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Review Article

Role of Solvents in Improvement of Dissolution Rate of Drugs: Crystal Habit and Crystal Agglomeration

Maryam Maghsoodi*

Drug Applied Research Center and School of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

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Abstract

Crystallization is often used for manufacturing drug substances. Advances of crystallization have achieved control over drug identity and purity, but control over the physical form remains poor. This review discusses the influence of solvents used in crystallization process on crystal habit and agglomeration of crystals with potential implication for dissolution. According to literature it has been known that habit modification of crystals by use of proper solvents may enhance the dissolution properties by changing the size, number and the nature of crystal faces exposed to the dissolution medium. Also, the faster dissolution rate of drug from the agglomerates of crystals compared with the single crystals may be related to porous structure of the agglomerates and consequently their better wettability.

It is concluded from this review that in-depth understanding of role of the solvents in crystallization process can be applied to engineering of crystal habit or crystal agglomeration, and predictably dissolution improvement in poorly soluble drugs.

Introduction

Crystallization from solvents is commonly used for the purification of drugs during their final stages of manufacturing and it has been demonstrated that under certain conditions crystals with completely different appearance are produced.[1] The crystallization technique can change the crystal properties such as habit, polymorphism and size. A crystalline solid is characterized by a definite external and internal structure. Habit describes the external structure, and polymorphic state refers to the internal structure of a crystal. One of the important factors, which affect the bioavailability and therapeutic efficacy of drug, is the existence of active ingredients in various crystal forms having different internal structure.[2] Most drugs appear in different crystal forms. The impact of crystal form on pharmaceutical development has been the subject of numerous reviews with Singhal and Curatolo providing one of the most recent articles in 2004.[3] In particular, the influence of crystalline modification on drug dissolution and bioavailability has been considered. There have been numerous reports demonstrating the influence of polymorphic and crystalline form on dissolution rate and/or oral bioavailability. These have included discussions on the crystalline forms of chloramphenicol palmitate,[4] phenobarbital,[5] spironolactone[6] and carbamazepine[7] in which metastable crystalline forms have provided enhanced dissolution behaviour. It was suggested that where large free energy differences between polymorphs exist, the greater solubility of the metastable form could be exploited to enhance absorption and bioavailability. Although the utilisation of metastable polymorphs offers a route to improved dissolution, concerns still exist with respect to conversion of these materials to more stable crystalline forms during processing and storage which limits the potential benefits of using metastable forms for enhancing dissolution behaviour. Problems caused by polymorphic changes of drug substances are described by several authors. For example in 1998 several lots of capsules of the drug ritonavir failed the dissolution test. A polymorphic form, which was hitherto unknown, with greatly reduced solubility was formed.[8]

But dissolution rate cannot only differ for various polymorphic forms, but also for various habits of the same drug.[9] However, crystal habit has been paid scant attention. Moreover, crystal habit is usually considered critically only when certain problems are detected during processing/storage of a dosage form. Crystal habits influence many morphology characteristics, rheological and technopharmaceutical behavior and, therefore, drug bioavailability from dosage forms.[10] Crystal habit influences particle orientation, thus modifying the flowability, packing, compaction, syringability, suspension stability, and dissolution characteristics of a drug powder. Thus the optimization of crystal properties through modification of habit without the formation of a polymorphic form seems to provide an alternative means of modifying the dissolution behavior of drugs.[11-13]

The overall shape of a growing crystal is determined by the relative rate of growth of its various faces. Growth rate of a surface will be controlled by a combination of structurally related factors such as intermolecular bonds

***Corresponding author:** Maryam Maghsoodi, Tel: (+98) 41-33392608, Fax: (+98) 41-33344798, Email: maghsoodim@tbzmed.ac.ir

and dislocations, and by external factors such as supersaturation, temperature, solvent and impurities.[14-16] Among those external factors, solvent strongly affects the habit of crystalline materials; however, the role played by solvent interactions in enhancing or inhibiting crystal growth is still not completely understood.[17]
Furthermore, according to literature solvent composition has been used to tailor the dissolution properties of drugs by agglomeration of crystals. One interesting method for agglomeration of crystals is denoted spherical crystallization that combines several processes into one step, including synthesis, crystallization, separation and agglomeration.[18-22]
This review focuses on the studies related to the role of solvents in enhancing drug dissolution by modifying crystal habit or agglomeration of single crystals.

Influence of solvents on modification of crystal habit

Researches in field of crystallization have been properly demonstrated the effects of solvents on changing crystal habit and in turn on dissolution properties. Crystallization of tolbutamide (TBM) from various solvents resulted in different crystal habit. Crystals that were obtained from methanol and ethanol show a plate-like crystal habit. Needle-like crystals were produced from solvents like acetone. A more cubic crystal habit was obtained using ethyl acetate as crystallizing solvent. In tetrahydrofuran, prismatic crystals were obtained. The TBM crystals showed differences in dissolution profiles depending on the crystallizing solvent. Crystallization of TBM from methanol and ethanol produced small, circular, platy crystals that exhibited higher dissolution than rod-like crystals of pure TBM powder. After 60 min, 86% and 81% drug were dissolved in methanol and ethanol, respectively, while only 67% drug was dissolved in pure TBM drug powder. Needle-like crystals, cubic-shape crystals, and prismatic crystals obtained from acetone, ethyl acetate, and tetrahydrofuran, respectively, showed decreased dissolution relative to pure TBM powder.[23] In another study, it has been reported that modified crystals of trimethoprim having different habits but belonging to the same sieve fraction and polymorphic state exhibit significantly different dissolution profile. The habit modification of dipyridamole by crystallisation using different solvents has been reported.[24] The dissolution rate of rod shaped particles crystallised from benzene was notably more rapid than for rectangular needle shaped crystals produced using methanol. In studies of ibuprofen, precipitatin of the drug from ethanol and acetone produces small, circular platy crystals that exhibit higher dissolution than the flat, rod like crystals obtained from propylene glycol and 2- propanol.[25] Assaf et al has shown that the crystallization medium has major effect on mefenamic acid (MA) crystal habit. Crystallization of MA in acetone resulted in needle shape crystals, while crystallizing in ethanol and isopropanol resulted in plate shaped crystals. The dissolution rate of crystals showed significant differences in the order of acetone> ethanol> isopropyl alcohol.[26] These investigations clearly indicate that the crystallizing solvent strongly influences the crystal habit. This might be due to the solute-solvent interaction at various crystal–solution interfaces, which leads to altered roundness of the interfaces, changes in crystal growth kinetics, and enhancement[27] or inhibition[28] of growth at certain crystal faces. Thus it is assumable that polarity of the solvent and the interaction that leads to its preferential adsorption at selected faces of the solute are critical factors in determining the habit of a crystallizing solid. Furthermore, as concluded from these studies the amount of drug dissolved from different crystal habits of drugs depends on the size and number of crystal faces exposed to the dissolution medium. For example, as explained above mefenamic acid crystals prepared from acetone resulted in needle -like shape with higher dissolution rate compared with the plate- like crystals prepared from alcohols which has been attributed to higher specific surface area of needle crystals than that of plate crystals.[26] Although, various studies demonstrate the importance of crystal habit in altering the dissolution profile, the influence of solvent on the wettability of the obtained crystals cannot be ruled out. It is known through studies of crystallisation and comminution that exposure of different crystal faces determines the nature of those faces,[29] which in turn will influence the wettability and subsequent dissolution of drug. The crystallization of sulfadiazine from ammonia solution significantly reduces the dissolution rate, indicating reduced wettability of the outer surface.[12] This seems to be because the outer face of the crystallizing solid is influenced by the liquid from which it is being crystallized. Depending on the solvent used for crystallization, internalization of the functional groups that are less attracted to the liquid takes place.[30] In the study that MA was crystallized from acetone, ethanol and isopropanol, interaction between acetone and mefanamic acid resulting in crystals with a higher solubility and wettability (Schiff_base reaction) which was confirmed with a contact angle data. This surface modification in MF crystals is caused by surface-solvent interactions, which affect the growth rate of polar faces differently. Depending on the nature of the solvent, difference is mainly caused by the hydrogen bond interactions. Solvents influence the crystal growth from dissolved drug molecules through various mechanisms. Solvent properties such as polarity, molecular weight, and interaction with dissolved drug are factors that influence the direction in which crystals grow on nuclei. It is suggested that polar solvents were preferentially adsorbed by polar faces and non-polar solvents by nonpolar faces. Both alcohol and acetone as crystallization media interact through hydrogen bonds with MA hydroxyl groups. As the interaction of acetone will be stronger than alcohol due to its relatively high polarizability, and has better ability to form Schiff-base reaction (π =0.71 for acetone and 0.54 for alcohol), the growth of crystals from that side is more inhibited and crystal growth is continued from other sides.[31] The

formation of different habits of drugs is also attributed to interactions of drug and these crystallization solvents. In another study about phenytoin, the morphology of crystals produced under similar conditions following recrystallization from ethanol and acetone was shown to be needle-like and rhombic respectively.[32] This change in habit was ascribed to stronger interaction of acetone with the hydroxyl groups of phenytoin, due to its relatively high polarizability. Although there were some differences in dissolution rate observed between crystalline powders of different morphology, these differences were predominantly attributed to changes in surface area rather than improvements in the wetting of more polar surface moieties. Chow et al.[33] however, when correcting for the contribution of surface area, have suggested that the crystal habit of doped crystals had a notable role to play in the enhancement of intrinsic dissolution rate of phenytoin due to an increased abundance of polar groups.

Effect of solvents on enhancing dissolution rate of crystals due to change in size, number and wettability of crystal faces as a consequence of crystal habit modification can be explained by the Noyes–Whitney dissolution model Eq.(1)

$$DR = {dX}/{dt} = \frac{A \times D}{h}(C_s - {X_d}/{V})$$

where DR is the dissolution rate, A is the surface area available for dissolution, D is the diffusion coefficient of the drug, h is the thickness of the boundary layer adjacent to the dissolving drug surface, Cs is the saturation solubility of the drug, Xd is the amount of drug dissolved at time t and V is the volume of dissolution media. The surface area of drug available for dissolution is dependent on the size and number of crystal faces and their ability to be wetted by dissolution medium.[34]

Influence of solvents on agglomeration of crystals

The particle size of poorly soluble drugs is always an issue due to its impact on dissolution properties. Micronized drug particles (smaller than 10 μ) have a large specific area and provide a way to improve the dissolution rate,[35] however, micronization by milling is extremely inefficient, can cause physical and chemical instability and produces powder with high free surface energy and electrostatic tendencies and thus poor flowability due to high energy input during the micronization process.[36] Therefore, downstream handling of such small crystals in the pharmaceutical industry such as direct tablet-making or capsule-filling processes tends to be difficult, tedious and expensive. The alternative is to produce small crystals directly in the crystallization. Whatever the micronization procedure is, the small crystals tend to adhere together and form dense aggregate in dissolution medium due to hydrophobic characteristics, and thus decrease in crystal size is not always reflected in improved dissolution properties.[37] For this reason, it is more beneficial to transform the microcrystalline drug itself into a porous agglomerated form during crystallization process. Because the loose adhering of microcrystals together in agglomerates restricts the formation of dense aggregate and hence guarantee the improved dissolution properties. Spherical crystallization is an interesting method to in situ agglomerate of the small crystals during the crystallization, and hence gain favourable downstream processing characteristics combined with improved dissolution properties.

There are two main methods for spherical crystallization: spherical agglomeration (SA) and emulsion solvent diffusion (ESD). In both processes is used a solvent that readily dissolves the compound to be crystallized (good solvent), and a solvent that act as an antisolvent generating the required supersaturation (poor solvent). In the ESD method,[38] the "affinity" between the drug and the good solvent is stronger than that of the good solvent and the poor solvent. The drug is dissolved in the good solvent, and the solution is dispersed into the poor solvent, producing emulsion (quasi) droplets, even though the pure solvents are miscible. The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent phase, and the poor solvent diffuses into the droplets by which the drug crystallizes inside the droplets and forms agglomerates.

In SA 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 SA method, a third solvent called the bridging liquid is also added in a smaller amount and acts as an interparticle binder that promotes agglomeration.[39] 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 interfacial tension effects and capillary forces.[40] The SA method has been applied to several drugs, and it has been found that the product properties are quite sensitive to the amount of the bridging liquid.[41] Spherical crystallization has been described as a very effective technique in improving the dissolution behaviour of some drugs that are characterized by low water solubility and a slow dissolution profile. An improvement in dissolution properties of the spherical agglomerates of Ibuprofen has been reported.[42] Spherical agglomerates of Ibuprofen were obtained by cooling down an ibuprofen- saturated solution in an ethanol/water mixture which was based on the difference of solubility of ibuprofen in ethanol and in water. Dissolution results of the agglomerates and primary crystals of ibuprofen were expressed either as a percentage of dissolved drug without consideration of shape and particle size or in relation to the original sample surface. Considering the fact that the smaller particle size of primary crystals showed higher specific

surface area compared with the agglomerates, surprisingly, the dissolution was faster from the agglomerates than from primary crystals, particularly when it is expressed more realistically as a function of the surface area. The flat faces of the small crystals of ibuprofen could adhere to each other and produce very dense aggregates. While, in agglomerates fine primary crystals compacted loosely which resulted in high porosity in these structures. Therefore, the faster dissolution rate of drug from the agglomerates compared with primary crystals was ascribed to porous structure of the agglomerates and consequently better wettability of these particles. Spherical agglomerates of meprobamate were prepared in a mixture of the partially miscible solvents by using spherical crystallization technique.[43] Dissolution rate of drug from the agglomerates was faster than those of the primary crystals which were attributed to better wettability of the agglomerates. The dissolution profiles of fenbufen exhibit better dissolution behaviour for spherical agglomerates than for single crystals. The standard deviations are also much lower for spherical agglomerates. In this study the powder bed wettability of spherical agglomerates and single crystals were also evaluated. According to the obtained results spherical agglomerates showed markedly higher wettability compared to single crystals. Therefore, faster dissolution rate of the agglomerates could be linked to the better wettability of the spherical agglomerates. Dissolution studies were also carried out on these spherical agglomerates stored for 1 month at different relative humidities (RHs) which results showed that the dissolution profiles remained unchanged.[44] Other investigations demonstrating the potential dissolution benefits of the agglomerates particulate drugs produced using spherical crystallization technique include reports on mefenamic acid,[45] ketoprofen,[46] piroxicam,[47] salicylic acid,[48] carbamazepine,[49] and terbinafine.[50]

Conclusion

According to this review article, it is consultable that the proper selection of solvent during crystallization may be used beneficially for enhancing the dissolution of poorly soluble drugs through modifying crystal habit or by formation of agglomerated crystals. These increases in dissolution appear to be derived from a combination of changes to the size and number of crystal faces exposed to the dissolution medium as well as the nature of those faces which in turn will influence the wettability and subsequent dissolution of drug. Although showing potential as a crystal habit modification or agglomeration of crystals approaches to dissolution rate enhancement, there are only a limited number of examples reported where these approaches have resulted in notable enhancement of systemic exposure in human subjects or in suitable animal models. However, there are enough references[51,52] available in the literature wherein it has been proved that in vitro dissolution data are good predictor of in vivo performance in reality. Therefore, it can be safely concluded that the improvement obtained in the modified crystals will give better bioavailability and better therapeutic activity clinically. However, further exploration of this field is required to fully establish this approach as an effective means of intentionally augmenting the bioavailability of poorly soluble drugs.

Ethical Issues

Not applicable.

Conflict of Interest

The authors declare that they have no conflict of interest.

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