material / bridging liquid)	Study	Reference
Salicylic acid / chloroform	Agglomerate formation and growth observed in-situ by image analysis. Effect of process parameters (solids concentration, agitation rate, bridging liquid-solid ratio) on agglomeration kinetics, size, structure and mechanical properties of agglomerates.	[39]
	Novel visualisation technique developed to analyse ex-situ wetting between bridging liquid droplets and particles. In-situ visualisation technique designed to observe particles, bridging liquid droplets and agglomerates in a reactor. Effect of agitation rate and bridging liquid quantity on agglomerate size.	[36]
Benzoic acid /toluene	Effect of bridging liquid amount and feed rate on agglomerate size distribution, morphology and mechanical properties. Measurements of agglomerate properties during the course of the process used to identify mechanisms of agglomerate formation.	[37]
Bucillamime / dichloromethane	Effect of bridging liquid quantity and agitation rate on agglomerate size and mechanical properties – to investigate the coalescence mechanism.	[40]
Calcium carbonate / kerosene	Wetting of particles to form flocs. Effect of process parameters (stirrer speed, solids concentration, bridging liquid droplet size) on floc size and shape – determined using image analysis combined with Fourier analysis.	[41]

5. Modelling of spherical agglomeration

Several modelling approaches have been developed for spherical agglomeration systems. Many of the initial modelling studies have focused on agglomeration in suspension systems to reduce the complexity of the problem; focusing solely on developing more accurate and physically relevant agglomeration kernels. However, the first few modelling studies made first order approximations for the growth kinetics of their agglomeration processes [7,31,57,63]. These approaches did not differ from crystallisation kinetics in that growth was estimated as a growth rate (length/time) as opposed to an agglomeration rate (based on an agglomeration kernel/rate). Growth rate approximations

alone do not truly describe the agglomeration phenomena. The modelling studies discussed henceforth extend the initial modelling work and focus on the development of agglomeration kernels and population balance models that improve the predictability of the spherical agglomeration process.

5.1 Modelling agglomeration in suspension processes

Bemer [34] studied the spherical agglomeration of powdered glass from both an experimental and modelling perspective. Based on the previously mentioned experimental observations, a population balance model was developed to predict the changes in the agglomerate size distribution (ASD). Bemer [34] found that when following traditional granulation (agglomeration via coalescence/consolidation only) population balance models, the ASD was predicted to continuously increase; contradictory to experimental observations. To overcome the inaccuracies of coalescence only models, Bemer [34] developed a model that included coalescence from collisions, growth mechanisms (e.g. layering) and breakage mechanisms (e.g. crushing). Referred to as the coalescence-breakage model, the coalescence term was redefined from a coalescence frequency and efficiency model; the model worked well at predicting steady-state ASDs. However, the suggestion that there is a breakage mechanism during spherical agglomeration has yet to be validated experimentally and cannot be generalised to all systems.

Bemer's [34] experimental and modelling studies were agglomeration in suspension processes with no crystal growth or nucleation to be considered. However, as spherical agglomeration expanded to crystallisation systems the added complexity of nucleation, growth and agglomeration occurring simultaneously required innovative model development and further understanding of the interplaying kinetics. David et al. [79] began tackling this issue by formulating an agglomeration rate kernel that incorporated particle concentration, supersaturation, energy dissipation, crystalliser size and the size of agglomerating crystals. David et al. [80,81] followed their initial work by then

developing a multi-layer agglomeration model that considers the efficiency of agglomeration based on the collision mechanism (i.e. Brownian, laminar, or turbulent).

$$\beta_{i,j,b} = k_{Ab} G \frac{(S_i + S_j)^2}{S_i S_j} \quad (7)$$

$$\beta_{i,j,l} = k_{Al} G (S_i + S_j)^3 \left(\frac{P}{\nu}\right)^{1/2} \quad (8)$$

$$\beta_{i,j,t} = k_{At} G \frac{(S_j + S_i)^2}{S_j} f\left(\frac{S_i}{S_j}\right) ND \left(1 - \frac{(S_j + S_i)^2}{\lambda_c^2}\right) \quad (9)$$

$\beta_{i,j,b}$, $\beta_{i,j,l}$, and $\beta_{i,j,t}$ are the agglomeration rates at the Brownian, laminar, and turbulent scales, respectively. k_{Ab} , k_{Al} , k_{At} , are the agglomeration rate constants at the Brownian, laminar and turbulent scales, respectively. In Eq. (7-9), G is the growth rate and S_i (S_j) is the size of agglomerating particles. In Eq. (8), P is the dissipated power per unit mass and ν is the kinematic viscosity. In Eq. (9), f is the Marchal's relative size function, N is the stirring speed, D is the particle diffusivity, and λ_c is the Taylor microscale. As per David et al. [79-81], Brownian collisions occur at or below the Batchelor microscale, laminar collisions occur above the Batchelor microscale and below the Kolmogorov microscale, and turbulent collisions occur between the Kolmogorov and Taylor microscale. As particles increase in size, their collision mechanism (microscale/flow field) changes from Brownian (Eq. (7)) to laminar (Eq. (8)) to turbulent (Eq. (9)). Above the Taylor microscale, Eq. (9) reduces to zero as the size of agglomerates becomes too large and the system is too turbulent to produce a successful agglomeration event. The agglomeration rate kernels accounted for changes in the collision mechanism and were a function of the supersaturation and temperature through the growth rate which served as the efficiency term. Agglomeration is enhanced by inter-particle growth or agglomerative bond formation; when supersaturation increases, the strength of the liquid bridge between two particles increases leading to subsequent inter-particle growth and higher agglomeration efficiency [82]. It is important to note that the work of David et al. was not specific to

agglomeration in suspension systems, but rather crystallisation processes that exhibit agglomeration. This distinction is important because crystallisation processes that exhibit agglomeration do not necessarily follow the same mechanisms or kinetics as agglomeration in suspension processes; since there is no bridging liquid addition. However, as shown experimentally by Bemer [34], the effects of hydrodynamics, particle size and particle concentration are relevant to both.

Madec et al. [83] used a Monte Carlo approach to solve their multidimensional kernel which was specific to agglomeration in suspension systems. Their kernel incorporated the composition of bridging liquid (Eq. (11)), which made the model more representative of the experimental agglomeration rate processes discussed in Section 4. As mentioned in Section 3, there is an optimal range for the ratio of bridging liquid to solute volume (BSR); below or above this critically optimal range would produce loosely compacted agglomerates or paste-like amorphous agglomerates, respectively [46,55,56].

$$\beta = \beta_0(L_i^3 + L_j^3) \left((c_i + c_j)^\alpha \left(100 - \frac{c_i + c_j}{2} \right)^\delta \right)^\alpha \quad (10)$$

$$c_i = \frac{\text{volume of liquid}}{\text{volume of the agglomerate}} * 100 \quad (11)$$

$$\delta = \left(\frac{1 - c_{opt}}{c_{opt}} \right) \alpha \quad (12)$$

Eq. (10) is the agglomeration kernel used in the Madec et al. study [83]. Here, β is the agglomeration rate, β_0 is the agglomeration rate constant, L_i (L_j) is the size of the agglomerating particles, c_i (c_j) is the composition of bridging liquid in each particle, δ is the weight coefficient for the solid particles, α is the weight coefficient for the liquid droplets, and c_{opt} is the optimal bridging liquid composition. The composition function (last term in Eq. (10)) is derived such that the collisions can only occur between particles with sufficient, not excess, bridging liquid composition, *i.e.* $c_i = 0$ and $c_i = 100$

will not yield a collision. The weighting coefficient for the solid particles is a function of the optimal bridging liquid composition and weighting coefficient of the droplets (Eq. (12)) to ensure that an agglomeration event cannot occur until wetting has occurred. This unique incorporation of the bridging liquid composition served as the efficiency term by which the process would reach equilibrium. The results of their multidimensional kernel (size, composition) were more realistic simulations of the ASDs which could better predict the growth mechanisms explained by Bemer [34]. The study was limited to agglomeration only systems (no nucleation, growth) and required some prior knowledge of the system composition. Moreover, the study did not consider the hydrodynamics of the system, the internal structure of the agglomerates, and did not track the population of bridging liquid droplets. To address some these issues, a coupled simulation approach using computational fluid dynamics (CFD) and Monte Carlo to track droplet and particle populations was suggested referring to a previous study by Madec et al. [84].

Blandin et al. [10,39] carried out a combined experimental and modelling study which focused on understanding and modelling the size enlargement period studied by Bemer [34]. In their work, key aspects of agglomeration in suspension processes were identified and described to better model and predict the process. Agglomerates are created through a four-step mechanism: i) bridging liquid droplets capture solid particles and form agglomerate nuclei, ii) compaction of the agglomerate nuclei occurs due to collisions causing a rapid decrease in mean diameter, iii) growth via coalescence and consolidation then occurs due to the hydrodynamics and process conditions, i.e. agitation rate and BSR, and iv) the limit of compactibility determines when agglomeration ends. For the system studied by Blandin et al. [10], the agglomerate size exhibited a strong relation to BSR, a weak relation to solids concentration and an inverse relation to agitation rate. The relationship between process variables and final agglomerate mean size could be determined by Eq. (13).

$$L_{nb} = \alpha C_s^{0.3} N_{PTD}^{-0.6} BSR^{2.1} \quad (13)$$

In Eq. (13), L_{nb} is the final agglomerate size, α is a proportionality constant related to material properties, C_s is the solid concentration, and N_{PTD} is the stirrer speed. Based on experimental observations, a “growth via coalescence only” agglomeration model was developed.

$$\frac{\partial \Psi(L,t)}{\partial t} = R_A(L,t) \quad (14)$$

In Eq. (14), Ψ represents the number density function and R_A represents the agglomeration rate distribution. The agglomeration model considered the size (L) and concentration of the agglomerating particles (N_i or N_j). The agglomeration rate distribution can be broken down into its agglomeration rate (r_{agg}), a function of the meeting probability (f), the agglomeration efficiency (eff) and the concentration of particles (N_i or N_j) in the process (Eq. (15-16)).

$$r_{agg}(l,t) = K(i,j,t)N_i(t)N_j(t) \quad (15)$$

$$K(i,j,t) = f(i,j,t)eff(i,j,t) \quad (16)$$

$$f(i,j,t) = C_{coll}\alpha(i,j,t)\left(\frac{\pi}{4}\right)(S_i + S_j)^2[\overline{u(S_i)^2} + \overline{u(S_j)^2}]^{0.5} \quad (17)$$

$$\left\{ \begin{array}{ll} \frac{f_{adh}(i,j,t)}{f_{sep}(i,j,t)} - 1 & \text{if } f_{adh}(i,j,t) \geq f_{sep}(i,j,t) \\ eff(i,j,t) = 0 & \text{otherwise} \end{array} \right. \quad (18)$$

In Eq. (17), f , is described by a function of the target efficiency (α), agglomerate sizes (S_i, S_j), and collision velocity (u) [85]. The target efficiency is a function of the agglomerate and fluid densities as well as the fluid viscosity. The collision velocity is calculated from the particle-fluid relative velocity and is a function of energy dissipation. In Eq. (18), the agglomeration efficiency, eff , is defined as the ratio of adhesive to disruptive forces. The disruptive force (f_{sep}) is simply a function the shear stress, dissipation energy, and the corresponding characteristic area. The adhesive force (f_{adh}) is a function of the deformation energy, which is calculated by the agglomerate strength (based on porosity, BSR)

and the collision energy (based on primary particle size, interfacial energy, binding force). The adhesive force is then proportional to the deformation, porosity, binding force, and area to volume ratio (Eq. (19)). The simulations from this work showed good agreement with experimental data when the necessary parameters were fit to the data.

$$F_{adh}(i, j, t) \propto \left[\frac{def^{max}(i, j, t)}{L_p/2} \right]^2 (1 - \mathcal{P}(t)) F_{bridge} \left(\frac{S_i^2 + S_j^2}{S_i^3 + S_j^3} \right) \quad (19)$$

A key difference between the work of Blandin et al [10] and Bemer [34] is that the latter ignores breakage and fragmentation due to the observation that agglomerates created through an agglomeration in suspension process remain soft and do not fragment/break, but rather deform and compact upon collisions. This agrees with all the other modelling studies reviewed here. The key to all modelling studies is the use of experimental observations to develop models that describe critical rate processes occurring during the agglomeration process, i.e. agglomerate nuclei formation, agglomerate growth, agglomerate deformation and consolidation and compaction. Bemer [34] observed different size enlargement regimes during agglomerate formation and used a combined coalescence and breakage model to better predict these growth regimes. David et al. [81] observed differences in agglomeration as particles change their fluid flow regimes with changes in particle size and used a multilayer agglomeration kernel to describe agglomeration during crystallisation. Madec et al. [83] incorporated the composition of bridging liquid in individual agglomerates as the efficiency term in their multidimensional agglomeration kernel. Blandin et al. [10] developed a comprehensive model that accounted for both the mechanistic phenomena (e.g. deformability, collision efficiency, and compaction) and process conditions (e.g. energy dissipation, BSR, particle size).

5.2 Modeling simultaneous crystallisation and agglomeration

Although the studies reviewed in Section 5.1 show advancements in the modelling of agglomeration in suspension, there still exist areas where significant progress can be made. The literature is divided between studies of crystallisation that exhibit agglomeration and studies of agglomeration of particles already suspended in solution. However, many of the experimental spherical agglomeration studies are combined crystallisation and agglomeration studies [37,46]. There is an opportunity to further improve modelling in this area by using the experimental understanding of the combined nucleation, growth, and agglomeration rate processes. Another area of opportunity is in the development of agglomeration kernels that have physical significance with regards to the process as opposed to empirical kernels, as well as the ability to track the changes of the primary (internal) particles. A challenge with the development of these more sophisticated models is validation. As the number of mechanisms represented increases, so do the number of model parameters required to be fitted to the data. Experiments that isolate specific rate processes and accurately measure the kinetics of that process as a function of process conditions and formulation properties are essential for high quality model development and validation. This type of study is currently lacking.

To address issues of tracking the two populations during agglomeration in suspension, Ochsenein et al. [86] developed a coupled population balance model (PBM) framework for the agglomeration of needle-like crystals. The coupled PBM framework is composed of a 2-D population balance equation (PBE) that describes the 2-D growth of the needle-like primary crystals. The primary crystal population is coupled to a PBE that describes the agglomeration of the needle-like crystals. The unique coupling of the PBM allowed the authors to derive a 2-D agglomeration kernel that considered both characteristic lengths of the agglomerating particles as well as their orientation. Peña et al. [87] extended the work of Ochsenein et al. [86] by using a coupled PBM to track the total crystals, un-agglomerated crystals and agglomerates of a spherical agglomeration process that exhibited nucleation, growth, and agglomeration. In their work, the coupled PBM was used in an optimisation framework to achieve a target primary crystal mean size for bioavailability, and a target

agglomerate mean size for manufacturability. Both studies included first principles based calculations for agglomeration efficiency, whilst the latter [87] also formulated a first principles based porosity estimate.

5.3. Summary

Compared to other agglomeration processes, such as wet granulation, there have been relatively few papers concerned with modelling spherical agglomeration. The population balance has been shown to provide an excellent framework for this modelling. However, general, predictive modelling should track several populations: single crystals, agglomerates and bridging liquid droplets. Therefore, coupled or multidimensional PB models are necessary.

Analogous to wet granulation prior to the last decade, there has been too strong an emphasis on a single rate process – agglomeration by coalescence. As discussed in Section 2, spherical agglomeration is a combination of many rate processes including nucleation (immersive or distributive), consolidation, coalescence and possibly breakage. As the quantitative understanding of these rate processes improves, this knowledge should be transferred into the population balance model rate expressions, so that general, predictive models can be developed.

6. Co-agglomeration and use of additives

A further technique, based on the spherical agglomeration method is co-agglomeration. This is where a drug is crystallised and agglomerated with another drug or excipients/additives. For example, polymeric additives are often incorporated to improve the physical and mechanical properties of the agglomerates. Disintegrants may also be added to promote drug release *in vivo*. For the pharmaceutical industry, co-agglomeration has become an extremely promising technique as

it can allow the production of a desired formulation and properties in a single step, thereby reducing the number of unit operations and the associated time and cost.

Co-agglomeration of two different materials has been reported Pagire et al. [88] using a spherical agglomeration technique. Here, spherical agglomerates of carbamazepine-saccharin co-crystals were successfully produced using various bridging liquids. Furthermore, the authors also conducted a computational study of isothermic heats of adsorption of the bridging liquid solvents at crystal surfaces to understand the interactions occurring at the liquid-solid interface.

The effect of the incorporation of excipients has been reported in several studies. For example, spherically agglomerated carbamazepine crystals containing sodium starch glycolate as a disintegrant evidenced a significant improvement in dissolution properties compared to pure carbamazepine agglomerates [89]. However, the yields were much lower; this being attributed to the sedimentation of sodium starch glycolate which could only be dispersed in the good solvent. Improved dissolution properties were also reported for spherical agglomerates of bovine serum albumin protein which were successfully agglomerated with the incorporation of mannitol as a disintegrant [90].

The effect of the incorporation of hydroxypropyl methyl cellulose (HPMC) in spherical agglomerates of aceclofenac has also been studied [17]. An increase in the concentration of HPMC resulted in an increase in agglomerate size. This was attributed to the presence of HPMC on the surfaces leading to increased particle-particle interactions and the subsequent squeezing out of the bridging liquid to the particle surface, ultimately leading to an increase in size. Although agglomerate porosity decreased with HPMC content, porosities were still higher than that for pure aceclofenac alone; explaining the improved drug release of the aceclofenac-HPMC agglomerates. An increase in dissolution rate was also observed for spherical agglomerates of mefenamic acid containing HPMC,

together with improved compressibility [91]. The increased dissolution rate of drug-HPMC spherical agglomerates has also been attributed to improved wettability of the surface [29]. In this study, Sano et al [29] also incorporated a surfactant (sodium carboxymethylcellulose) into tolbutamide during spherical agglomeration, and the increased dissolution rate was attributed to enhanced wettability and solubility in the presence of the surfactant.

Improvements in micromeritics and physico-mechanical properties of spherical agglomerates incorporating polymers have also been reported for mebendazole [92] and phenytoin [93,94]. In their studies into phenytoin spherical agglomeration, Kawashima et al. [93,94] observed a significant increase in the mechanical strength when polyethylene glycol (PEG) was incorporated into the agglomerates. This was a result of reduced surface roughness in the presence of PEG and the formation of PEG solid bridges between the primary crystals within the agglomerate. The presence of PEG in the agglomerates also increased dissolution rates in aqueous solutions as a result of higher wettability of the agglomerates with water [93]. An increase in PEG concentration was also seen to reduce the agglomerate size, and it was proposed that PEG lowers the cohesive force required for agglomeration by lowering the interfacial tension and wettability of the bridging liquid [94].

Mixtures of polymeric additives have also been investigated by Jitkar et al. [24]. The authors reported that certain combinations of polymers and co-polymers could be used to tailor agglomerate sphericity and dissolution profiles. For example, a unique combination of hydroxymethyl propylcellulose – hydroxypropyl cellulose – polyethylene glycol incorporated into etodolac resulted in a product with improved flowability and dissolution.

Although co-crystallisation via the spherical agglomeration method has been shown to enhance product quality, the properties of the agglomerates are often simultaneously affected by the additive-induced properties of the solvent system such as viscosity and interfacial tension which may

be disadvantageous. Furthermore, as spherical agglomeration requires the use of a bridging liquid, co-agglomeration using this technique is a complex process and choosing the appropriate solvent system is a challenge, particularly when attempting to precipitate hydrophobic drugs and hydrophilic excipients together. Therefore, co-agglomeration has mainly been carried out using the quasi emulsion diffusion method, as no additional bridging liquid is required.

7. Comparison of spherical agglomeration with other spherical crystallisation methods

Developing spherical agglomeration and spherical crystallisation processes requires similar considerations which include understanding the phase diagram of the solvent system and the effects of process parameters (e.g. concentration, agitation rate, residence time). Several studies have been carried which compare the properties of drugs formed by both spherical agglomeration and quasi emulsion solvent diffusion (QESD). The QESD technique is regarded to be simpler than the spherical agglomeration method. However, difficulties have been reported in keeping the system emulsified and ensuring appropriate diffusion of the poor solvent into the dispersed phase [95]. Therefore, for this method to be successful, it is usually necessary to also add an emulsifier [96,97]. Spherical agglomeration can be considered the more flexible method given that it usually requires a simpler solvent system and can be carried out simultaneously with crystallisation or post-crystallisation [14]; allowing for finer control over the primary crystals and agglomerate properties. However, selection of the appropriate bridging liquid can be difficult, especially when considering the toxicity of potential residual bridging liquid in the final agglomerates.

Comparisons between the two methods for the spherical crystallisation of tolbutamide were carried out by Sano et al. [96] using sucrose fatty acid ester as the emulsifier in the QESD method. The resultant agglomerates produced via QESD were dense and exhibited high mechanical strength. Their highly spherical morphology also gave them exceptional flowability. In contrast, the agglomerates obtained via the spherical agglomeration method were less dense and less strong.

However, their more porous structure and rougher surfaces gave them a much higher specific surface area, yielding a much higher dissolution rate compared to QESD formed agglomerates. This greater bioavailability is also reported in Sano et al. [15]. It is suggested that the differences in agglomerate structure between the spherical agglomeration and the QESD methods are a consequence of their different mechanisms [96]. In the spherical agglomeration method, agglomerates are formed over time from precipitated microcrystals giving them a relatively low density and a rough surface covered with fine, acicular particles. However, during QESD, quasi-emulsion drops crystallise out immediately from the surface inwards. This yields very dense, highly spherical agglomerates with a smooth surface. These contrasting morphological properties were also observed by Kawashima et al. [49] in their study of tranilast. Furthermore, similar differences in the properties of buccillamine produced by the two techniques were reported by Morishima et al. [16]. Here, compacts of agglomerates produced from QESD evidenced higher hardness compared to those produced via spherical agglomeration, which was attributed to a greater degree of plastic deformation during compression.

Spherical agglomeration requires the use of a bridging liquid which is generally not favourable for co-agglomeration of APIs with excipients if the wettability of the API and excipients differ. For this reason, co-agglomeration of APIs with excipients or additives has been mostly carried out using QESD.

Co-agglomeration of APIs with excipients via QESD only occurs for certain volumetric ratios of solvent and anti-solvent. The amount of excipient relative to the API also affects the final product properties. Perumal et al. [98] constructed a ternary phase diagram consisting of ibuprofen, ethanol and Eudragit to find the regime where microencapsulation of ibuprofen and Eudragit was possible via QESD. Outside the feasible region co-agglomeration did not occur; instead very long, stringy, firm masses of Eudragit were recovered. In this region, Eudragit tended to preferentially partition into

the organic phase. Knowledge of the phase diagram also proved to be a good method of identifying a suitable design space to achieve desired drug release profiles. Previously, Kachrimanis et al. [99] studied the effect of Eudragit polymer on the QESD of ibuprofen, and observed that crystal yield was greatly reduced in the presence of Eudragit; presumably due to changes in the metastable zone width of the API due to the polymer's micellisation and solubility. Kawashima et al. [100] have reported that the porosity of the final microspheres can be controlled by varying the concentrations of API and polymer while keeping the drug to polymer ratio constant.

Emulsion based precipitation methods have also been used to prepare core-shell microcapsules of API and polymer. Dowding et al. [101] have prepared microcapsules of an API in an oil core surrounded by a polymer shell. Their dispersed phase consisted of an API, the shell forming polymer (polystyrene), a good solvent for the polymer (dichloromethane) and a poor solvent (hexadecane). Firstly, the good solvent was removed by slow heating which precipitated the polymer and caused it to migrate to the outer parts of the droplets, forming a shell. After some time, the heating rate was increased to speed up the rate of evaporation of the good solvent and form the microcapsules. The formation of the polymer core was dictated by the relative magnitude of the interfacial tensions at the interface of the oil, polymer, and continuous phase. The factors that affect the release rate of the API from the microcapsules are the thickness of the polymer shell and its porosity which can be controlled by the polymer concentration and rate of solvent evaporation, respectively. Rapid evaporation leads to fast release of the API due to high porosity in the shell, whilst slow evaporation decreases the shell porosity. The nature of the oil core also affected the yield of the API in the microcapsules; non-volatile oil with higher oil-water partition coefficients were found to give higher yield of the API.

QESD has been used to form agglomerates of API with excipients that are insoluble in either of the solvents. When the solvents and anti-solvents diffuse, the API precipitates. The excipients get

trapped inside the precipitating API emulsion and co-agglomerates of API and excipient are formed. Pawar et al. [102] prepared co-agglomerates of ibuprofen with talc using a QESD method although the method of agglomeration nor the mechanism were identified in their paper. Multiple surfactants have also been used to control the size of the agglomerates formed in QESD [103].

All the studies suggest that when selecting a method for spherical crystallisation, there will be a 'trade off' in the properties of the agglomerates obtained. Therefore, the most desirable product property will need to be identified to select the most appropriate method. Moreover, when considering final drug formulation, or potentially formulating in suspension, spherical agglomeration via bridging liquid addition can prove difficult given the differences in wettability between APIs and excipients. Therefore, QESD methods are currently regarded to be more suitable for co-formulation in suspension.

8. Continuous spherical agglomeration

As evidenced throughout the previous sections, spherical agglomeration creates advantages in the micromeritic properties of suspended particles that lead to the improved recovery of high-value solid particles. These advantages provide the opportunity for improved process design and efficiency, making spherical agglomeration a process intensification technique. Combining the inherent advantages of spherical agglomeration with the advantages of continuous operations can significantly improve process efficiency, adaptability and productivity. The first example of continuous spherical agglomeration was the preparation of spherical wax matrices of sulfamethoxazole by Kawashima et al. [50]. In their study, the authors focused on understanding the fundamental agglomeration mechanisms in a single-stage continuous mixed suspension, mixed product removal (CMSMPR) crystalliser. The biggest difference between batch and continuous spherical agglomeration was in the size enlargement regime. Unlike batch spherical agglomeration, which undergoes a zero-growth period and then a fast growth period before levelling off at an

equilibrium size [34], a continuous process undergoes a fast growth period immediately before a size reduction period, prior to finally leveling off at an equilibrium size. The initial fast growth period in continuous processes is a result of the reduced slurry density and bridging liquid dispersion at the onset. The initial particles and bridging liquid added to the system tend to flocculate together into very large agglomerate nuclei due to their limited availability, hence reducing dispersion and resulting in very large agglomerates. As operation continues, the size reduction period is attributed to an increase in slurry density and increased dispersion of bridging liquid leading to smaller agglomerate nuclei and smaller agglomerates. The balanced addition rate and dispersion of particles and bridging liquid leads to the equilibrium size, i.e. steady state. Overall, the same trends exist in terms of final agglomerate properties as a function operating conditions. Bos and Zuiderweg [57] also found that there were differences in the size enlargement regime between batch and continuous when using a multi-stage CMSMPR in series. Tahara et al. [104] also used a one-stage CMSMPR for a spherical crystallisation technique via emulsion solvent diffusion (ESD). Although the ESD technique differs from spherical agglomeration, Tahara et al. [104] used a solvent recycling technique that can potentially be incorporated into spherical agglomeration systems to allow for a higher yield from the crystallisation process. A CMSMPR operates at a single point in the phase diagram which reduces yield. However, including a solvent recycle stream allows for a yield closer to that of a batch system.

Peña and Nagy [56] extended the work of Kawashima et al. [50] and Bos and Zuiderweg [57] by using a two-stage CMSMPR system. The two-stage system was a combined crystallisation and agglomeration study. The first stage served as the crystal nucleation and growth dominated stage through the addition of solution and anti-solvent. The control parameters for the first stage included the solvent to anti-solvent ratio (SASR), residence time and agitation rate. The second stage served as the agglomeration dominated stage through the addition of slurry from the first stage and bridging liquid addition. The control parameters for the second stage included bridging liquid to solid

ratio (BSR), residence time and agitation rate. The advantage of the two-stage system is the ability to tailor both stages individually to create particles tailored to both primary particle and agglomerate particle specifications.

Peña et al. [59] extended the work of Peña and Nagy [56] using a plug-flow type system. The system used in their study was an oscillatory flow baffled crystalliser (OFBC). The benefits of using a plug-flow type system is the ability to have control over the crystal and agglomerate size distributions as well as spatial distribution of the temperature profile and spatially distributed solvent addition streams. The OFBC provides the ability to operate at lower flow rates and smaller volumes (shorter lengths) while still achieving turbulent mixing. The control parameters for the OFBC include the SASR, BSR, oscillation amplitude and frequency, temperature profile, and residence time. Together with the control parameters, crystallisation and agglomeration mechanisms can be carried out independently in different segments along the length of the OFBC. Pena et al. [59] divided the system into a nucleation/growth and agglomeration zone. Nucleation/growth occurred through solution and anti-solvent addition at the inlet of the crystalliser and agglomeration is initiated through the addition of bridging liquid at a downstream segment. The OFBC system provides the ability to carry out different mechanisms within one system without having to transfer slurry from one vessel to another and without affecting or changing the operating conditions inside the system which can be an issue in a MSMPR.

9. Conclusions

Spherical agglomeration is a promising technique with which to control the micromeritic properties of crystals to create end products with superior attributes. Furthermore, the enhanced properties of the crystals may allow for a reduction in the number of unit operations during industrial processing, reducing time and costs. Therefore, spherical agglomeration is inherently a process intensification

technique that can potentially drive the shift towards improved process efficiency in traditional industries such as pharmaceuticals and bulk chemicals.

Studies have shown that there are many formulation and operational parameters which influence the properties of the final agglomerates produced by spherical agglomeration and their consequent functional attributes. Therefore, optimisation of the operating conditions has been an important avenue of research. In most studies, this has been carried out on a trial and error basis for single, case study systems due to a lack of mechanistic understanding and process analytical technologies (PAT). From solvent selection to final product properties, there are many key decision variables that ultimately lead to a successful spherical agglomeration procedure. Understanding the ternary phase diagram for the system is critical to selecting the solvent and bridging liquid. A bridging liquid should exhibit good wettability (measured by capillary rise or Washburn's test) and a low contact angle with the solid of interest. It should also be immiscible with the suspension solvent system to allow for preferential wetting of the solid particles. The combination of bridging liquid and crystallisation solvent can influence the crystal polymorph and morphology so the method of bridging liquid addition and crystallisation should be examined carefully.

The bridging liquid to solid ratio (BSR) is the most critical parameter. Many different systems studied in the literature show a highly non-linear relationship between BSR and critical product attributes such as agglomerate size, analogous to the liquid binder content in wet granulation. However, unlike wet granulation, there is currently no general way to quantitatively predict *a priori* what the correct BSR will be. This is an important area for future research. Furthermore, the size, morphology and concentration of solids in the system can affect the process parameters necessary for a successful agglomeration experiment and can influence the controlling rate mechanisms, e.g. changing from immersion to distributive nucleation.

An understanding of the rate processes occurring during the agglomeration process is imperative to control and predict final product properties. A few studies give important insights into the rate processes occurring during spherical agglomeration including coalescence, consolidation, growth via layering, deformation, fragmentation and breakage. These rate processes are analogous to those in wet granulation and the extensive literature on that topic can be used as a guide to understanding spherical agglomeration. For, example, the importance of the initial wetting and agglomerate nucleation step by either immersion or distribution nucleation is highlighted, and a general classification of the rate processes is given in Fig. 2 as a starting point for any analysis. There remains considerable scope for further studies to quantify the impact of process parameters and formulation properties on each rate process. Moving forward, a mechanistic understanding should be enhanced by the emergence of sophisticated on-line analysis techniques and PAT tools (e.g. particle vision measurement, focused beam reflectance measurement). Combined with the traditional off-line characterisation methods, on-line PAT gives an opportunity to further enhance our understanding of the spherical agglomeration rate processes and the effects on final product properties.

Population balance models have been proposed that take into consideration these agglomeration phenomena. However, more mechanistic and modelling studies are required to enable experimental design and the specific tailoring of product properties. Specifically, models that can track the different populations/phases (i.e. primary crystals, agglomerates, droplets) are needed so that physically relevant agglomeration kernels can be developed that take into consideration the effects of process conditions (i.e. agitation rate, BSR). Such models will be important for model driven design approaches with a substantial reduction in the required experimentation at all scales.

Spherical agglomeration methods may be used for co-agglomeration of APIs and excipients, allowing direct incorporation of final formulation blends into the spherical agglomerates. Co-agglomeration of API and excipients adds another process intensification attribute to the process that can lead to direct compression of agglomerates, further reducing the required number of unit operations and costs in pharmaceutical manufacturing. Co-agglomeration with excipients via spherical agglomeration can be difficult and is not applicable to all systems due to differences in solubility and wettability of APIs and excipients in a specific solvent system. For such situations, a quasi-emulsion solvent diffusion (QESD) method should be considered. QESD can allow the incorporation of API and excipients of different hydrophobicity into spherical agglomerates, providing a method of overcoming differences in wettability.

Most research thus far has been carried out using batch systems. However, continuous spherical agglomeration processes have also been successfully reported. The pharmaceutical industry is experiencing a paradigm shift from batch to continuous processing. Continuous processing has the potential to significantly reduce plant size and footprint whilst generating a more consistent product at higher levels of productivity. Combining the process intensification benefits of spherical agglomeration with continuous processing can have a significant impact on the future of pharmaceutical manufacturing.

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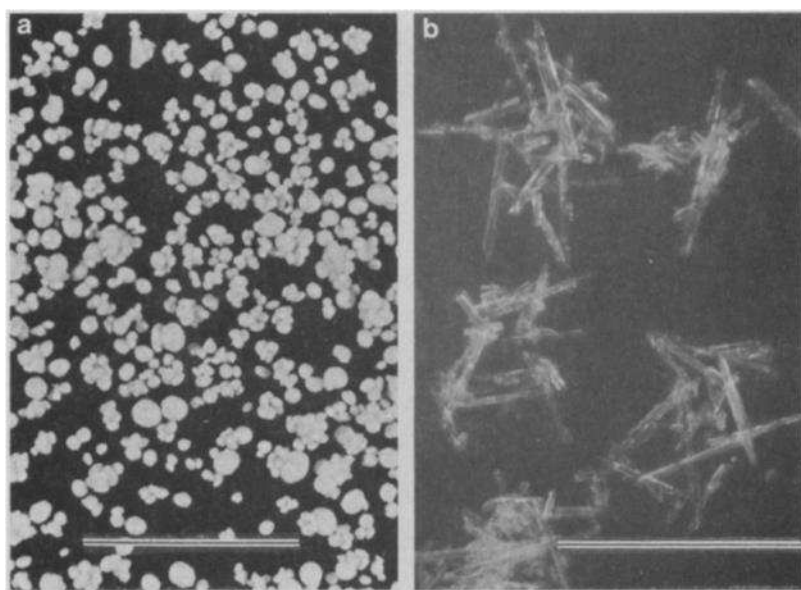


Figure 1

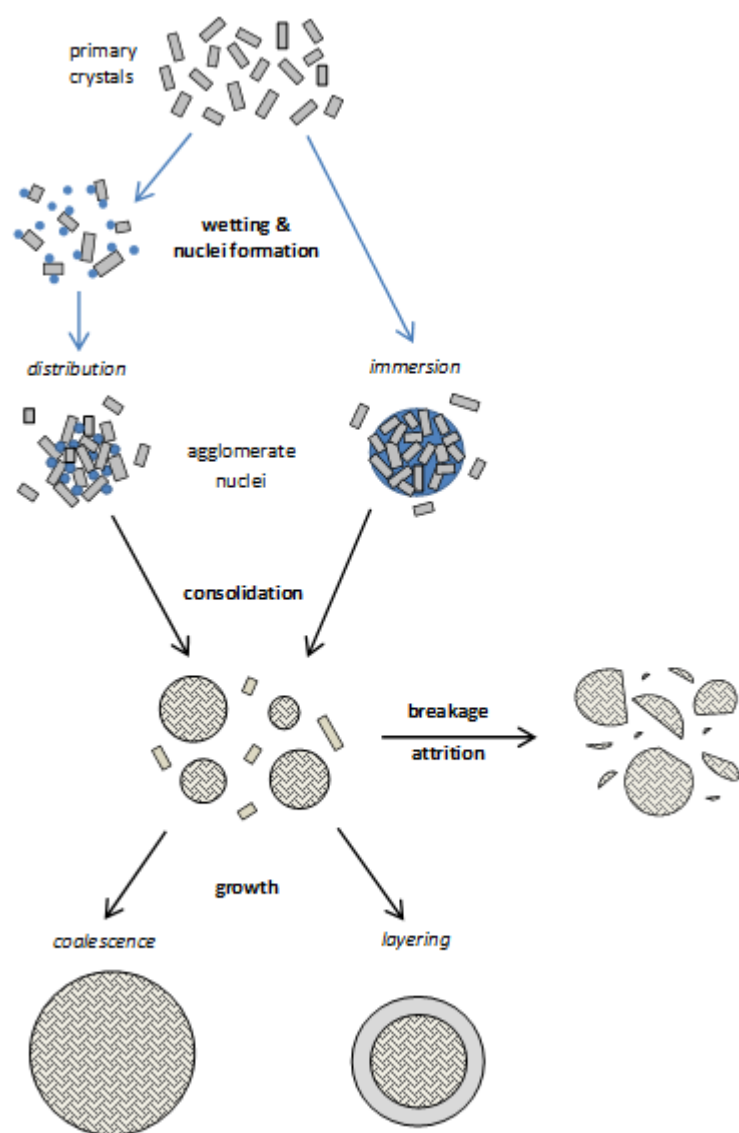


Figure 2

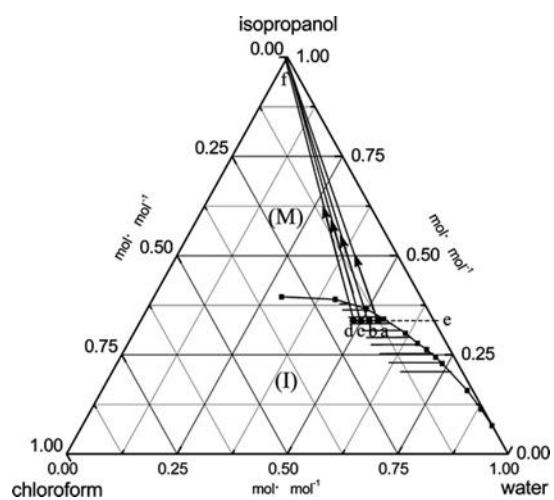


Figure 3

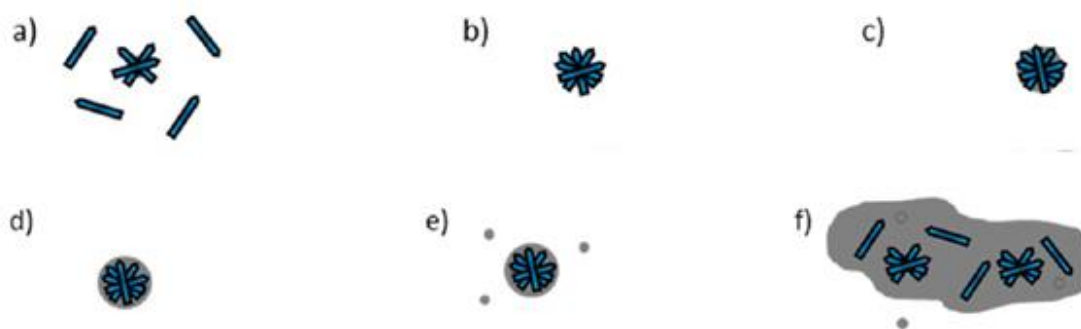
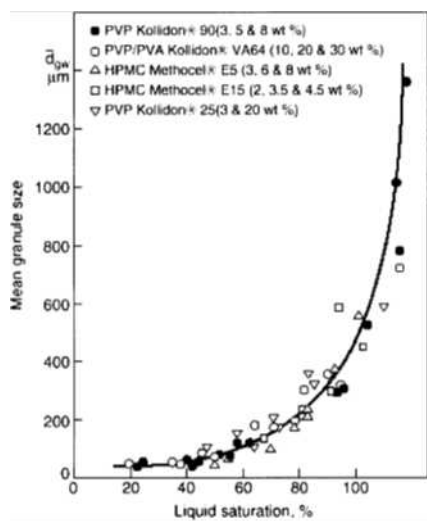


Figure 4

ACCEPTED MANUSCRIPT

A



B

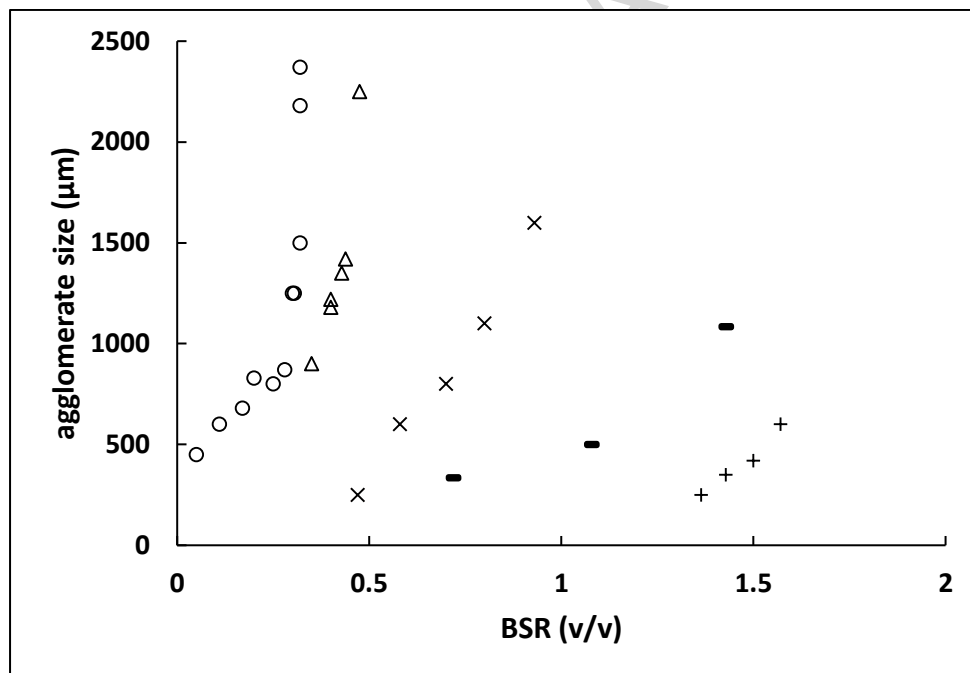


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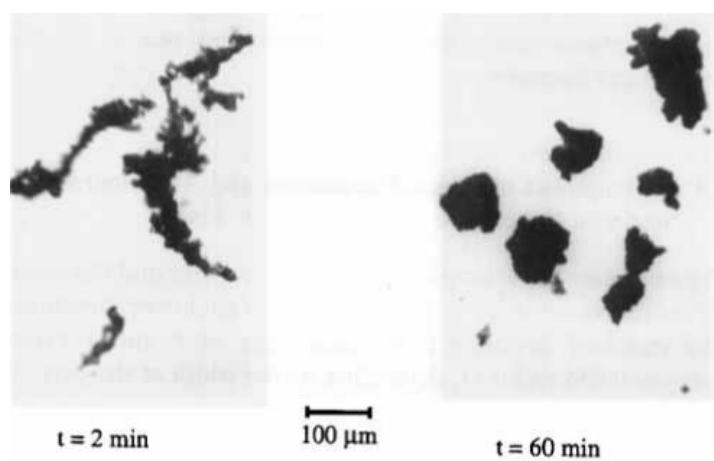


Figure 6

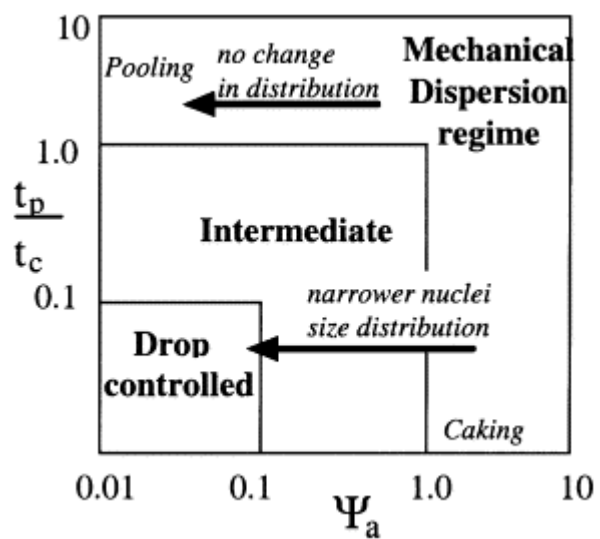
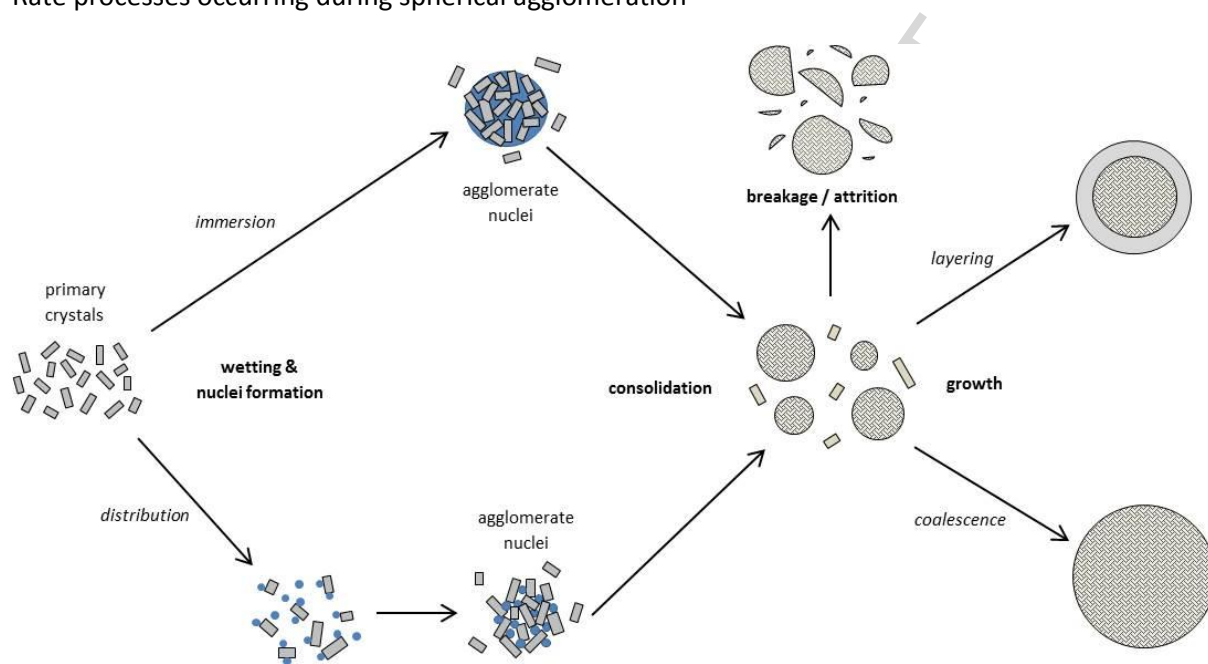


Figure 7

Graphical abstract text:

Rate processes occurring during spherical agglomeration



Highlights

- A critical review of spherical agglomeration
- Understanding of controlling parameters summarised
- Identification and classification of key rate processes
- Current state of modelling approaches described
- A frame work for future research identified

ACCEPTED MANUSCRIPT