Materials Science

151

Synthesis and characterization of co-crystals and proton-transfer complexes of adenine

P. J. Cox and M. Byres

The Robert Gordon University, Schoolhill, Aberdeen, AB10 1FR, UK.
E-mail: p.j.cox@rgu.ac.uk

Objectives To examine hydrogen-bonded solid-state complexes of adenine. A crystal that contains the compound of interest together with one or more chemical entities may be known as a complex, adduct, co-crystal, salt, solvate, clathrate, etc. Many medicinal compounds are formulated as salts to enhance bioavailability and co-crystals and clathrates are of interest as they can alter the physical properties of an active ingredient without modification of covalent bonds. We are currently studying several compounds, such as 8-hydroxyquinoline, adenine, antipyrene, caffeine, sulfamethazine, theophylline and urea, for their ability to form multicomponent crystals with carboxylic acids, especially with benzoic acid and its hydroxy derivatives.

Methods Prior to formation, the molecular structures of reacting species were examined for suitable hydrogen bonding groups. Grinding the two substances together in a ball mill followed by an IR scan plus a melting point determination can give an indication that it is possible to form a new product. Suitable crystals for X-ray crystallographic analysis are subsequently obtained from solution.

Results Resulting complexes are often co-crystals or proton-transfer complexes (salts) and, as shown in Table 1, these may be anhydrous or solvated.

Conclusions When complementary heterosynthons are present and pKa values are similar then it is possible for co-crystals to form, e.g., adenine (pKa = 4.15) with benzoic acid (pKa = 4.20). When pKas are somewhat different a proton-transfer complex can result, e.g., adenine with 2-hydroxybenzoic acid (pKa = 2.98). The pKa and hydrogen bonding capabilities are important but other factors such as steric interaction, molecular packing and stability need to be considered. Also, to prevent formation of solvates, poorly hydrogen-bonding solvents such as acetonitrile can be used. Slurrying of interacting solids using small volumes of solvent is also a technique that may be used to obtain suitable multicomponent crystals.

Table 1 Adenine complexes

Co-former	Product
AA	$[Adenine]_2[AA][MeOH]_2$
BA	$[Adenine][BA]_2$
2-HBA	$[Adenine]^+[2\text{-}HBA]^-[MeOH]$
2,6-DHBA	$[Adenine]^+[2,6\text{-}DHBA]^-$
2,6-DHBA	$[Adenine]^+[2,6\text{-}DHBA]^-[H_2O]$
3,5-DHBA	$[Adenine]^+[OH]^-$ $[3,5\text{-}DHBA]^-[H_3O]^+$

(AA = adipic acid, BA = benzoic acid, HBA = hydroxybenzoic acid, DHBA = dihydroxybenzoic acid).

152
Development of a method for the prediction of humidity-induced crystallisation of amorphous drugs

L. C. Grisedale[1], S. A. Barker[1], D. Q. M. Craig[1] and M. J. Jamieson[2]

[1]University of East Anglia, Norwich, Norfolk, NR4 7TJ and [2]GlaxoSmithKline, Medicines Research Centre, Stevenage, SG1 2NY, UK.
E-mail: susan.barker@uea.ac.uk

Objectives Although amorphous drugs have been studied extensively as a means of improving biopharmaceutical performance, there remains the challenge of understanding and predicting their physical stability. It is believed that drugs are unstable above, and possibly below, their Tg. Hancock et al (1995) have suggested that a maximum storage temperature of (Tg – 50°C) is used to ensure stability. However, if the drug is exposed to water vapour then plasticization effects may result in lowering the Tg to a value akin to the storage temperature. Royall et al (1999) suggested a model whereby the twin effects of storage temperature and water levels on Tg could be predicted and displayed as a phase diagram, with the likelihood of instability being mapped according to these parameters. The authors stored their model drug over a range of humidity conditions in order to obtain sufficient data for the model. Here, we propose an extension to that model, in which two simple experiments only are required to predict instability for an amorphous drug.

Method Samples of spray dried salbutamol sulphate were prepared by using a Büchi Mini-Spray Dryer B-290. Samples were then studied by MTDSC (TA Instruments Q1000) using the following conditions: equilibrated at 0°C and heated to 200°C with an underlying heating rate of 2°C min^{-1} and modulation amplitude of ±0.212°C every 40 s. Both hermetically sealed and pinholed pans were used.

Results The water content of the material was 2.0% ± 0.2% (n = 4). The material displayed a complex set of thermal events including water loss (pinholed pans), the Tg itself, melting and decomposition, with many of these events overlapping. MTDSC provided an extremely effective means of separating these events, notably the separation of the Tg from the water loss and onset of degradation. It was observed that the Tg could be seen in the reversing heat flow signal; the degradation and water loss events were shown to be kinetically hindered and hence appeared in the non-reversing signal; work is ongoing to study the degradation mechanism and kinetics in light of these findings. The Tgs observed using the pinholed and hermetic pans were 121.2 °C ± 0.12 (n = 4) and 81.7 °C ± 0.26 (n = 4), respectively. Essentially, the two pans provide Tg values for dry and plasticized material as the pinhole allows water loss prior to the glass transition.

Conclusion Royall et al (1999) used a derivation of the Gordon-Taylor equation to predict the water content and temperature combinations corresponding to the Tg and the (Tg – 50°C) values of the drug; however the Gordon-Taylor equation does necessitate the use of certain assumptions, one being the ideality of the water plasticization process. Here we are able to use the two Tg values at known water levels to provide a semi-empirical approach to estimating the Gordon-Taylor parameters. We are then able to use the Royall et al (1999) approach to derive an instability phase diagram based on these two measurements.

Hancock, B. C., et al (1995) *Pharm. Res*. **12**: 799–806
Royall, P. G., et al (1999) *Int. J. Pharm*. **192**:39–46

153
An investigation into the potential use of zein as a novel tablet excipient

G. M. R. Georget, S. A. Barker and P. S. Belton

University of East Anglia, Norwich, Norfolk, NR4 7TJ, UK.
E-mail: susan.barker@uea.ac.uk

Objective To assess the potential of the maize storage protein zein as a novel tablet excipient.

Methods Commercial zein powder (Acros Organics) was characterised by a range of physical techniques. Direct compression (DC) and wet granulated (WG) tablets containing zein, calcium hydrogen phosphate (CHP), polyvinylpyrrolidone (PVP) and magnesium stearate (MS) as excipients and theophylline as a model drug were prepared using a Manesty E press fitted with 13 mm normal concave punches. Dissolution studies were conducted using BP apparatus 2 in 0.1 M HCl, purified water and pH 6.8 buffer.

Results Particles in the commercial zein powder were predominantly plate-shaped, with a typical maximum diameter of 800 μm. Grinding resulted in a smaller diameter, with a more random particle geometry. Simple DC of commercial zein was possible, but the tablets so produced were weak, even when applying high compression forces. This was ascribed to the low bulk density and the extensive elastic recovery of zein. Particle size reduction resulted in denser and stronger tablets. To overcome the elastic recovery of the zein, CHP was added at 30% and DC tablets were successfully produced. Tablets produced by WG using PVP 1% as binder showed improved physical properties compared to the DC tablets. Figure 1 illustrates the appearance of tablets produced as described above. Raman and IR data on zein showed that random coils, α helices and β sheets predominated, with the relative content remaining essentially unaffected during processing, indicating that zein based formulations will be robust, i.e., insensitive to minor changes in production conditions. Dissolution profiles in water and 0.1 M HCl show that only a limited amount of theophylline was released after 5 h, suggesting that zein could act as a potential vehicle for oral controlled drug release. Given the apparent lack of interaction between zein and acid, it may be used as a carrier for acid-labile drugs.

Conclusion Zein shows promise as a tablet excipient; further work is ongoing to fully characterise its utility.

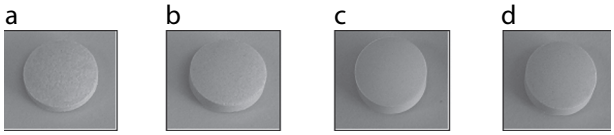

Figure 1 Zein tablets: (a) DC: unground zein, b) DC: ground zein and CHP, d) WG: ground zein, CHP, and PVP.