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Modification of Crystal Habit and Its Role in Dosage Form Performance

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ABSTRACT

Crystallization is often employed for purifying a drug substance. Use of different solvents and processing conditions may change the crystal habit, besides altering the polymorphic state. Furthermore, altered habit may result from crystal growth during storage. Hence, there is a need to understand the factors influencing crystal habit and to evaluate critically its role in the performance of dosage forms. Establishing the physicotechnical properties of different habits of a drug will help to recognize lot-to-lot variations in raw materials and to ensure reproducibility of dosage form performance.

INTRODUCTION

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. Polymorphism, which is the definite arrangement of molecules within a solid, has been known to influence various physicochemical and biological properties of a crystalline moiety. However, crystal habit has been paid scant attention. Moreover, crystal habit is usually considered critically only when certain problems are detected during the processing/storage of a dosage form. Crystallization is commonly employed as the final step for purification of a drug. Use of different solvents and processing conditions may alter the polymorphic state and/or habit of the purified drug, leading to variation in raw material characteristics. Hence, changes in crystal habit should be given due attention for ensuring reproducibility of results during the preformulation phase.

In addition, crystal habit influences particle orientation, thus modifying the flowability, packing, compaction, syringability, suspension stability, and dissolution characteristics of a drug powder. Furthermore, alteration of habit due to polymorphic transformations during storage may lead to changes in physical stability of dosage forms. Therefore, it seems imperative to study the factors influencing crystal habit, its relationship with poly-

morphism, and its role in influencing the performance of dosage forms. A few primary factors that alter crystal habit and the influence of altered habit on dosage form performance are summarized in Table 1.

HABIT MODIFICATION

The internal structure or polymorphic state represents the molecular arrangement within a crystal and is manifested in the form of a definite heat of fusion ΔH_f value. The external structure or crystal habit is the outer appearance of a crystal and is described by its length, width, and thickness.

Different habits may be produced when the environment of a growing crystal affects its external shape without changing its internal structure (1). The alteration in habit is caused by the interference with the uniform approach of crystallizing molecules to different faces of a growing crystal (2). Crystal growth may be impeded by adjacent crystals growing simultaneously or contacting container walls. As a result, the development of plane faces may be inhibited, leading to formation of a tabular (moderate development of parallel faces), platy (excessive development of parallel faces), prismatic, acicular (inhibited width), or bladed (flattened acicular) crystal habit (3).

Thus, a single internal structure of a compound can have several different habits. In the case of delayed crystallizing crystal, an irregularly shaped crystal may be produced since it is constrained to occupy only the spaces left between already crystallized moieties. Such irregularly shaped crystals are described as *anhedral* or *allotriomorphic*, and those bound by plane faces are known as *euhedral* or *idiomorphic*. However, anhedral crystals do have a regular arrangement of building blocks in the crystal lattice.

Many factors are known to influence the crystallization process. However, it is difficult to delineate the role of a process variable on crystal habit because an alteration of the variable often leads to change in both deposition and dissolution rate of the material during the crystal growth phase. In addition, the processes are interactive and not independent of each other. For example, a change in the temperature alters the viscosity of the crystallization solvent and changes the saturation level of the solute. Hence, an increase in temperature affects both deposition and dissolution rate of the solute on crystal nuclei, with the net result being dependent on other factors like initial supersaturation level, nature of the cosolvent, rate of agitation, and cooling rate.

Therefore, the complexity of the crystallization process itself seems to have hindered detailed investigation into this field. Nevertheless, due to the great impact on dosage form performance, there is a need to recognize the important factors that influence crystal habit.

Degree of Supersaturation

The degree of supersaturation of the mother liquor or the difference in its concentration on opposite sides of the growing crystal affects crystal habit. The effect of supersaturation on the change in habit can be described by an equation, $y/x = k\Delta G^n$, where y/x is the ratio of crystal length to breadth; k is a coefficient of proportionality depending on diffusion; ΔG is the degree of supersaturation (moles/1000 moles of solvent at the moment of nuclei formation); and n is a number that depends on the crystallographic classification and chemical composition of the substance (4).

Barium sulfate precipitation is reported to be controlled initially by the nucleation reaction and finally by the growth reaction. The growth kinetics can be represented by the equation

$$\frac{da}{dt} = -k(Co - C)^{2/3} \cdot a^q$$

where a is the mean ionic activity of Ba^{2+} and SO_{42}^{-}; t is the time; Co and C are the molar concentrations of barium sulfate available at t_o and t, respectively; k incorporates the kinetic constant and shape factor; and q is proportional to the rate of change of the mean ionic activity and surface of the particle (5).

However, Nielsen (6–8) reported the growth of barium sulfate to be controlled by some sort of chemical reaction in which the crystal formation is a fourth-power step. The precipitation was found to be diffusion controlled when the concentration was greater than 0.4 mM and could be characterized by the equation

Table 1

Influence of Process Variables of Crystallization on Crystal Habit and Dosage Form Performance

Process Variable of Crystallization	Possible Influence on Crystal Habit*	Possible Influence on Crystal/Dosage Form Performance[a]
Supersaturation		
1. More saturation or significant solute–solvent interaction	Rate of nuclei formation is greater than crystal growth	Fine particles are produced
	More growth in one direction producing needle-shaped crystals	Needle-shaped crystals exhibit poor flowability and cause bridging in hopper
2. Less saturation or insignificant solute–solvent interaction	Platy crystals are produced	Platy crystals exhibit greater dissolution, but are not preferred for tablet dosage form
Rate of cooling and degree of solution agitation		
1. Rapid cooling	Rapid crystal growth occurs and asymmetric (thin platy crystals) are produced	Platy crystals are not preferred for tablet dosage forms
2. Slow cooling	Rate of crystal growth decreases, and symmetric crystals are produced	Using symmetric, compact crystals gives more predictable and consistent performance
3. High speed of agitation	Even distribution of crystallizing solute on the nuclei produces elongated crystals with small particle size distribution	Desirable particle size range can be obtained; such crystals exhibit good flowability and less sedimentation in suspensions
4. Low speed of agitation or unstirred solutions	Crystallizing molecules deposit on selected crystal face, producing large platy crystals	Crystals with large particle size are unsuitable for formulations
Nature of crystallizing solvent		
1. More affinity for crystallizing solute	Formation of nuclei is delayed and fine, symmetric crystals are produced	Desired crystal size with better dissolution and flowability
	Interaction of certain functional groups between solvent and solute may impede growth at selected crystal faces	Elongated crystals may be produced that are suitable for formulations due to their better flowability and sedimentation behavior
	Requires a high ratio of crystallizing solute:crystallizing solvent for producing well-defined shaped crystals	
2. Less affinity for crystallizing solute	Nuclei are formed immediately and crystal growth is rapid; relatively larger crystals are produced	
	A low ratio of crystallizing solute:crystallizing solvent is required for obtaining well-defined shaped crystals	
Temperature of crystallizing solvent		
1. Low temperature	Rapid nuclei formation due to spontaneous decrease in saturation level produces irregular shaped crystals	Irregular (dendritic) shaped crystals are not suitable for tableting
2. High temperature	Nuclei formation is delayed and fine, symmetric crystals are produced	Desirable shape and size of crystals can be obtained that are suitable for dosage forms
Presence of impurities		
1. Adsorbable ions, solute molecules	Inhibition or excessive growth of certain crystal faces	Desirable crystal morphology can be obtained during purification by recrystallization
		Prevention of crystal growth in suspensions
2. Structural compatibility between polymer and drug	Interaction of functional groups between polymer and crystallizing solute restricts growth at certain crystal faces	Prevention of habit transformation

[a]No generalization can be made with regard to influence of process variables of crystallization on crystal habit and dosage form performance because the influence of a process variable is interactive and not independent of the other variable. The influences listed here should be used as a guideline only.

$$k_o \cdot t = \int_0^a a^{-1/3}(1-a)^{-1} \cdot da$$

When the concentration was less than 0.4 mM, the kinetics could be described by the equation

$$k_R \cdot t = \int_0^a a^{-2/3}(1-a)^{-4} \cdot da$$

where a represents the degree of precipitation. Hence, an initial concentration less than 0.5 mM produced small prismatic crystals, and a concentration between 0.5 and 1.5 mM produced distorted prisms (corners grew more than the middle of the faces). However, at concentrations greater than 1.5 mM, the corners grew much more than other parts of the crystal, giving them a star-shaped appearance.

It has been suggested that star-shaped crystals are produced during diffusional control of the growth rate since the concentration of crystallizing solute is greatest at the corners. On the other hand, rectangular-shaped crystals are obtained when the concentration of depositing solute is the same over the entire surface. This takes place when the rate of consumption of the solute is slower than the rate of diffusion.

Crystals of anhydrous cholesterol obtained from ethanol under quiescent conditions with a low supersaturation value are platelike; those from shaken solution are elongated; and those precipitated from stirred solution are needlelike. The same trend has been observed by using acetonitrile or methanol as the crystallizing solvent (9). Formation of needlelike crystals at high supersaturation of less-polar solvent can be attributed to the significant solvent–solute interaction. This probably results in preferential blocking of some faces, forcing the crystal to grow in one direction, resulting in a needlelike habit. Similarly, platy crystals are formed when the interaction is less.

Solute–solvent interaction is reported to influence the habit of stearic acid (10). It is worth noting that addition of small amounts of surfactants forces stearic acid crystals to grow only in one modification regardless of the nature of the solvent and crystallization conditions. This is due to the modification of solute–solvent interaction by the added surfactant molecules. Therefore, in the absence of significant solute–solvent interaction (using relatively inert solvents), the degree of supersaturation will perhaps predominantly govern crystal habit. Supersaturation also influences the particle size of crystallizing solute. At high supersaturation, nucleation is more rapid than growth. This results in precipitation of fine particles. However, in thermal recrystallization, growth is faster than nucleation, and large crystals are produced (11).

Rate of Cooling and Degree of Solution Agitation

Rate of cooling alters the crystal habit due to its influence on degree of supersaturation. Cooling a supersaturated solution of drug or pouring it into a crystallizing solvent maintained at low temperature immediately decreases the solubility of the drug and results in rapid deposition of drug molecules on the nuclei.

Rapid cooling of a solution of naphthalene in ethanol or methanol produces thin plates, whereas slow cooling produces compact crystals. This is because of slow deposition of drug molecules on the crystal faces at a low rate of cooling (12). It has been suggested that rapid cooling usually produces needle-shaped crystals because an elongated shape is most efficient in dissipating heat (13). With a decrease in the rate of cooling, the rate of crystal growth also decreases and results in replacement of asymmetric crystals by symmetric crystals (14). Slow cooling of a solution of acetazolamide in boiling water produces elongated prisms, whereas faster cooling produces platy crystals (15). Similarly, cooling an aqueous saturated solution of paracetamol from 65°C to 25°C produces polyhedral crystals. However, when concentrated solution in hot ethanol is added to water (3°C), platy crystals are obtained (16). Hence, modulation of the rate of cooling during crystallization could be employed as an effective means to modify crystal habit.

Although degree of solution agitation has not been studied exclusively, it is logical to expect its effect on crystal habit through its influence on saturation level at the solvent interface of the nuclei. This results in formation of large (platy) crystals from quiescent solutions and elongated crystals from stirred solutions (9).

Nature of Solute

To crystallize a chemical entity by the solvent-change method, it is essential first to make it soluble in an appropriate solvent. Hence, once this has been

done, the source of solute should not influence the crystal habit provided the nature of impurities remains the same. It has been found that, while recrystallized pig insulin precipitates in a perfect rhombohedral shape, cattle and sheep insulin exhibit a twinned appearance. However, in the presence of urea or a halogen in the mother liquor, perfect rhombohedral crystals are produced (17). Although no reason for such findings has been suggested, the role of impurities in the source material cannot be ruled out.

Nature of Crystallizing Solvent

Cholesterol crystallizes as needles from ethanol and methanol and as plates from acetonitrile (9). Resorcinol crystallizes as fine needles from benzene, but as thin prisms from butyl acetate. Similarly, iodoform crystallizes as hexagonal bipyramids from aniline and as prisms from cyclohexane (18). Sulfamerazine solution in acetone, when evaporated at room temperature, produces irregular crystals. Slow evaporation of an ethanolic solution of sulfamethoxazole gives colorless, shining, transparent crystals, whereas a mixture of acetone and ethanol (6°C) produces cylindrical-shaped crystals. Sulfamethazine crystallizes from acetonitrile solution (15°C) into prismatic and platy shapes. While sulfamethoxypyridazine crystallizes as prismatic-shaped crystals from methanol on slow evaporation, sulfacetamide yields large triagonal crystals (19). Crystal habits of paracetamol (20) and other drug crystals (21,22) have also been reported to be modified by a change in the crystallizing solvent.

Crystallizing solvent influences the crystal habit due to modification of the intensity of the solute-solvent interaction. These interactions at various crystal/solution interfaces lead to altered roundness of the interfaces, change in crystal growth kinetics, and enhancement (23) or inhibition of growth (24) at certain crystal faces. 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. Nitrofurantoin forms a monohydrate when crystallized from formic acid–water (2 : 1) due to greater interaction of its polar regions with water than with formic acid. These water molecules are retained at the active sites during crystal growth, while desolvation of formic acid occurs more readily, thereby producing an altered habit (25).

Crystals of ibuprofen precipitated from ethanol and acetone (solvents having high surface tension and dielectric constants and less specific gravity) are thin and circular shaped, whereas those obtained from propylene glycol and 2-propanol are rod shaped (26). Similarly, recrystallization of sulfadiazine from ammonia solution produces long, prismatic, smooth-edged crystals (27).

It is worth noting that different habits of a drug can be obtained using the same solvent by altering the process variables of crystallization, such as cosolvent : crystallizing solvent ratio, temperature of cosolvent and crystallizing solvent, and rate of cooling. Cosolvents having high affinity for trimethoprim require a higher ratio of cosolvent to crystallizing solvent for producing a well-defined morphology. A decrease in the initial supersaturation due to elevated temperature of cosolvent or crystallizing solvent delays crystallization and produces small crystals with an equidimensional morphology. This seems to be due to slow and uniform deposition of the solvent molecules on the nuclei. However, variation of cooling rate does not appreciably affect the habit because of spontaneous precipitation of the drug (28).

Presence of Impurities

Sodium chloride normally develops only cubic faces. However, in the presence of urea, it develops octahedral faces (29,30). Habit modification due to the addition of impurities has been found to depend on the anionic and cationic substituent groups and the nature of substitution (31–34). It has been reported that, at a low saturation level, increasing the additive concentration (cationic or anionic surfactants) results in cessation of growth on certain faces, whereas at high saturation, the additives have relatively less effect on the habit of adipic acid. Furthermore, anionic and cationic surfactants as impurities modify the habit to needles and flakes, respectively (35,36). Addition of traces of *n*-alkanoic acids in the crystallization medium results in development of additional crystal faces on regular hexagonal plates of adipic acid crystals (37).

Impurity molecules generally adsorb on all crystal faces, totally inhibiting crystallization, or on selective faces, leading to an altered morphology. The adsorbed molecule may become incorporated into the crystal surface, thereby introducing lattice strains that influence the apparent solubility of the

developing face. Alternatively, a structural compatibility between the additive and crystallizing molecule may be operative. This leads to inhibition of active sites necessary for crystal growth. Another mechanism may involve the impurity serving as a template for nucleation during the crystallization process. This mechanism offers a great advantage if the impurity is known to grow into a well-defined crystal habit. Hence, depending on the nature of impurity and the mechanism in operation, different habit modifications are possible.

Polyvinylpyrrolidone (PVP) forms a netlike structure over developing crystals and allows sulfathiazole to grow out in fingerlike protrusions. The effective pore size in the net and growth inhibition depend on the relative transport rates of PVP and sulfathiazole to the crystal surface (38). However, prevention of transformation of carbamazepine (amorphous) to its dihydrate form (needles) at low concentrations of hydroxypropylmethylcellulose (HPMC) in tablets cannot be explained by the simple adsorption mechanism because the polymer chain is entangled and less mobile to enwrap all growing sites effectively. Hence, HPMC serves as a template for heterogeneous nucleation, to which carbamzepine dimer attaches through hydrogen bonding. More specifically, structural matching between interatomic distances in the crystal lattice and intraatomic distances along the polymer chain seems to be responsible for transformation inhibition (39).

Hence, there is a need to carry out exhaustive crystallization trials during the preformulation phase and to find out the association of polymorphic forms with new crystal habits. This will help in validating dosage form performance at the particulate level.

RELATIONSHIP BETWEEN CRYSTAL HABIT AND POLYMORPHISM

Although the importance of polymorphism has been recognized a long time, it was only in 1963 that Milosovitch (40) and Shell (41) discovered the influence of polymorphic form on compression characteristics to be a "complex function of crystal habit, anisotropy and effects due to the inherent differences in the crystal structure of the polymorphs." A study of changes in crystal habit accompanying polymorphic transformation will help in delineating the role of crystal habit in dosage form performance.

Sulfathiazole form I (hexagonal prisms) and form II (prismatic rods) are reported to melt at 173°C–175°C and 200°C–202°C, respectively. On slow heating, hexagonal prisms transform to rods below 173°C (42). In supportive evidence, hexagonal plates of sulfathiazole obtained by slow crystallization from warm alcohol have been demonstrated to undergo a transition to prisms at 155°C–162°C, the exact transition temperature being dependent on the heating rate employed (43). Higuchi et al. (44) obtained sulfathiazole (form II) in the shape of long rods by evaporating a supersaturated propanol solution at 80°C. This indicates that form II of sulfathiazole may exist in prism or rod shapes, depending on the solvent and method of crystallization. Moustafa and Carless (45) also observed that different solvents produce sulfathiazole crystals of different shapes, but all could be placed in the same category (form I) since they possessed similar infrared (IR) and differential scanning calorimetric (DSC) properties. The transformation of succinylsulfathiazole from form I to II (in commercial suspension) resulting in the formation of long needles (46) points out the influence of additives and storage temperature in altering the habit of crystals and their polymorphic state.

Dimorphic prednisone alcohol is associated with tabular and columnar habits under the same set of crystallization conditions (47). The five crystalline modifications of cortisone acetate (three anhydrous [I, II, and III], two hydrates [IV and V]) exist in different morphologies. Forms I and II are needles (spear shaped) and square ended (from benzene), respectively. Form II also crystallizes as transparent prisms from chloroform. Forms III, IV, and V are prisms, columnar (spear ended), and needles, respectively (48). This indicates that the same polymorphic state may exist in different habits (form II as needles and prisms). At the same time, different polymorphic forms may be present in the same habit (forms I, II, and V as needles and prisms and II and III as prisms). Calcite, a polymorph of calcium carbonate, shows four different crystalline habits, all belonging to the same class (3). Similarly, procaine penicillin has been obtained in prismatic rodlike and flat scalelike habits, both belonging to the same form as determined by X-ray diffraction (49).

Polymorphic transformation has been found to a accompany change in habit of an experimental material, HMX (cyclo-tetramethylene tetranitra-

mine). The needles of HMX (II) gradually dissolve at 110°C to yield sturdy rods of HMX (I), which is the stable form at 110°C (50). The spontaneous change in crystal characteristics of novobiocin (in suspension) is associated with change in habit from irregularly shaped particles (1–5 μ) to needle and rodlike crystals through the formation of fragile spheroids (~30 μ) that are neither amorphous nor truly crystalline. The transformation proceeds rapidly at high temperature and is directly proportional to concentration (51). Similarly, cholesterol, on conversion from anhydrous to monohydrate form, undergoes habit transformation from needles to plates (52).

Polderman et al. (53) reported that cortisone acetate suspension can be heated to 60°C without resulting in the formation of needle-shaped crystals of the water-stable form. However, others (54,55) found polymorphic transformation of cortisone acetate to be accompanied with habit modification from small, micrometer-size round particles to long broad needles (60 μ length) when kept undisturbed in water (24 h) at room temperature. Cortisone alcohol is adsorbed on the most dense lattice plane, thus preventing the growth of needle-shaped cortisone acetate crystals (56).

A similar phenomenon involving the effect of surface-active agents in retarding the growth of needle habit of sodium acid urate has been proposed to be due to adsorption or competitive inhibition (57). The difference in the melting points of thick prismatic (139°C–142°C) and thin blades and needle-shaped (127°C–133°C) crystals of aspirin having identical optical and spectral properties has been attributed to crystal habit rather than polymorphism (58). Summer et al. (59) reported alteration of the original crystal shape of aspirin without phase transformation on compression. However, compression may sometimes lead to changes in surface characteristics due to polymorphic transformation (60).

Hence, a crystallization process may lead to polymorphic transformation with habit change (42,43,46–48,50–52,54,56,57,60), polymorphic transformation without habit change (48), or habit change without polymorphic transformation (3,48, 49,57–59).

It is noteworthy that when a polymorph of a compound crystallizes in different habits and when such a substance constitutes a large proportion of the bulk, the polymorph of choice would be the one with the habit that exhibits best performance in a dosage form. However, the conditions leading to habit change with or without polymorphic transformation cannot be generalized and need careful studies during the preformulation phase.

CRYSTAL HABIT IN RELATION TO DOSAGE FORMS

Role in Tablet Formulation

Kregiel in 1951 (61) reported that substances belonging to the cubic crystal system present no difficulty for direct compression into tablets. The binary compounds are found predominantly in the cubic and hexagonal system and are characterized by higher symmetry than ternary and more complex compounds found in the rhombic, monoclinic, and triclinic systems (62). The low-symmetry structures, such as carbonates of calcium, lead, nickel, potassium, silver, and sodium, do not form tablets on direct compression (63), indicating that symmetricity is a prerequisite for direct compression.

The flat needles of aspirin align themselves parallel to the punch face, forming a layered structure that exhibits low lateral stress transmission characteristics (64). An increased radially transmitted stress with flaky powdered materials (65) reinforces the above contention. Apart from the mechanical influence of crystal shape, another dominant factor that results from the anisotropy of cohesion and hardness (of low-symmetry crystals) also contributes to the ease of compression. As crystal habit varies, the dominant faces vary in relation to this anisotropy and tend to orient the crystals during a packing or compression process.

The regular spherical particles of spray-dried lactose form stronger tablets compared to angular particles on direct compression (66). Similarly, replacement of platy habit (form B) by nonplaty (form A) crystals of tolbutamide obliterates powder bridging in the hopper and capping of tablets (67). The cubic sodium chloride crystals pack in a bricklike fashion and exhibit greater density than the dendritic crystals. In addition, the reduced slip between dendritic crystals makes rearrangement difficult and results in greater loss of compaction force to the die wall (68). Ibuprofen is generally crystallized industrially from hexane in the form of elongated needlelike crystals. This shape has been reported to be unsuitable for tableting due to poor

flow properties. Equidimensional crystals obtained using methanol and other solvents have been reported to possess better compaction features and flow properties (69). Crystal morphology of excipients such as powdered cellulose (70) and calcium alumina trihydrate (71) has also been reported to influence the strength, content uniformity, and disintegration time of tablets.

The platelike nitrofurantoin crystals undergo greater densification and plastic deformation than the needlelike crystals. In addition, tablets prepared from needlelike crystals exhibit a higher degree of axial recovery following ejection. This seems to be due to development of larger nonpolar faces in platelike crystals that were crystallized from formic acid than polar faces of needlelike crystals crystallized from a formic acid–water mixture. The relative abundance of these faces probably affects the magnitude and strength of bonding during compaction (72).

An orthorhombic structure is characterized by high molecular density and weak interplane bonds. During compression, these planes act as slide planes, which can undergo higher densification. Hence, orthorhombic paracetamol crystals exhibit greater deformation during compression and lower elastic recovery during decompression compared to monoclinic crystals (72). These platy crystals of paracetamol have been recently shown to exhibit lower correlation coefficient values for Heckel plots and strain rate sensitivity, indicating greater fragmentation compared to polyhedral crystals. Tablets compressed from platy crystals show higher elastic recovery, suggesting that these crystals undergo less plastic deformation (16).

It is important to recognize the changes taking place in the internal structure and morphology of crystals during compression. These changes are opposed by intermolecular forces that restore the crystal to its original form and result in elastic recovery of materials. Hence, if the intermolecular forces are exceeded, then plastic flow occurs. It has been demonstrated for aspirin that the displacements occurring along slip planes inside the crystal move in an orderly manner to a new location, with the molecular packing arrangement remaining unchanged. However, cubic sodium chloride crystals possess numerous potential slip planes for plastic deformation, and microscopic examination does not reveal shearing effects. This indicates that shearing occurs at the molecular level in cubic sodium chloride crystals (74). An increase in compression pressure decreases the crystallinity of lactose, producing stronger tablets due to the more activated crystals dissipating acquired energy by interparticle bonding (75,76). Hence, an equidimensional habit that undergoes the highest degree of densification and exhibits a tendency to form new bonds at the fragmentation sites during compaction seems to offer great advantage for tablet formulation. On these lines, a recently reported metastable modification (I) of acetazolamide (elongated prismlike) seems to be a better choice than the triclinic modification II (platelike) available commercially (15).

Role in Dissolution

The amount of drug dissolved depends on the size and number of crystal faces exposed to the dissolution medium. It has been shown that the lifetime of potassium ferricyanide crystal is proportional to the smallest length of the crystal face in contact with liquid paraffin–water interface. Furthermore, nonisometric dissolution of the crystal face indicates a change in crystal shape during dissolution (77). The shape factor of a single crystal of potassium dichromate changes significantly after 50% dissolution and is dependent on the degree of nonisometricity of the crystal (78). Such a mechanism needs to be carefully studied, especially for needle and rodlike nonisometric crystals.

The dissolution rate is also known to be influenced by the presence of additives. Hydroxypropyl β-cyclodextrin has been found to be more effective than PVP in inhibiting the crystal growth and enhancing the dissolution of nifedipine (79). A combination of eudragit RS and cellulose acetate phthalate has been shown to alter the habit and sustain the release of an iron chelator besides improving the flowability (80). Precipitation of ibuprofen from ethanol and acetone produces small, circular-platy crystals that exhibit higher dissolution than the flat, rodlike crystals obtained from propylene glycol and 2-propanol (26). The crystallization of sulfadiazine from ammonia solution significantly reduces the dissolution rate, indicating reduced wettability of the outer surface (27). 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 (81). In

addition, the presence of sodium chloride does not increase the wettability, but enhances the dissolution rate of recrystallized sulfadiazine. This indicates the influence of sodium chloride in opposing the effect of ammonia on the orientation of sulfadiazine molecules. Although these studies demonstrate the importance of crystal morphology in altering the dissolution profile, the influence of polymorphism cannot be entirely ruled out.

It has been recently reported that modified crystals of trimethoprim having different habits but belonging to the same sieve fraction and polymorphic state exhibit significantly different dissolution profiles. Symmetric crystals dissolve faster due to equal exposure of all the surfaces. However, symmetric crystals having a higher size factor (length × breadth) exhibit slow dissolution during the early phase. But, during the later phase, as the size factor decreases, the dissolution rate increases. It is noteworthy that aggregation (lower zeta potential) retards the dissolution of highly symmetric crystals (28). Therefore, habit modification seems to provide an alternative means of modifying the dissolution behavior of drugs. As a corollary, this method may be used advantageously for enhancing the dissolution of less-soluble polymorphs.

Role in Suspension Formulation

The thixotropic behavior of aliphatic urethanes is better when needle-shaped clusters are present (82). The apparent viscosity of acicular hematite suspension is greater than that of spherical crystals of pigmental hematite (83). Shell (41) envisaged easier syringability of platelike crystals compared to needle-shaped crystals. However, no systematic study seems to have been done to clearly bring out the role of crystal habit in suspensions.

The influence of crystal habit on suspension stability is envisaged to be more pronounced than that on tablet formulation. This is because of greater space available for reorientation of particles during settling. In addition, selection of a stable habit is necessary from the viewpoint of crystal growth that often accompanies storage.

The investigation of trimethoprim suspension shows that crystals with high shape factor ($1/L \times 1/B$) exhibit high sedimentation volume and are easily redispersed. During settling, these crystals perhaps form an end-to-face rather than an end-to-end framework as it will result in a decrease in the free energy of the system. Hence, despite having a high zeta potential, the anisometric particles tend to induce "self-flocculation," which produces a scaffoldlike, porous pack structure that is less susceptible to overhead pressure of settling particles. The crystals with irregular shape undergo close-fit orientation and exhibit low sedimentation volume with caking after storage. The massive increase (six times) in sedimentation volume by employing a rod-shaped habit demonstrates the utility of crystal habit modification in enhancing the physical stability and elegance of a low-dose drug suspension (28).

CONCLUSION

Crystal habit is influenced by the process variables of crystallization. Hence, the crystallization methods used for purifying a drug may result in production of different polymorphs of a compound that may be associated with change in habit. Crystal habit plays an important role in influencing the packing, flowability, dissolution, compressibility, and sedimentation characteristics. The judicious selection of a polymorphic state from physical stability or pharmacokinetic point of view may not solve the problem if the selected polymorph of the compound exhibits different habits. Also, polymorphic transformations may result in alteration of habit, thereby affecting the properties of a dosage form. Hence, a critical evaluation of crystal habit along with polymorphism during preformulation will help in maintaining batch-to-batch uniformity of raw materials and ensure reproducibility of dosage form performance.

REFERENCES

1. Takubo, H.; Kume, S.; Koizumi, M. J. Cryst. Growth **1984**, *67*, 217.
2. Haleblian, J.K. J. Pharm. Sci. **1975**, *64*, 1269.
3. Hartshone, N.H.; Stuart, A. In *Practical Optical Crystallography*; American Elsevier: New York, 1964; 1–46.
4. Grzymek, J. Przemysl Chem. **1937**, *21*, 279.
5. Johnson, R.A.; O'Rourke, J.D. J. Am. Chem. Soc. **1954**, *76*, 2124.
6. Nielsen, A.E. J. Colloid Sci. **1955**, *10*, 576.
7. Nielsen, A.E. Acta Chem. Scand. **1957**, *11*, 1512.
8. Nielsen, A.E. Acta Chem. Scand. **1958**, *12*, 951.
9. Garti, N.; Karpuj, L.; Sarig, S. Cryst. Res. Technol. **1981**, *16*, 1111.

10. Garti, N.; Wellner, E.; Sarig, S. J. Cryst. Growth **1982**, *57*, 577.
11. Carstensen, J.T.; Ertell, C.; Jean-Marie, G. Drug Dev. Ind. Pharm. **1993**, *19*, 195.
12. Tipson, R.S. In *Separation and Purification Part I*; Weissberger, A., Ed.; Interscience: New York, 1956; Vol. 3, 433.
13. Carstensen, J.T. In *Theory of Pharmaceutical Systems: Heterogeneous System*; Academic Press: New York, 1973; Vol. 2, 145–147, 262.
14. Malkin, V.I. Problem Metalloved. I Fiz. Metal., Sbornik **1955**, *4*, 113.
15. Griesser, U.J.; Burger, A.; Mereiter, K. J. Pharm. Sci. **1997**, *86*, 352.
16. Garekani, H.A.; Ford, J.L.; Rubinstein, M.H.; Rajabi-Siahboomi, A.R. Int. J. Pharm. **1999**, *187*, 77.
17. Danish Patent 87,001, March 9, 1959.
18. Wells, A. Phil. Mag. **1946**, *37*, 184.
19. Nalini, D.; Tiwari, R.K.; Singh, T.P. J. Sci. Res. **1980**, *2*, 137.
20. Nath, B.S.; Khalil, S.S. Ind. J. Pharm. Sci. **1984**, *46*, 106.
21. Lindberg, W. Neves Jahrb. Mineral. Abhandl. **1956**, *89*, 149.
22. Hendrickson, R.C.; Shulman, S. Microchem. J. **1961**, *5*, 588.
23. Davey, R.J. Solvent effects in crystallization processes. In *Current Topics in Materials Science*; Kaldis, E., Ed.; Elsevier: Amsterdam, 1982; Vol. 8, 429–479.
24. Berkovitch-Yellin, Z. J. Am. Chem. Soc. **1985**, *107*, 8239.
25. Marshall, P.V.; York, P. Int. J. Pharm. **1989**, *55*, 257.
26. Khan, G.M.; Jiabi, Z. Drug Dev. Ind. Pharm. **1998**, *24*, 463.
27. Hammouda, Y.E.; El-Khordagui, L.K.; Darwish, I.A.; El-Kamel, A.H. Eur. J. Pharm. Sci. **1999**, *8*, 283.
28. Tiwary, A.K.; Panpalia, G.M. Pharm. Res. **1999**, *16*, 261.
29. de Rome, J.B.L. In *Crystallographie*; L'Impremerie de Monsieur: Paris, 1783; Vol. 1, 379.
30. Compte de Fourcroy, A.F.; Vauquelin, L.N. Ann. Chim. Phys. **1799**, *32*, 130.
31. Whetstone, J. Trans. Faraday Soc. **1955**, *51*, 973.
32. Whetstone, J. J. Chem. Soc. **1956**, 4841.
33. Whetstone, J. J. Chem. Soc. **1957**, 4284.
34. Whetstone, J. J. Chem. Soc. **1957**, 4289.
35. Michaels, A.S.; Colville, A.R., Jr. J. Phys. Chem. **1960**, *64*, 13.
36. Michaels, A.S.; Tausch, F.W. J. Phys. Chem. **1961**, *65*, 1730.
37. Faribrother, J.E.; Grant, D.J.W. J. Pharm. Pharmacol. **1979**, *31*, 27P.
38. Simonelli, A.P.; Mehta, S.C.; Higuchi, W.I. J. Pharm. Sci. **1970**, *59*, 633.
39. Kathendler, I.; Aoury, R.; Friedman, M. J. Controlled Release **1998**, *54*, 69.
40. Milosovitch, G. Drug Cosmet. Ind. **1963**, *82*, 557.
41. Shell, J.W. J. Pharm. Sci. **1963**, *52*, 100.
42. Groves, D.C.; Keenon, G.L. J. Am. Chem. Soc. **1941**, *63*, 97.
43. Guillory, J.K. J. Pharm. Sci. **1967**, *56*, 72.
44. Higuchi, W.I.; Bernardo, P.D.; Mehta, S.C. J. Pharm. Sci. **1967**, *56*, 200.
45. Moustafa, M.A.; Carless, J.E. J. Pharm. Pharmacol. **1969**, *21*, 359.
46. Moustafa, M.A.; Khalil, S.A.; Ebian, E.R.; Motawi, M.M. J. Pharm. Sci. **1974**, *63*, 1103.
47. Biles, J.A. J. Pharm. Sci. **1961**, *50*, 464.
48. Callow, R.K.; Kennard, O. J. Pharm. Pharmacol. **1961**, *13*, 723.
49. Macek, T.J. Am. J. Pharm. **1965**, *137*, 217.
50. Teetsov, A.; McCrone, W.C. Microscope **1965**, *15*, 13.
51. Mullins, J.D.; Macek, T.J. J. Am. Pharm. Assoc. (Sci. Ed.) **1960**, *49*, 245.
52. Loomis, C.R.; Shipley, G.G.; Small, D.M. J. Lipid Res. **1979**, *20*, 525.
53. Polderman, J.; Bloo, J.H.; Fokkens, J. Pharm. Wkl. Ned. **1958**, *93*, 45.
54. Carless, J.E.; Moustafa, M.A.; Rapson, H.D.C. J. Pharm. Pharmacol. **1968**, *20*, 630.
55. Ostwald, W.Z.Z. Phys. Chem. **1900**, *34*, 495.
56. Carless, J.E.; Moustafa, M.A.; Rapson, H.D.C. J. Pharm. Pharmacol. **1968**, *20*, 639.
57. Allen, D.J.; Milosovich, G.; Mattocks, A.M. J. Pharm. Sci. **1965**, *54*, 383.
58. Schwartzman, G. J. Pharm. Pharmacol. **1972**, *24*, 170.
59. Summers, M.P.; Enever, R.P.; Carless, J.E. J. Pharm. Pharmacol. **1976**, *28*, 89.
60. Ibrahim, H.G.; Pisano, F.; Bruno, A. J. Pharm. Sci. **1977**, *66*, 669.
61. Kregiel, L. Ph.D. thesis; University of Maryland: Baltimore, 1951; 27.
62. Jaffe, J.; Foss, N.E. J. Am. Pharm. Assoc. (Sci. Ed.) **1959**, *48*, 26.
63. Stillwell, C.W. In *Crystal Chemistry*, 1st Ed.; McGraw-Hill Book Co., Inc.: New York, 1938; 259.
64. Windheuser, J.J.; Misra, J.; Eriksen, S.P.; Higuchi, T. J. Pharm. Sci. **1963**, *52*, 767.
65. Higuchi, T.; Shimamoto, T.; Eriksen, S.S.P.; Yashiki, R. J. Pharm. Sci. **1965**, *54*, 111.
66. Alpar, O.; Hersey, J.A.; Shotton, E. J. Pharm. Pharmacol. **1970**, *22* Suppl., 1S.
67. Simmons, D.; Ranz, R.; Gyanchandani, N.; Picotte, D. Can. J. Pharm. Sci. **1972**, *7*, 121.
68. Shotton, E.; Obiorah, B.A. J. Pharm. Pharmacol. **1973**, *25* Suppl., 37P.
69. Gordon, R.E., Amin, S.I. Eur. Pat. 0 120 587 BI, 1986.
70. Szabo, R. Pharm. Ind. **1992**, *54*, 79.

71. Veesler, S.; Boistelle, R.; Delacourte, A.; Guyot, J.C.; Guyot-Herman, A.M. Drug Dev. Ind. Pharm. **1992**, *18*, 539.
72. Marshall, P.V.; York, P. Int. J. Pharm. **1991**, *67*, 59.
73. Joiris, E.; Di Martino, P.; Berneron, C.; Guyot-Herman, A.-M.; Guyot, J.-C. Pharm. Res. **1998**, *15*, 1122.
74. Hess, H. Pharm. Tech. **1978**, *2*, 38.
75. Huettenrauch, R. Pharmazie **1977**, *32*, 130.
76. Huettenrauch, R. Acta Pharm. Tech. **1978**, *Suppl. 6*, 55.
77. Schoonen, A.J.; de Vries, N.G.W.; Huizinga, T. J. Pharm. Sci. **1979**, *68*, 163.
78. Dali, M.V.; Carstensen, J.T. Pharm. Res. **1996**, *13*, 155.
79. Uekama, K.; Ikegami, K.; Wang, Z.; Horiuchi, Y.; Hirayama, F. J. Pharm. Pharmacol. **1992**, *44*, 73.
80. Venkataram, S.; Khohlokwane, M. J. Microencapsulation **1996**, *13*, 519.
81. Buckton, G. J. Pharm. Pharmacol. **1995**, *47*, 265.
82. Hendrickson, R.C.; Shulman, S. Microchem. J. **1961**, *5*, 587.
83. Nunecane, H.; Senna, M.; Kuno, H. Nihon. Reoroji. Aakkaishi. **1983**, *11*, 132.