
Recrystallization of Drugs – Effect on Dissolution Rate

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1. Introduction

Undoubtedly, a broad range of beneficial pharmaceutical agents available today is one of the greatest scientific achievements. In recent years, numerous chemical and pharmaceutical researches have been led to the production of a vast number of new potential drug candidates. However, many of these new compounds are in a biopharmaceutical classification of low solubility keeping drug dissolution rate as the limiting step for absorption of these drugs [1]. Many efforts are being performed to reformulation of present drugs to solve problems such as low solubility, dissolution, bioavailability, flowability, compressibility, dosing problem, stability and toxicity. Appropriate drug dissolution rate is necessary for attaining proper oral drug therapy. The bioavailability of orally administrated drugs depends on their absorption from the gastrointestinal (GI) tract [2]. In this rout of administration, poorly water soluble drugs show low bioavailability because of their low solubility in GI media. The rate limiting step in the absorption of these drugs is the dissolution rate of them in the GI fluids rather than their diffusion through the GI membrane [3]. There are several techniques have been used for enhancing dissolution rate of these drugs such as: physical and chemical modification, preparing solid dispersion, complexation, solubilization, lquisolid technique, changing in crystal habit and so on [4].

As we know, certain kinds of drugs might be existed in a variety of solid-state forms, including polymorphs, solvates, hydrates, salts, cocrystals and amorphous solids. Then, selection of the proper form of the drug would be severely important to a drug development processes. Crystallization of a drug is an important thermophysical process in pharmaceutics that a drug molecule precipitates in the medium due to supersaturation [5]. In general, crystallization may be defined as the phenomena in which a solid compound precipitates from a saturated solution (through cooling or evaporation) in the form of crystals [6]. Enhancement of dissolution rates

of water insoluble drugs (Sulfathiazole, Prednisone and Chloramphenicol) by crystallization has been investigated by Chiou et al in 1976 [7].

According to numerous papers, crystal habit can be modified by recrystallizing the drug. This process can affect the physical and physicochemical properties. Variation in crystalline habit is one of the proceeding trends in order to increasing the solubility, dissolution rate and bioavailability of the poorly soluble drugs [8]. This process could potentially be utilized to a wide range of drugs with different crystalline forms. Different crystals show different dissolution rates and then different biological responses. Therefore the modification of crystal properties should affect the bulk dissolution rate. Burt and Nickel (1979) by using the single crystal dissolution method demonstrated that the different forms of the same crystals prove different dissolve rates. Habit modification normally occurs when the environments of growing crystals have effects on its external shape without changing its internal structure [9]. Kobayashi et al (2000) reported different dissolution rates for carbamazepine, where the dihydrate form of the drug in simulated fluids (pH 1.2) had notably slower dissolution rates than the anhydrous forms (forms I and III). Due to the rapid conversion of metastable polymorph (form III) to the dehydrate form, this polymorph showed greatest rates of dissolution at the initial stages but reductions at later time [10].

2. Dissolution rate of drug

As previously mentioned, the dissolution and release rate of a drug molecule are essential to identification of drug characterization. The drug dissolution rate is an amount of a solid dosage form that goes into solution in a certain amount of time. In the dissolution test, the drug solubility is the main parameter that affects the rate of dissolution [11]. The poor dissolution rates of poorly water soluble drugs are still a challenge in the pharmaceutical industry [12, 13]. The absorption rate of a poorly water soluble drug in an orally administered solid dosage form is controlled by its dissolution rate in the fluid present at the absorption site and the dissolution rate is often the rate-determining step in its absorption [14].

The size and shape have very important role in the separation process which will in turn affect the yield and quality of the resulting fractions during the crystallization process [15]. Crystal habit influences particle orientation, therefore can modify the flowability, packing, compatibility, syringability, physical stability and dissolution profile of a drug molecule. For example, it has been showed that symmetrically shaped crystals of Ibuprofen have better compaction and flow properties than needle shaped crystals [16]. Therefore optimization of crystal properties is an alternative method for modifying the dissolution properties of drugs and therefore bioavailability of them [17].

There are many various factors that affect the dissolution rate of a drug substance. Some of these factors include: concentration of the drug solution, size and surface area of the drug substance, any movement or stirring, temperature, nature and type of drug matter and the mass or volume of the drug [8]. By breaking a drug into smaller pieces, its surface area is increased. When particle becomes smaller, because of greater interaction with the solvent, the

solubility will be increased [18]. According to Noyes-Whitney equation, when particle size is reduced, the total effective surface area is increased and thereby the dissolution rate is enhanced. Indeed, when the total surface area of the drug particles is increased, the drug dissolves more rapidly because the action takes place only at the surface of each particle and then increases its dissolution rate [19-21]. Rising of temperature for liquids and solid solutes, not only increases the amount of the dissolving solute but also can enhanced the dissolving rate [22]. When the amount of solute in the solution is low, dissolution occurs relatively rapidly. In the point that no solute can be dissolved, dissolution takes place more slowly. In the case of liquid and solid solutes, stirring leads to fresh portions of the solvent in contact with the solute, then the increased dissolution rate was obtained [23].

So far many techniques have been used to increase the solubility and therefore the dissolution rate of poorly water soluble drugs. Methods such as cosolvency and microemulsion techniques [24-27], crystal habit modification, complexation [28-31], formulation in proper salt form [32, 33], preparation of solid dispersion [8, 34-39], liguosolid technique [19, 40-44] and particle size reduction [45-48] are some of these techniques. There are several disadvantages in the use of each technique. For example, the salt formation process is complex procedure and the dissolution enhancement is not always predictable in this process. Furthermore, this method is not possible for neutral compounds [49]. As another example, solubilization techniques normally show poor stability and insufficient acceptability of patients [50]. For choosing a suitable technique for a certain drug, some certain aspects such as the properties of drug, nature of excipients and nature of dosage form should be considered [51]. Crystal habit of a solid stated form can be modified by recrystallizing process. Then this process can affect the physical and physicochemical properties such as the melting point, solubility, true density, dissolution profile, flowability and tabletability [52].

3. Recrystallization of drugs

Most active pharmaceutical ingredients are manufactured in the crystalline form for their chemical stability during transportation, packaging and storage. Recrystallization is the simple and inexpensive method for purifying solid organic materials whereby a crystalline form of a compound may be obtained from other solid-state forms of the same substance [53]. In the pharmaceuticals, recrystallization is the process most often applied for the purification of solid active pharmaceutical ingredients (APIs) [54]. Indeed, production of another crystalline form as well as purification are the two main aspects in the recrystallization process of drugs. Generally, a hot saturated solution of the drug is prepared using a solvent with appropriate boiling point and then the solution is cooled and a new crystalline form of the drug is separated [53]. This process occurs due to the lower solubility of new crystalline form of the drug in the relevant solvent at lower temperatures. The recrystallization process of a drug has been schematically illustrated in figure 1.

Recrystallization of the drug in a suitable solvent leading to altering physical and chemical properties of obtained particles. These properties are consist of the wettability, melting point,

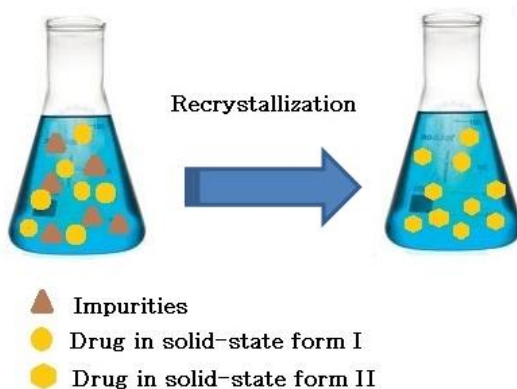


Figure 1. Schematic illustration of the drug recrystallization process.

solubility, dissolution rate, flowability and compactibility [55]. There are some reports about the recrystallization process and its effects on different properties of drugs [56-58]. This technique has been used for huge or small quantities of materials and very effective and efficient results were obtained.

Various factors including thermodynamic (*e.g.*, solubility, solid-liquid interfacial tension, solvent activity, temperature, *etc.*), kinetic (*e.g.*, supersaturation, molecular mobility, metastable zone width), and molecular recognition (hydrogen bonds, non-covalent bonds, molecular networks) may influence on the rate and mechanisms by which crystals are formed from liquid solutions [59, 60]. The driving force for crystallization is supersaturation. 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) [61]. The next step is the formation of macroscopic crystals from stable nuclei, known as crystal growth. This step is controlled by internal (crystal structure) and external factors (temperature, impurities, supersaturation, solvent type) and determines the particle morphology [62].

It was shown that changing of crystal habit by recrystallization has significant effect on dissolution rate. Nogami and Kato found that the recrystallized thin crystal of the aspirin shows better dissolution and excretion behavior compare to the commercial aspirin [63].

Valsartan (VAL) is a potent, highly selective and orally active antihypertensive drug with sparingly solubility in aqueous media (especially in gastric fluids). Therefore its absorption is limited by its dissolution rate. Nalluri et al. prepared and investigated the recrystallized form of this drug. According to their results (evidenced by the DSC and powder X-RD studies), by applying of the recrystallization technique, VAL can be transposed into either amorphous phases or amorphous dispersions. The recrystallized VAL exhibited improved aqueous solubility and dissolution properties and potentially therapeutic efficacy compared to an untreated drug [52].

Nokhodchi et al. recrystallized phenytoin in ethanol and acetone. According to their results, needle-like and rhombic crystal habits exhibit different dissolution rates. They suggested that the differences in dissolution rates for phenytoin were related with the surface area of various crystals with different shapes [64].

Carbamazepine is a poorly water soluble drug and its absorption may be unpredictable. This drug is applied as first line monotherapy for seizures in elderly patients. Proven efficacy and less cost are two major advantages of carbamazepine. Mahalaxmi et al. recrystallized carbamazepine by using two solvents and at different cooling conditions. Their outcomes showed improved dissolution behavior of the treated drug [65].

Adhiyaman et al. reported different properties of dipyridamole crystals that prepared by the recrystallization process. Dipyridamole is a critical antiplatelet and peripheral vasodilator drug that has poor water solubility and then bioavailability, which limits its effectiveness in clinical tries. Their results showed that the prepared crystals of dipyridamole under optimized conditions, significantly improved the dissolution rate of the drug compared to untreated one [66].

Applying of solvents or high temperatures did not modify the crystalline form of ketoconazole. It was reported that adjusting of growth of crystal faces can affect on the physicochemical properties of the ketoconazole crystals. It was demonstrated that habit modification and different degrees of crystallinity are significant parameters in the enhancement of the dissolution rate [67].

3.1. Recrystallization steps

Choosing a proper solvent is the first step of the recrystallization process. After selection of a proper solvent, an impure compound is dissolved in the minimum amount of a hot solvent. Then solution is decolorized with activated charcoal (if needed) and any insoluble material is filtered off. If the crystal formation process occurs too rapidly, impurities may become trapped in the crystals. Slowly cooling of the resulting solution to induce crystallization is the next step. Finally the crystals are collected, washed and dried. Figure 2 shows steps of the recrystallization process [9, 66, 68].

3.1.1. *Choosing a proper solvent*

The most important feature of the recrystallization technique is the selection of the solvent. There are two main facts in purification of solid organic materials by the recrystallization method: different solids have different solubilities in a given solvent and most solids are more soluble in hot than in cold solvents [69, 70].

Numerous solvents are employed for recrystallization of drug compounds. Selection of the recrystallization solvent should be performed on a case-by-case basis [9, 68]. This is due to the variant solubility of different organic compounds in these solvents. It is clear that, at the first, the material should be introduced into solution and then can able to come back out of solution. Choosing the appropriate solvent is very important in recrystallization, because it leads to

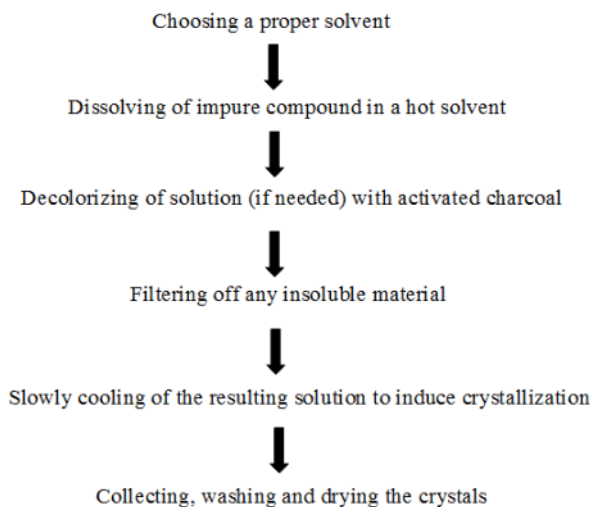


Figure 2. Steps of the recrystallization process.

increasing our yield of product [9, 25, 68]. This selected solvent should have a lower boiling point than the melting point of the solid that being recrystallized. Furthermore, the drug should be soluble in the boiling solvent but have poor solubility in the same solvent after cooling [25, 64].

3.1.2. Melting point of drug and solvent

A melting point is employed to identify a substance and to get an indication of its purity. The melting point of a solid is the temperature at which the vapor pressure of the solid phase becomes equal to the vapor pressure of the liquid phase. Purity of a recrystallized drug is evaluated by observing its color and by measuring its melting point range. According to literature, the boiling point of the recrystallization solvent should be lower than the melting point of the compound to be recrystallized. If it is higher than the melting point of drug, the drug will “oil out”, the process in which a drug is insoluble in a solution at a temperature above its melting point [9, 66, 68].

3.2. Common procedures for recrystallization

Different polymorphs of active pharmaceutical ingredients can be obtained through recrystallization processes based on solvents, solid-state transitions and vapor deposition [54].

In the controlled kinetic or thermodynamic conditions, crystallization of drug polymorphs can be performed from a solvent system. Supercritical fluid techniques are used for micronization and recrystallization of different drugs. According to the reports, modification of solid state

characteristics, such as crystal habit, crystallinity and polymorphism, has been successfully achieved through recrystallization of drug particles using various supercritical antisolvent (SAS) processes [70, 71]. This technology by using carbon dioxide gas is able to modify the solid state properties of drugs, such as characteristics of particles (size, shape, surface, crystal structure and morphology), crystallinity and polymorphism leading to affecting their dissolution rate and bioavailability [72]. The supercritical antisolvent technique is based on injection of an organic solution (containing drug crystals) into supercritical carbon dioxide. During the mixing, supercritical CO₂ is quickly dissolved in the organic solution and leads to the precipitation of solutes (drug) by an antisolvent effect. Then supercritical CO₂ efficiently extracts the organic solvent, leads to achieving completely solvent-free products [71]. Figure 3 shows recrystallization of a drug by using the supercritical antisolvent (SAS) process schematically.

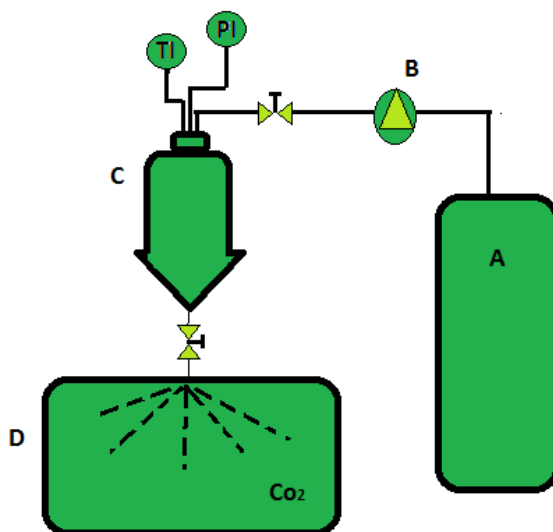


Figure 3. Recrystallization by using the supercritical antisolvent (SAS) process. A) Drug solution in good solvent; B) Peristaltic pump; C) Spraying gun for drug solution; D) Chamber with saturated CO₂ gas

Some drugs have also been recrystallized by the spherical agglomeration technique in order to modify their dissolution properties. For poorly water soluble drugs, a water immiscible organic solvent can act as an external phase and a 20 % calcium chloride as a bridging liquid [73]. The spherical crystallization is a particle size enlargement method that includes crystallization and agglomeration using bridging liquid [74]. Indeed, this method is a particle design technique that crystallization and agglomeration can be performed simultaneously in one step to transform crystals directly into the compacted spherical form [75, 76]. By using of this method, direct tableting of drug instead of further processing like mixing, granulation, sieving

and drying is possible [73, 76, 77]. In 1986, Kawashima applied the spherical crystallization method for size enlargement of drugs in the pharmaceutical field. Martino et al prepared spherical propyphenazone crystals by the agglomeration recrystallization technique using a three solvent system [78]. Figure 4 shows the mechanism of the recrystallized agglomerates formation by the spherical agglomeration method.

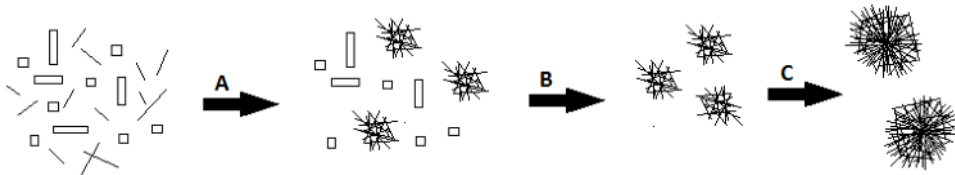


Figure 4. Mechanism of the recrystallized agglomerates formation by the spherical agglomeration technique; A) Recrystallization by addition of bridging liquid, B) Random coalescence, C) Enlarged spherical agglomerates.

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. A poor solvent (as an antisolvent) is used to generate the required supersaturation [74, 77].

Polymorphs may also be generated through solid-state transition by recrystallization of metastable polymorphs and amorphous forms, or through desolvation of solvates (including hydrates) [60]. Physical vapor deposition (PVD) method is an atomistic deposition procedure in which material is vaporized from a solid or liquid source in the form of atoms or molecules and transported in the form of vapor through a low pressure environment to the substrate where it condenses [60, 79].

4. Mechanism of recrystallization that effects on dissolution rate

In the nature, crystals can be categorized into seven crystal systems with various properties. Each of these crystal systems has differences in the relative sizes of their faces as well. This variation is called crystal habit modifications. In fact the morphology of a crystal depends on the growth rates of the different faces of it. Fast growing faces have little or no effect on the growth form while slow growing faces have more influence. Environmental conditions and structure and defects of crystal governed the growth of a given face [80]. The interaction of the solvent at the different crystal solution interfaces may cause to modified roundness of growing crystal faces (or edges), changes in crystal growth kinetics and enhancement or inhibition of crystal growth at certain faces [54]. Figure 5 shows the crystal habits arising from growth inhibition at crystal faces.

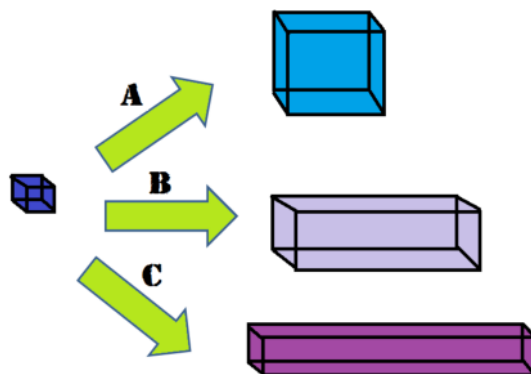


Figure 5. Crystal habits arising from growth inhibition at crystal faces; A) Growth equal in all dimensions, B) Growth inhibited in one dimension, C) Growth inhibited in two dimensions.

In pharmaceutical manufacturing, a crystal habit of a drug molecule is an important characteristic. Different crystals have different planes, specific surface and free surface energy. Therefore they show different physicochemical properties such as dissolution rate, flowability and compressibility [68]. The existence of the drug structure in various crystalline shape influence on the bioavailability and biological efficacy of a drug [66]. The crystalline form that has the improved dissolution rate and solubility is useful for developing the efficient pharmaceutical product of drugs [68, 81].

The primary mechanism of recrystallization is the long-range motion of grain boundaries that removes dislocations from the material [82]. According to numerous reports wettability and consequent dissolution rate of different crystalline forms of drugs could be determined by exposure of diverse crystal faces [83]. The constituent molecules of a crystalline material are part of an orderly three-dimensional structure [84]. Depending on the crystallization conditions, these molecules arrange in different forms. This crystalline form of material is known as polymorphic and each of its crystal ordering is called a polymorph. Indeed, the polymorphs are substances with the same chemical composition but presenting different crystalline forms [85]. Different crystalline forms include various crystallographic systems, lattice parameters and position of the atoms in the elementary cell [86]. Under different conditions, a crystalline drug is crystallized into different polymorphic forms. Polymorphs of a substance show different physical properties, such as solubility and dissolution properties. In fact, crystals with higher free energy show higher solubility. Since the molecules in crystals with high energy have weaker solid-solid interactions compared to crystals with lower energy, they exhibit higher affinity for the solvent in the surroundings [87]. Figure 6 shows the probable consequences of a different crystal form in solubility.

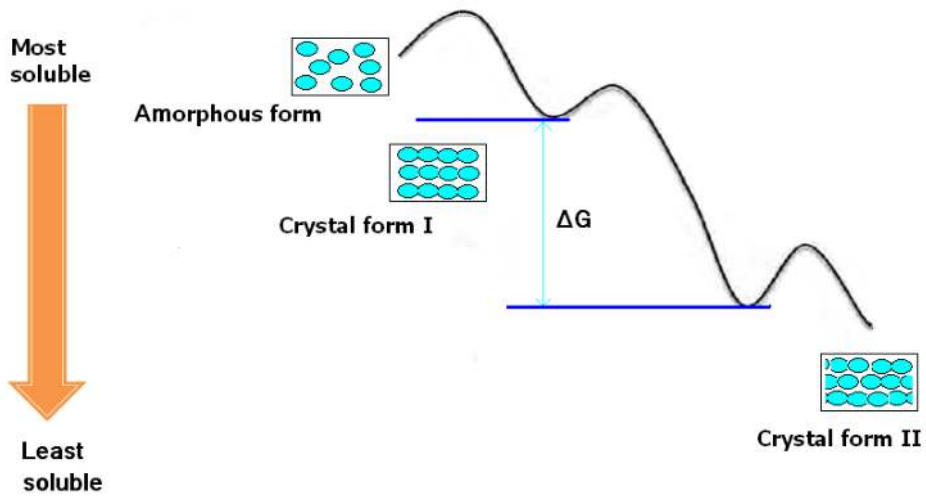


Figure 6. Probable consequences of a different crystal form in solubility

Figure 7 show formation of different crystals following by recrystallization of the initial crystalline form schematically. First, the reaction between solid and solvent breaks the solid crystalline substances (opens the amorphous lattice for amorphous substances). This creates cavities in the solvent (known as phase change) and, hence, molecules of solid become molecules of solute. Then solute molecules recrystallized into another crystalline form(s) [88].

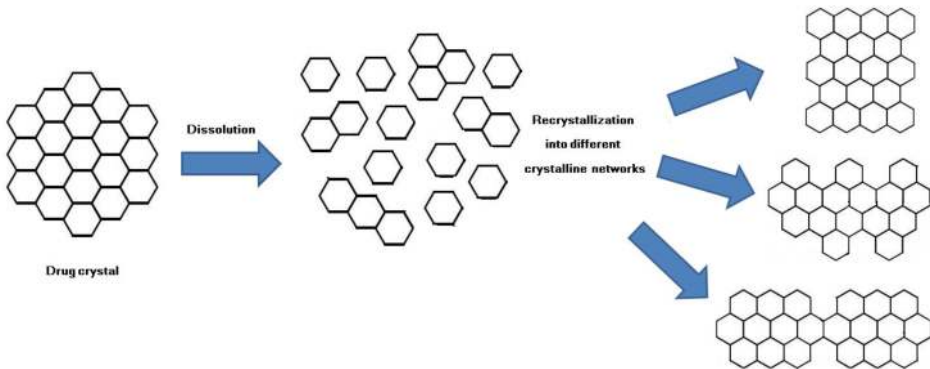


Figure 7. First the reaction between solid and solvent breaks the solid crystal for crystalline substances (opens the amorphous lattice for amorphous substances). This creates cavities in the solvent (known as phase change) and, hence, molecules of solid become molecules of solute. Then solute molecules recrystallized into another crystalline form(s).

Additional information is necessary for control of the nucleation and crystal growth. Dunitz and Bernstein have evaluated the disappearing polymorphs by considering various examples. They state that "once a particular polymorph has been obtained, it is always possible to obtain it again; it is only a matter of finding the right experimental conditions" [89].

5. Effect of excipients and additives on the recrystallization process

Crystal morphology engineering is a useful tool for improving tableting efficiency of pharmaceutical solids. Pharmaceutically accepted excipients can be applied as crystal habit modifiers to overcome the toxicity and/or environmental concerns [90]. Excipients and polymers have a major role to prepare the recrystallized form of a drug. The difference in the physicochemical properties of the drug molecules and the excipient is the main factor in selection of a solvent system for the recrystallization process. The presence of additives such as the polymeric material and surface active agents can influence molecular aggregation during crystallization. Viscosity of the medium and surface tension are reduced by the surfactants that affect the nucleation process. The presence of these additives in the spherical agglomeration process may also reduce the processing time and improves the bioavailability and the micrometric properties of drug [91].

Various polymers like hydroxy propyl methylcellulose (HPMC), poly ethylene glycol (PEG), ethyl cellulose (EC) and poly vinyl pyruvate (PVP) can be used to improve poor compressibility and handling qualities of pure drugs by crystallization techniques [92]. This improves the micromeritic and drug release properties of the crystals as well.

Crystallization is inhibited by some of the polymers such as methylcellulose, Hydroxypropyl methyl cellulose (HPMC), Polyvinylpyrrolidone (PVP). Among these, PVP has been found to be the most effective in inhibiting crystallization of drugs. These antinucleant polymers are incompatible in both size and size of the host molecules of the growing crystals surface. Then, their incorporation into the lattice alters growth characteristics of the host molecules [93]. Recrystallization of the amorphous drug may be avoided by entry of stabilizing hydrophilic excipients in the composition. Indeed, stabilizing excipients are prevented recrystallization of amorphous drug particles by steric hindrance and/or the formation of hydrogen bond with drug molecules [94]. As a noticeable point, the stabilizing excipients should be hydrophilic for improving the wetting properties of drug particles and these hydrophilic excipients should not be hygroscopic as well.

6. Methods for characterization of crystals

There are different analytical methods and techniques for characterization of various properties of crystals and therefore efficiency of the recrystallization procedure. Measuring of size, crystal size distribution and surface microtopographic observations can help to prediction of growth mechanisms of crystal faces under different conditions. Monitoring the surface

topography during crystal growth can display events that are not evident from morphology studies. Some characterization techniques of the crystals are collected in table 1.

Technique(s)	Characteristic(s)
Sieve analysis, laser diffraction, and computerized image analysis.	Size and size distribution of crystals [95].
Optical microscope	Size, morphology and shape of crystals [96].
Scanning electron microscopy	Size, surface topography, polymorphism and crystal habit [95].
X-ray powder diffraction	It is important for establishing batch-to-batch reproducibility of a crystalline form. The type of crystal can be determined by using this technique. An amorphous form does not form a special pattern [97].
Fourier Transform Infrared spectrometer (FTIR)	It is much more beneficial for identifying between solvates and anhydrous form [95].
Differential scanning calorimeter (DSC)	It can measure the heat loss or gain resulting from physical or chemical changes within a sample. If a mixture of drugs and polymer is crystallized together then variation in properties of crystals can be evaluated with DSC [75].
Angle of repose, angle of spatula, angle of fall and Carr's index.	Flowability [98].
Contact angle of water to the compressed crystals	Wettability (As the contact angle is decreased the wettability is enhanced) [99].
By measuring the interfacial tension between the bridging liquid and the continuous phase, contact angle and the ratio of the volumes of the bridging liquid and solid particles.	The strength of the agglomerated crystals [78].
From the comparison of stress relaxations and elastic recovery the compressibility of the spherical and single crystals can be evaluated.	Compressibility [100].

Table 1. Characterization techniques of the crystals

Understanding the thermodynamic and kinetic behavior of the system is necessary for developing of reliable processes. There are various techniques that can be informed us about crystallization kinetics and growing mechanisms.

Various information can be obtained by using of an optical microscopy (inverted microscope); studying of crystallization processes *in situ*, monitoring of the transformations in suspensions, determination of transformation times, screening and characterization of additive/solvent interactions with specific crystal faces, identification of nucleation mechanisms and measuring the crystal growth rate [96]. Three latter mentioned points can be achieved by using an electron microscopy and atomic force microscopy techniques as well. Monitoring of molecular association processes that direct nucleation and crystal growth can be performed by Raman

spectroscopy [95]. Spectrophotometry and chromatography techniques are applied for measuring of the concentration of solute in solution and supersaturation process, and a diffraction calorimetry spectroscopy for monitoring the solid phase composition of crystals [101, 102].

7. Conclusion

The solubility, dissolution rate and crystal properties of a drug substance play a key role in the pharmaceutical development, manufacturing and formulation. Low solubility of a certain crystalline form of a drug leads to the low dissolution rate and bioavailability and therefore reduced biological responses. Low solubility reduces also rates of drug clearances and then increases the toxicity of the drug product. Drug crystals can be modified by the recrystallization technique and this process can affect the physical and physicochemical properties such as melting point, solubility, true density, dissolution profile, flowability and tabletability. The recrystallization method is simple and inexpensive enough for scaling up to a commercial level. This method has showed an efficient role in the increasing of the bioavailability of poorly soluble drugs. Understanding the thermodynamic and kinetic behavior of the system is necessary for the development of suitable recrystallization processes. Under controlled conditions, recrystallization may lead to enhanced surface area and revelation of more polar surface moieties, therefore cause to enhanced dissolution rate. Conversion to a more stable polymorph, recrystallization of the amorphous material or reduced chemical stability are some of the recrystallization problems in regard to solubility and dissolution rate of drugs.

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