Molecular interactions between solvent and pharmaceutical compounds in crystallization of polymorphic systems

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Abstract

Polymorphism in pharmaceutical solids is a major issue that has medical, financial and legal implications. There are many thermodynamics and kinetics factors which affect the polymorph selectivity during the crystallization process such as nucleation temperature, supersaturation and type of solvent. Among these parameters, type of solvent is a major kinetic factor that has drawn the attention of researchers. Literature is ripe with research showing the effect of solvent on the polymorph selectivity, mainly using the polar and non-polar terminology, but seldom the researchers have explained the effect of solvent at molecular level.

This work looks into the effect of solvent and the corresponding intermolecular interactions on the polymorphic selectivity. Two case studies on the effect of solvent will be discussed for polymorphic systems of stearic acid (used for tablet coating) and ranitidine hydrochloride (H_2-receptor antagonist drug).

Introduction

Polymorphism is the phenomenon that a chemical substance crystallizes in more than one crystal structure with different arrangements and/or conformations of the molecules in the crystal lattice. It has been shown that around one-third of organic substances show crystalline polymorphism under normal pressure conditions. A further one third are capable of forming hydrates and solvates (Henck et al., 1997). Borka and Haleblian (1990) published a list of about 450 pharmaceutically important materials that exhibit polymorphism.

There are a number of factors, which affect the selectivity of different polymorphs of a given substance in crystallization processes. These factors include the type of solvent, degree of supersaturation, crystallization temperature, rate of cooling, impurities and additives, surface of crystallization vessel, suspended particles, seeding and flow regime. Among these parameters the type of solvent is a major factor in polymorphic selectivity and also morphology. This effect arises mainly from the solvent-solute interaction at molecular level. The very first obvious solvent effect on crystallization is related to the solubility. Traditionally, it is believed that “like dissolves like” and three main categories of solvents are noted. The first category is the hydrogen donors such as water and methanol, which are polar. This category is known as dipolar protic solvents. The second category, dipolar aprotic solvents, is also polar but they are not able to donate hydrogen for bonding such as acetonitrile and nitrobenzene. The last category is the nonpolar solvents that are also aprotic such as pentane and benzene. The primary application of the solubility is to estimate the crystallization throughput or yield especially in cooling or antisolvent crystallizations. It is also a useful method for determining the thermodynamic stability regions of polymorphs since the more stable form has the lowest solubility. However, the thermodynamic stability of the polymorphic systems is not a function of employed solvent and exhibits the same behavior in all solvents.

The solvent-solute interactions during cluster formation for nucleation and also crystal growth can significantly affect the ultimate crystal structure and morphology. If the solvent-solute is strongly bonded at a special surface, the rate-limiting step of growth is the removal of the solvent from the face. In this case the bonded surfaces grow slowly or do not grow and the solvent has the inhibition role (Black et al., 1991). Mirmehrabi et al. (2004a) showed that the polymorphism in ranitidine hydrochloride is a function of the type of crystallization solvent. They suggested that in anhydrous less polar or non-polar solvents the intramolecular hydrogen bonds are expected to be strong and thereby lead to Form 1 production where crystal growth is restricted. But in aqueous and/or more polar solvents the intramolecular hydrogen bonds of the nitroethenediamine moiety are expected to be weakened or disrupted and thereby lead to Form 2 production, where large well-defined crystals are formed.

This presentation discusses the influential properties of solvents in crystallization of polymorphic compounds for two case studies of stearic acid and ranitidine hydrochloride.

Results

The majority of pharmaceutical compounds contain hydrogen-bonding sites to be effective in biological processes of human body. As a result, dipole-dipole interaction and hydrogen bonding play the main role in solvent-solute interaction at molecular level in crystallization of pharmaceutical compounds. The first step toward understanding the solute-solvent interaction is the determination of charge distribution in the solute and solvent molecules. Identifying the functional groups of the organic solute that dictate the crystal chemistry is the next step. A group consideration method was developed for calculating the charge distribution in the molecule using the electronegativity of each atom. The results are comparable with the quantum mechanics charge calculation especially for the chain molecules. For polycyclic molecules the electronegativity method did not offer proper partial charge calculation.

Since hydrogen bonding is a direct dipole-dipole interaction between hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) then the hydrogen bonding ability is a function of partial electronic charges on the donor and acceptor atoms. The hydrogen bonding ability was correlated with the partial charges and also molecular dipole moment using the experimental data available in literature (Abraham et al., 1989).

Stearic acid, $C_{18}H_{36}O_2$, is an aliphatic chain molecule with 17 carbons which terminates with a carboxylic group. It has four known polymorphs (Sato et al., 1984; Mirmehrabi and Rohani, 2004d).

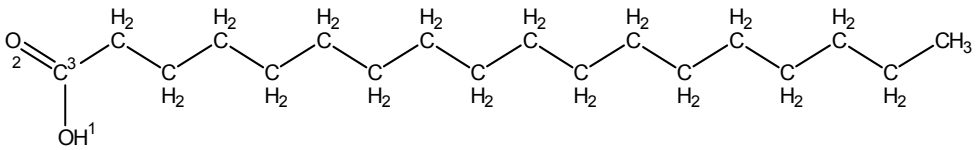


Table 1 shows the charge distribution in the stearic acid that has been calculated using the developed group consideration method.

Using the developed correlations the hydrogen bond ability of stearic acid with dipole moment of 1.76 will be:

$\log(K_\alpha)$ = 2.03 Donor ability from O_1

$\log(K_\beta)$ = 1.20 Acceptor ability from O_1

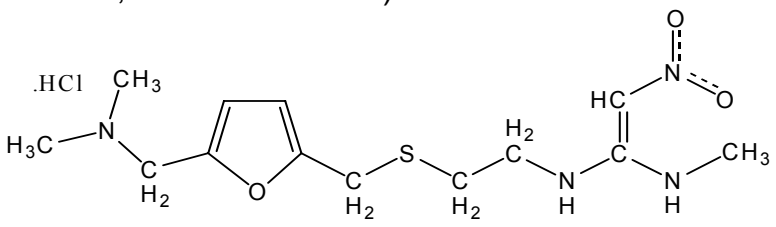
$\log(K_\beta)$ = 1.24 Acceptor ability from O_2

Although this molecule is not polar but from above results it can be seen that both hydrogen donating and accepting ability of the stearic acid are relatively high so that there is a high tendency between stearic acid molecules to establish hydrogen bonding with each other and also with solvent molecules. This phenomenon favours the crystallization of Form B in the presence of hydrogen donating solvents and Form C in the presence of molecules that are not able to donate hydrogen including aprotic solvents and also solvents that are only hydrogen acceptor such as acetone.

Table 1- Charge distribution in the stearic acid molecule

Atoms	Partial Charge
O1	-0.2779
O2	-0.2661
C3	0.0714
C4	0.0202
C5	-0.0362
C6	-0.0513
C7	-0.0563
C8	-0.0588
C9	-0.0603
C10	-0.0613
C11	-0.0620
C12	-0.0625
C13	-0.0630
C14	-0.0633
C15	-0.0636
C16	-0.0640
C17	-0.0643
C18	-0.0651
C19	-0.0651
C20	-0.0692

Ranitidine hydrochloride (RAN-HCl) exists in two solid forms with different morphology and physical properties. Tautomerism occurs in the nitroethenediamine moiety of the molecule and it is the reason of polymorphism in the solid state of RAN-HCl (Mirmehrabi et al. 2004a, 2004b and 2004c).



Solvent has a major effect on the polymorphic isolation of RAN-HCl through hydrogen bonding with nitro group. Strong hydrogen bond donors such as methanol and water interact with oxygen atoms of the nitro group and pull the electron cloud from C=C to $C=NO_2$ and result in nitronic acid tautomer which is the predominant tautomer in Form 2 ranitidine hydrochloride. So, the presence of methanol and water in the crystallization media leads to the formation of Form 2 ranitidine hydrochloride.

Conclusions

Solvent is one of the most important kinetic factors that govern the polymorphism. It can play a role from the very early stage of cluster formation via hydrogen bonding and dipole-dipole interaction to the growth process and the final crystal morphology through surface attachment. In this presentation, a new method is introduced for partial charge distribution in the solvent and solute molecules. Furthermore, the hydrogen bonding ability of these molecules can be predicted using the obtained partial charges. The effect of solvent has also been shown in directing the crystallization process toward the formation of special polymorphs of stearic acid and ranitidine hydrochloride.

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