The solid state properties of pharmaceutical compounds have a decisive impact on dosage form development, stability, and in vivo performance of the drug. Many pharmaceutical drugs are problematic per se due to their inappropriate physical and mechanical properties and poor aqueous solubility. The micromeritic properties of drug particles, such as shape and size, are of essential importance for the formulation of solid high-dose units (1). The particle size of poorly soluble drugs is always an issue due to its impact on dissolution properties. Micronized drug particles (smaller than 10 μm) have a large specific area and provide a way to improve the dissolution rate (2), but high energy input during the micronization process gives rise to increased free surface energy, electrostatic tendencies, and thus poor flowability and/or compressibility of powders and low bulk density (3), which makes them difficult to use in downstream processing in the pharmaceutical industry such as direct tablet-making or capsule-filling processes. In addition, micronized drug substances tend to agglomerate and the increase in surface area is not always reflected in improved dissolution (4).

Spherical crystallization of drugs is the process of obtaining larger particles by agglomeration during crystallization. The most common techniques used to obtain such particles are spherical agglomeration and quasi-emulsion solvent diffusion. Ammonia diffusion systems and crystalllo-co-agglomeration are extensions of these techniques. By controlling process parameters during crystallization, such as temperature, stirring rate, type and amount of solvents, or excipient selection, it is possible to control the formation of agglomerates and obtain spherical particles of the desired size, porosity, or hardness. Researchers have reported that the particles produced have improved micromeritic, physical, and mechanical properties, which make them suitable for direct compression. In some cases, when additional excipients are incorporated during spherical crystallization, biopharmaceutical parameters including the bioavailability of drugs can also be tailored.

Keywords: spherical crystallization, agglomeration, solvent diffusion, improved particle properties

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It is also known that the particle shape or «crystal habit» can influence the packing, flowability, compressibility, dissolution, and sedimentation properties of pharmaceutical powders (5, 6). For example, it has been demonstrated that symmetrically shaped crystals of ibuprofen possess better compaction and flow properties than needle-shaped crystals (7).

Physico-mechanical properties of crystals, such as melting point, solubility, true density, dissolution profile, flowability and compactibility, can be modified by recrystallizing the drug in different ways that affect the physical and chemical properties of formed particles. For example, ibuprofen crystals were grown from various solvents and, by using various crystallization conditions, it was shown that various crystal forms with various crystal shapes were obtained: cubic, needle-shaped, and plate-shaped crystals. Differences in true density, flowing properties, and tabletability were determined for these different particles (7, 8).

Poor physical and mechanical properties of drug particles have been traditionally masked by various granulation methods, such as the conventional and widely used wet granulation, which produces agglomerates with higher bulk density, better flowability, and compressibility/compactibility. Most common techniques of wet granulation are high-shear and fluid bed wet granulation, which generally involve mixing, atomization, and spraying of granulation liquid on powders, drying steps, sieving, and so on. Both agglomeration methods are energy-consuming process steps in dosage form production and can impair the stability of moisture- or heat-sensitive drugs or can cause transformation of the physical form of drugs (9). Other agglomeration techniques, such as dry granulation, hot-melt granulation, melt extrusion, spray congealing, or melt solidification have been introduced in recent years, and have yielded some innovative solutions for improving the physical and mechanical properties of drug particles; however, they are still less economical than direct compression tableting.

In 1974, Kawashima and Capes (10) introduced the concept of obtaining larger particles by agglomeration during the crystallization step. Silica sand dispersed in agitated carbon tetrachloride and agglomerated with calcium chloride aqueous solutions was used as a model system. Some years later, Kawashima (11) used the «spherical crystallization» method for increasing the size of drug particles and defined it as «an agglomeration process that transforms crystals directly into compact spherical forms during the crystallization process.» Using this method, the precipitated crystals can be agglomerated during the final synthesis step (recrystallization) into more or less spherical particles with sizes between 300 and 500 μm without any binders. This paper describes spherical crystallization methods and outlines the potential of the particles obtained.

SPHERICAL CRYSTALLIZATION

Crystallization is a process of forming solid crystals that occurs when molecules start aggregating and precipitating from solution or melt. The rate and mechanisms by which crystals are formed from liquid solutions are determined by many factors: thermodynamic (e.g., solubility, solid-liquid interfacial tension, solvent activity, temperature, etc.), kinetic (e.g., supersaturation, molecular mobility, meta-stable zone width), and mo-
molecular recognition (hydrogen bonds, non-covalent bonds, molecular networks). The driving force for crystallization is supersaturation, which describes the exceeding of the saturated equilibrium concentration of solute (12–15). Supersaturation can be created by increasing the solute concentration (solvent evaporation) or decreasing the solute solubility (e.g., temperature change, antisolvent addition, pH change, salting out). The concentration threshold above which crystallization (nucleation) is observed is determined by the kinetic stability of supersaturated states and is regulated by nucleation mechanisms (homogenous, heterogeneous) and kinetics. The next step in crystallization is the formation of macroscopic crystals from stable nuclei, called »crystal growth«. Crystal growth is controlled by internal (crystal structure) and external factors (temperature, impurities, supersaturation, solvent type) and determines the particle morphology (12–15).

Under controlled conditions, such as solvent composition, temperature regulation, supersaturation generation, or mixing speed, crystallized particles can simultaneously agglomerate into spherical dense agglomerates (16, 17). The most commonly used spherical crystallization techniques are spherical agglomeration and quasi-emulsion solvent diffusion. In both processes, a good solvent that dissolves the compound to be crystallized is used, and a poor solvent that acts as an antisolvent is used to generate the required supersaturation. Other extensions of these techniques are crystallo-co-agglomeration and the ammonia diffusion system.

**Spherical agglomeration**

Various authors give this kind of agglomeration process different names (18). It is usually called »spherical agglomeration« when the process is aimed at producing final particulate material with special characteristics (19). When its aim is to facilitate manufacturing processes such as filtration or handling, the term »agglomeration in suspension« is used (18, 20). The term »selective agglomeration« is employed when it is used to separate a solid component from a mixture (21) or »oil(-assisted) agglomeration« when oil or some other organic liquid is used as a »bridging« liquid to facilitate the agglomeration process (22, 23). In addition to being used in producing spherical particles of pharmaceutical powders with improved physical properties, this kind of agglomeration is also useful for selective collection of one dispersed phase among many, such as may be desired in coal purification and mineral beneficiation (24, 25) or de-inking toner on printed paper for secondary fiber recovery (26), where hydrophobic particles are agglomerated to a sufficient size and then effectively removed by filtration or air flotation.

In the spherical agglomeration method, a solution of a compound in a good solvent is poured into the poor solvent, which is miscible with the good solvent. The affinity between the solvents must be stronger than the affinity between the good solvent and the compound, which causes immediate precipitation of crystals. In the spherical agglomeration method, a third solvent called the »bridging liquid« is also added in a smaller amount and acts as an interparticle binder that promotes agglomeration. The bridging liquid, which should not be miscible with the poor solvent and should wet the precipitated crystals, collects the crystals suspended in the system by forming liquid bridges between the crystals due to capillary negative pressure and interfacial tension at the solid-liquid interface (Fig. 1). Surfactants are usually avoided because the strength of liquid bridges is proportional to the interfacial tension between the bridging liquid and the solid (26).
Some authors have reported that the amount of bridging liquid has an impact on particle size distribution, but there is no general rule regarding how the quantity of bridging liquid affects the size of agglomerates and it seems to vary on a case-by-case basis. Some researchers report on the enlargement of agglomerates with increasing amounts of bridging liquid (19, 28), whereas in another study of the spherical agglomeration process the addition of a smaller amount of bridging liquid produced larger particles of acebutolol (up to 1,000 μm) and vice versa a larger amount of bridging liquid produced smaller particles (around 600 μm) (29). Katta and coworkers (30) noticed no change in the particle size of agglomerated benzoic acid with an increased volume of bridging liquid. However, it can be concluded from other studies that if the quantity of bridging liquid is too small, there is no significant agglomeration and when too much bridging liquid is used, the agglomerates become soft and pasty (18, 28, 31). Some authors emphasize the importance of the choice of bridging liquid and suggest how to determine the optimal one for spherical agglomeration. Regarding the importance of the bridging liquid wetting properties during the spherical agglomeration process, Amaro-Gonzales and Biscans (32) proposed a study of the capillary uptake of liquid in a powder medium using «Washburn’s test.» The best results during crystallization tests on lobenzarit disodium were obtained in the presence of n-hexane, which wetted solid crystals better than other liquids. Chow and Leung (33) postulated some rules for bridging liquid selection:

i) For compounds that are water soluble, a water-miscible organic solvent is used as the poor solvent and salt solutions of high concentration without common ions can be used as the bridging liquid.

ii) For compounds that are soluble in one or more organic solvents, water is employed as the poor solvent and a water-immiscible organic solvent as the bridging liquid.

iii) For compounds that are only soluble in water-miscible organic solvents, a saturated aqueous solution of the compound can serve as the poor solvent and an organic solvent as the bridging solvent.

iv) For compounds that are not sufficiently soluble in water or any organic solvent, a water-immiscible organic solvent can act as the poor solvent and salt solutions of high concentration without common ions as the bridging liquid. In addition, a binding agent such as PVP (M_r 40000) or PEG (M_r 10000) is required for agglomeration because the powders are not sufficiently soluble in bridging liquids to allow binding through recrystallization and fusion.
In addition to the amount and choice of bridging liquid, other process parameters during crystallization are also important for agglomeration kinetics and particle properties. One of the important process parameters is the agitation rate during the agglomeration process. It has been shown (18, 29) that increasing stirring speed makes the agglomeration process less efficient due to the shearing rate, disruptive forces, and higher probability of agglomerate collisions, which preferentially tear them apart. It has also been demonstrated that higher stirring speed at the same time results in decreased porosity and greater mechanical resistance of the agglomerates produced (18). Another important process parameter is the proportion of good solvent to poor solvent. Zhang and coworkers have recently reported that the mean particle size of cefotaxime sodium spherical agglomerates increased with an increase of the poor solvent chloroform content in the crystallization system, and at the same time the particle size distribution became narrower, which can be ascribed to higher supersaturation and more effective crystallization and agglomeration (31). In that study, the temperature and agitation speed had no notable impact on the agglomerated particle size, while in another study (34) higher temperature resulted in smaller particle size and increased density of agglomerated carbamazepine.

**Quasi-emulsion solvent diffusion**

The quasi-emulsion solvent diffusion (QESD) was first mentioned in 1989 by Kawashima and coworkers (35). The prerequisite of this method is that the interactions between the drug and the good solvent are stronger than the interactions between the good solvent and the poor solvent. The drug is dissolved in the good solvent and when the solution is dispersed into the poor solvent, quasi-emulsion droplets are created, even though good and poor solvents are miscible (29). Formation of an unstable emulsion is induced by the increase in interfacial tensions between both solvents (36). The good solvent gradually diffuses out of the emulsion droplets into the outer poor solvent phase, and the poor solvent diffuses into droplets, which reduces the solubility and eventually causes drug crystallization inside the droplets (37, 38). Residual good solvent in the droplets acts as a bridging liquid to agglomerate the generated crystals. Spherical agglomerates of crystals are then formed if the process parameters are set accordingly. The method is considered to be simpler than the spherical agglomeration method, but it can be

![Fig. 2. Proposed mechanism of QESD (adapted from 40).](image)
difficult to find a suitable additive to keep the system emulsified and ensure suitable diffusion of the poor solvent into the dispersed phase (Fig. 2) (39).

As previous studies have shown, solvent transfer is particularly influenced by two basic parameters (38, 40). One of them is the difference in temperatures $T_1 - T_2$, with $T_1$ being the temperature of the good solvent with dissolved drug before dispersion and $T_2$ the initial temperature of the poor solvent. A smaller difference in initial temperatures between the two phases accelerates the mass transfer of solvents and consequently the rate of crystallization is increased. The second parameter that influences the rate of solvent transfer is the initial mass ratio of good solvent to poor solvent and, as shown by Espitalier and coworkers (41), mass transfer of the good solvent (acetone) into the poor solvent’s phase (water) increased when the ratio between the good solvent and the poor solvent was high. At the same time, by increasing the initial ratio of good to poor solvents, the apparent density of the ketoprofen particles produced decreased. In a later study, the median diameter of particles produced was reduced using the higher temperature difference between $T_1$ and $T_2$ and a low ratio of good solvent to poor solvent. The results were explained by more intense creation of supersaturation. The effect of the overall temperature of the dispersed system on particle shape and size has been demonstrated by Zhang and coworkers (42). At higher temperatures, the agglomerated silybin particles were larger (0.89, 1.74, and 2.48 μm at 15, 23, and 30 °C, respectively) and more spherical (Fig. 3) (42), which was explained by a higher diffusion rate, increased interfacial tension, and higher kinetic energy of the droplets.

![Fig. 3. SEM images of: A) commercial silybin powder; silybin particles prepared at: B) 15 °C; C) 23 °C; D) 30 °C (from ref. 42 with permission).](image-url)

Some authors reported that an emulsifier must be used for the QESD method. Notcent and coworkers (44) conducted a study of spherical crystallization of salbutamol sulfate using the QESD method and tested several emulsifiers with different HLB (hydrophilic/ lipophilic balance). Only the use of the most lipophilic emulsifier in the study,
Abil EM 90 (polysiloxane poly alkyl polyether copolymer; HLB = 5), yielded spherical particles. A larger amount of emulsifiers dispersed in the poor solvent can cause a coalescence of particles and increase their surface roughness, whereas a lower proportion of emulsifier increases the apparent density of particles (40). In a study by Zhang and coworkers, a trial without surfactant resulted in relatively large spherical particles of silybin (6.68 μm) with coarse surfaces, and trials with lower or higher concentrations of surfactant yielded smaller particles (2.97 μm, 2.49 μm, and 2.48 μm at 0.01, 0.02, and 0.10 % SDS concentration, respectively) with narrower particle size distribution (42). Maghsoodi and Esfehani (43) prepared naproxen agglomerates with sodium lauryl sulfate as a surfactant and additionally incorporated polymer Eudragit RS100 and talc (as anti-adhesion agent) to obtain microparticles with desired dissolution properties.

Ammonia diffusion method

This is a modified spherical crystallization technique applicable to amphoteric substances, which are only soluble in acidic or alkaline aqueous solutions and insoluble in neutral aqueous solutions or organic solvents. It is therefore impossible to agglomerate them using conventional spherical crystallization techniques such as spherical agglomeration or the quasi-emulsion solvent diffusion method (44). In this technique, an aqueous ammonia solution is used as the good solvent and it also acts as a bridging liquid (44, 45). The poor solvent is selected on the basis of the drug solubility in that solvent and good miscibility with ammonia and water. Water-immiscible solvents such as hydrocarbons or halogenated hydrocarbons are a third component in the system, inducing liberation of the ammonia (44). The drug is dissolved in an aqueous ammonia solution and poured into a mixture of a poor solvent and a water-immiscible solvent. It is assumed that the poor solvent enters the droplets of aqueous ammonia solution and causes drug precipitation without forming ammonium salts. Simultaneously, the ammonia diffuses to the outer organic solvent phase and its ability as a bridging liquid becomes weaker, which then determines the final size of agglomerates (44, 46). It is important to find a suitable combination of solvents in order to attain a high crystallization rate. When too much immiscible or poor solvent is applied, the resultant agglomerates form a large solid mass or a paste and with too little solvent, drug crystals form without agglomeration (46).

Crystallo-co-agglomeration

Crystallo-co-agglomeration was invented by Kadam and coworkers (47) as an attempt to overcome the limitations of spherical crystallization techniques, which were restricted to size enlargements of single high-dose drugs only. It is a modification of the spherical crystallization techniques described above, in which a drug is crystallized and agglomerated with an excipient (48, 49) or with another drug (50). Similar to spherical agglomeration, a good solvent is used in this method to solubilize the drug, a poor solvent to cause drug crystallization and the bridging liquid, which is immiscible with the poor solvent, to form liquid bridges during the agglomeration process.

Crystallo-co-agglomeration is a complex process and is influenced by many formulation and process variables. The majority of drugs are hydrophobic, soluble in organic
solvents, and poorly soluble in water, whereas many excipients, such as diluents, disintegrants or glidants, are hydrophilic. Therefore the difference in the physical and chemical properties of drug molecules and the excipient is a major challenge in selecting a solvent system for the crystallo-co-agglomeration and dictates the yield of the process. Maghsoodi and coworkers (49) prepared spherical co-agglomerates with naproxen and disintegrants, either starch or sodium starch glycolate. Acetone was used as a good solvent and the bridging liquid, whereas water with dispersed disintegrant and a small amount of hydroxypropyl cellulose served as a poor solvent. Disintegrant was present in the acetone and aqueous phases during the agglomeration process, and so losses of disintegrant could not be avoided and final yields of the agglomerates prepared were within a range of 68 to 70 %.

Addition of various polymers such as polyethylene glycol, ethyl cellulose, or hydroxypropyl methylcellulose can improve the tensile strength or compressibility of agglomerates. Properties of the finished product are simultaneously affected by polymer-induced properties such as the interfacial tension, viscosity, and the rate of vaporization of the solvent used (51).

ADVANTAGES OF SPHERICAL CRYSTALLIZATION

Spherical crystallization techniques have been successfully applied to produce compacted spherical particles of drug substances that possessed improved micromeritic properties, such as uniform shape and size of particles, lower bulk density, and better flowa-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Method</th>
<th>Improved property</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>SA</td>
<td>Flow properties, compactibility</td>
<td>17</td>
</tr>
<tr>
<td>Cefotaxime sodium</td>
<td>SA</td>
<td>Flow properties, compressibility</td>
<td>31</td>
</tr>
<tr>
<td>Lobenzarit disodium</td>
<td>SA</td>
<td>Particle shape and size distribution</td>
<td>32</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>QESD</td>
<td>Particle shape, flow properties</td>
<td>36</td>
</tr>
<tr>
<td>Bucillamine</td>
<td>SA, QESD</td>
<td>Flow properties, compressibility</td>
<td>37</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>SA, QESD</td>
<td>Flow properties, compactibility</td>
<td>39</td>
</tr>
<tr>
<td>Salbutamol sulfate</td>
<td>QESD</td>
<td>Particle shape and size distribution</td>
<td>40</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>QESD</td>
<td>Flow properties, size distribution</td>
<td>41</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>ADM</td>
<td>Flow properties, compressibility</td>
<td>45</td>
</tr>
<tr>
<td>Norfloxacine</td>
<td>ADM</td>
<td>Particle shape and size</td>
<td>46</td>
</tr>
<tr>
<td>Naproxen</td>
<td>CCA</td>
<td>Flow properties, compactibility</td>
<td>49</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>SA</td>
<td>Compressibility, compactibility</td>
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</tr>
<tr>
<td>Naproxen</td>
<td>QESD</td>
<td>Compressibility, compactibility</td>
<td>53</td>
</tr>
</tbody>
</table>

bility. Consequently, the physical and mechanical properties (compressibility, compactibility) were also improved and the particles obtained were suitable for direct tableting (Table I).

Spherical crystallization techniques can be also exploited to incorporate various excipients into agglomerates, such as colloidal silica, surfactants, or polymers. In this case as well, the physical and mechanical properties of drugs are improved and the incorporated excipients also affect the wetting properties, solubility, dissolution rate, and hence the bioavailability of pharmaceutical drugs (Table II).

**CONCLUSIONS**

Spherical crystallization techniques have been widely used in the minerals industry and are attracting increased attention for the design and manufacture of high-value products such as pharmaceutical drugs because they offer a solution for improving their properties, enabling production of cost-saving direct-compression formulations and modulation of dissolution profiles for various needs. The spherical crystallization process appears to be simple enough and inexpensive for scaling up to a commercial level, but an extensive investigation must be carried out at the research and development stage to attain a sufficient level of understanding regarding the controlling mechanisms of simul-

<table>
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<th>Method</th>
<th>Improved property</th>
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</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>SA</td>
<td>Flow properties, compactibility, dissolution rate</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>CCA</td>
<td>Flow properties, compressibility, dissolution rate</td>
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<tr>
<td>Ibuprofen</td>
<td>QESD</td>
<td>Flow properties, compressibility, control of drug release</td>
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</tr>
<tr>
<td>Silybin</td>
<td>QESD</td>
<td>Dissolution rate</td>
<td>42</td>
</tr>
<tr>
<td>Naproxen</td>
<td>QESD</td>
<td>Flow properties, controlled release</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>CCA</td>
<td>Flow properties, compressibility, dissolution rate</td>
<td>55</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>CCA</td>
<td>Controlled release</td>
<td>48</td>
</tr>
<tr>
<td>Ibuprofen, paracetamol</td>
<td>CCA</td>
<td>Flow properties, compactibility, dissolution rate</td>
<td>50, 51</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>SA</td>
<td>Flow properties, solubility, dissolution rate, bioavailability</td>
<td>56</td>
</tr>
<tr>
<td>Mebendazole</td>
<td>SA</td>
<td>Flow properties, compressibility, dissolution rate</td>
<td>57</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>SA</td>
<td>Flow properties, compressibility, dissolution rate</td>
<td>58</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>SA</td>
<td>Flow properties, compressibility, solubility, dissolution rate</td>
<td>59, 60</td>
</tr>
<tr>
<td>Fenbufen</td>
<td>SA</td>
<td>Flow properties, dissolution rate</td>
<td>61</td>
</tr>
<tr>
<td>Piroxicam</td>
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<td>Flow properties, compressibility, dissolution rate</td>
<td>62</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>QESD</td>
<td>Compressibility, solubility, dissolution rate, bioavailability</td>
<td>63, 64</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>SA</td>
<td>Dissolution rate</td>
<td>65</td>
</tr>
</tbody>
</table>

SA – spherical agglomeration, QESD – quasi-emulsion solvent diffusion, CCA – crystallo-co-agglomeration
taneous crystallization and agglomeration involved in particle growth. Appropriate solvents, excipients, and process parameters must be defined for each drug and specific property desired, which may lead to prolonged experimental work, but spherical crystallization could solve bioavailability issues and shorten the subsequent manufacturing process of pharmaceutical dosage forms.

REFERENCES


Kjužne besede: sferična kristalizacija, aglomeracija, difuzija topila, izboljšane lastnosti delcev

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