## Material Science

### 40
### A novel method to evaluate powder flow properties using small sample quantities

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**Objectives** There are several methods in the literature to quantify powder flow, such as Carr's index, critical orifice diameter or powder rheometry. A disadvantage of these methods is that they require large sample sizes to perform a measurement. Novel, investigational and lab scale powder processing techniques, such as SEDS or freeze drying, may not produce sufficient sample sizes to allow the use of these techniques to quantify flow, an important consideration for pharmaceutical manufacturing processes.

**Methods** In the Xcelodose system, powder is retained in a dispense head (hopper) with a known number, diameter and surface area of holes. Tapping the dispense head via a solenoid will break powder bridges, dislodging the powder, causing flow onto an eight place balance below. For a given powder and dispense head the amount of powder dispensed is proportional to the number and frequency of taps. A variety of heterogeneous powders, as well as nine spray dried lactose:lactose monohydrate blends, with different flow properties, were tested using the Xcelodose system. The powders were tested in three hoppers with the same hole surface area but different hole diameters and the amount of powder dispensed recorded. From this a 'Flow Gradient' was calculated. These powders were then tested using Carr's index and Basic Flow Energy (BFE, Freeman Powder Rheometer) and these results compared.

**Results** For the group of heterogeneous powders there is a clear correlation between Carr's index and the Flow Gradient ($R^2 = 0.8376$, $P < 0.001$), allowing flow categorisation, similar to Carr's of the powders. With the lactose powders the BFE was also compared. A correlation between Flow Gradient and BFE of 0.8793 ($P < 0.01$) was observed for these 9 blends. This correlation improves to 0.9417 ($P < 0.001$) if only the 7 poorly flowing powders are included, suggesting the value of this technique for poorly flowing powders (Figure 1).

**Conclusions** A novel method for the measurement of flow properties with very small quantities of material has been developed and validated against different powder types and different established powder characterisation methodologies. The flow gradient method produces an excellent correlation with larger scale measurement methods and would be suitable to categorise powder flow when the amount of material is limited.

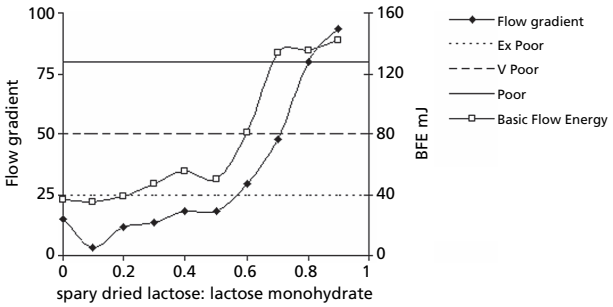


**Figure 1** Comparison of Flow Gradient and Basic Flow Energy for lactose blends.

### 41
### Forming amorphous and nanocrystalline APIs through solid-state interactions with cross-linked polyvinylpyrrolidone

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**Objectives** High throughput screening of new APIs (Active Pharmaceutical Ingredients) allows easier identification of compounds with therapeutic potential. However, many APIs currently under development are Biopharmaceutical Classification System (BCS) Class II compounds (i.e. high permeability but poor intrinsic solubility) (Amidon et al 1995). For Class II compounds, dissolved drug will be transported across the lipid membranes faster than newly dissolved solute can be produced to replace it (sink conditions). The bioavailability of these APIs will therefore typically be limited by dissolution rate within the aqueous environment of the gastrointestinal fluids. These physicochemical characteristics may be inherent in the chemical structure of the API but may also result from optimisation of lead compounds enabling site or receptor specificity (which results in increased lipophilicity). This resulting predominance of BCS Class II compounds in pharmaceutical development "pipeline" makes it apparent that we must first understand concepts of solubility, the process of dissolution and then establish strategies to optimise these factors; one such strategy is creating an amorphous API content. We have recently

reported that simple dry mixing of BCS Class II compound ibuprofen (IB) with cross-linked polyvinylpyrrolidone (PVP-CL) generated disruption of drug crystallinity and conversion to an amorphous form (Rawlinson et al 2005, 2007). It was not evident from these data if this unusual interaction, not requiring energetic processing, would transfer to other APIs. The objective of this study was to investigate the potential for disruption of crystallinity of API's with structural similarity to IB upon combining with PVP-CL in physical mixes (PMs); different proprionic acids were selected for this study.

**Methods** Fenbufen (FB), flurbiprofen (FL) and ketoprofen (KT) were combining in physical mixes (PMs) with PVP-CL. The crystallinity of all the APIs were monitored using several methods. Triplicate samples, from mixing APIs with PVP-CL, were analysed using differential scanning calorimetry (DSC), X-ray diffractometry (PXRD) and solid-state nuclear magnetic resonance (SSNMR).

**Results** Loss of crystallinity was observed for all APIs in the PMs with PVP-CL as measured by DSC, PXRD and SSNMR. DSC and PXRD data indicated almost complete disruption of the crystalline FB structure. However, SSNMR indicated a significant crystalline or nanocrystalline portion remained. Data for FL and KT indicated consistent decrease in crystallinity as measured by all three methods.

**Conclusions** Disruption of crystallinity was observed for FB, FL and KT upon combination with PVP-CL. The three methods of analysis were not in agreement in measuring crystalline content for FB. This may be due to FB converting to a nanocrystalline form that is not quantifiable with DSC and PXRD. Disruption of API crystalline structure to either a nanocrystalline or amorphous form would confer a solubility advantage.

Amidon, G. L., et al (1995) *Pharm. Res*. **12**: 413–420
Rawlinson, C. F., et al (2005) *J. Pharm. Pharmacol*. **57**: S99
Rawlinson, C. F., et al (2007) *Int. J. Pharm*. In press

## 42
## NMR cryoporometry and PFG studies of water diffusion in poly (lactic-co-glycolic acid) microspheres for drug delivery

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Biodegradable polymer microspheres are of interest for their potential use as controlled drug delivery devices, in particular poly(lactic-co-glycolic acid), PLGA, is a popular candidate because of its proven history for medical applications. During the preparation of polymer microspheres it is possible to encapsulate molecules that will be released as the microsphere swells and degrades. The mechanism for this degradation and hence drug release profile are dependent upon the internal structure of the microsphere and is determined by its preparation method and materials. The ability to characterise the structural changes of microspheres is essential to understanding the mechanism of drug release and therefore aid the design of a drug delivery system with a given release profile. NMR techniques provide a non-invasive, real-time tool to study structural evolution of polymer microspheres, including pore cavity sizes, tortuosity and percolation properties of porous networks.

**Objectives** To use nuclear magnetic resonance pulsed field gradient (NMR PFG) and cryoporometry experiments to study changes in the structure of PLGA microspheres for drug delivery. Real-time studies of changes in water diffusion within the microsphere structure can be used to better understand the evolution of the polymer structure and pore cavity growth during the swelling and degradation stages of the polymer lifecycle. This method of characterisation for internal microsphere structure can be used to compare batches of microspheres.

**Method** PLGA microspheres made by double emulsion w/o/w fabrication technique using different compositions of internal aqueous phase and organic phase are used in NMR PFG experiments to study their affect on the microsphere structure and swelling characteristics. We have studied ethyl acetate, dichloromethane and acetone as organic phase solvents and water or ammonium hydroxide as the aqueous phase for both drug encapsulated and blank microspheres. The swelling of microspheres in an aqueous environment, thought to be partly responsible for the burst release of an encapsulated drug, can be related to the changes in the diffusion coefficient of trapped water molecules within the pore structure of the microspheres.

**Results** Different organic and aqueous phases used in microsphere preparation by double emulsion technique produce different structures of polymer microspheres. These different structures affect the pattern of swelling evolution of microspheres when placed in an aqueous environment. A two-component model has been used to derive the diffusion coefficient of water entrapped within the pores. Statistically significant changes in the diffusion coefficient show the microsphere structure has evolved with time. Differences in diffusion coefficient for trapped water and the evolution of changes in diffusion coefficient are different for microspheres made by different recipe preparations.

**Conclusion** Method and materials of microsphere preparation determine the internal structure of the microspheres, which can be studied using NMR techniques, in particular PFG. These results show significant changes in the diffusion of water within the microsphere structure as the structure evolves in an aqueous solution. This study therefore shows that PFG NMR can be used to provide structural information on microspheres and their evolution over time, which may aid the future design of controlled drug delivery systems.

## 43
## An investigation into hydroxypropyl methylcellulose (HPMC)/gelatin interactions in aqueous solutions

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**Objectives** Polysaccharide- and protein-based hydrogels have been proposed as bases for biocompatible and biodegradable products with a variety of medical applications, including scaffolds, controlled release matrices, adhesives (Yin et al 2005). Moreover it is well know that macromolecules in solution can form interpolymer complexes through ordered interchain interactions. In this study, the interaction within binary systems composed of HPMC and the flexible ampholytic protein gelatin were investigated with a view to exploring whether such binary systems may form suitable matrices for drug delivery purposes. Despite the widespread use of these polymers individually, little is know regarding their combined use. Furthermore, we explore the use of a combination of mechanical and spectroscopic studies to investigate both the extent and mechanism of interaction.

**Methods** HPMC (used as received) was first dispersed in 1/3 of the water (at 80–85°C), stirred for 30 min and allowed to cool at the room temperature before pouring up to the required volume of water. Gelatin gel was prepared by stirring the solution for 10 min at 70°C. The two solutions obtained were then mixed before gelification and the gel was allowed to form at room temperature. Mechanical proprieties of the systems were studied by texture analyser using four different sets of tests with different combinations of cylinder probe size, test speeds, depths and sample dimensions after one week storage at 10°C. FT-IR spectroscopy was performed on each material alone as well as the mixtures at the same ratios as those used in texture analysis. The samples used for FT-IR were all stored for 24 h over $P_2O_5$ to remove sorbed water before gel preparation and deuterated water was used as a solvent.

**Results** Texture analysis investigation using an 8 mm cylinder probe, at 10 mm/s test-speed and 5 mm displacement on Gelatin 2%w/w mixed with increasing HPMC quantities (up to 1%w/w with increments of 0.1%w/w) showed evidence of a synergistic effect in terms of gel hardness and adhesiveness as the consequence of HPMC-Gelatin interaction. A maximum in hardness ($98.94 \pm 4.52$ g) and adhesiveness ($24.76 \pm 0.14$ g·s) were observed at concentration of HPMC 0.6% w/w, followed by a decrease at higher concentrations. All IR spectra of the mixtures showed distinctive spectral features for the protein (amide I and II bands at approximately 1650–1540 $cm^{-1}$) and for the polysaccharide (overlapped peaks at 1050 $cm^{-1}$). However, in the spectra of the mixtures, compared with those of each component alone, a shift to lower frequencies of the sugar peak and a reduction of the intensity of the amide signals were observed providing evidence of hydrogen bonding between the two macromolecular species.

**Conclusions** In this study we demonstrate evidence of interactions between HPMC and gelatin in an aqueous medium. By using mechanical and spectroscopic studies in conjunction we are able to provide information on both the mechanism and performance implications of the interaction.

Yin, Y., et al (2005) *J. Mater. Sci*. **40**: 4649–4652

## 44
## Dynamics of water vapour sorption in trehalose glasses

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**Objectives** To use Dynamic Vapour Sorption (DVS) experiments to study the dynamics of water sorption into spray-dried trehalose glasses. These glasses have considerable potential as excipients, but in order to utilise them in drug delivery it is necessary to control the glassy to crystalline transition. One of the recognized factors that influences the crystallisation is the sorption of water vapour; however, this process is complicated by the dual role of water in both plasticizing the glass and forming the dihydrate in the corresponding crystal. We have examined the rate of transition onset under different constant relative humidity (% RH) with a view to developing a model whereby we are able to quantitatively relate the environmental conditions to the water sorption, the plasticization and the formation of the dihydrate.

**Methods** Trehalose glasses were prepared using a Buchi Mini Spray Dryer B-290 from 8.5% (w/v) aqueous solutions. Microscopy and sizing studies confirmed the well-defined spherical nature of the product. The DVS analysis was performed on a Q5000 SA Thermogravimetric Analyzer (TA Instruments). Isohumidity experiments were carried out at 90, 80, 70, 60 and 50 % RH where the glass was held at constant relative humidity and the changes in weight over time were studied. The crystal hydrate structure and glass transition values were ascertained using a combination of thermogravimetric analysis, modulated temperature DSC and spectroscopic studies. Studies were conducted on glasses with initial humidities of 5.11, 6.30 and 7.43% in order to develop the kinetic model.

**Results** On exposure to high water vapour pressures (≥ 50% RH) the first stage is the simple sorption of water. The sample weight reaches a maximum and is followed by a sudden loss due to the expulsion of water to convert the majority of the glass the crystalline dihydrate. However, there is a continuing slow loss of water, which is attributed to the crystallisation of minor quantities of residual glassy material. The time taken for the major recrystallisation to occur increased with decreasing vapour pressure. For example, systems with an initial water content of 5.11%, took 28 min at 90% RH, while at 50% RH this increased to 227 min. For the systems with an initial water content of 7.43%, these times decreased to 21 and 219 min, respectively. By monitoring the uptake as a function of humidity and time it is possible to model the uptake based on Fickian Type II diffusion (postulated by Thomas & Windle 1981) through the glassy matrix, thereby allowing insight into the manner in which the water penetrates the spheres.

**Conclusions** The water uptake and subsequent crystallisation of amorphous trehalose has been studied with a view to developing a kinetic model that describes water movement through the glassy matrix followed by recrystallisation to the dihydrate form. In this manner it is intended that the storage stability of dosage forms based on amorphous trehalose may be better understood and the development of stabilisation strategies facilitated.

Thomas, N. L., Windle, A. H. (1981) *Polymer* **23**: 529–542

## 45
## Influence of the spray-drying concentration on the relaxation of an amorphous solid dispersion

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**Objectives** To study the effect of polymeric globule size on the relaxation of an amorphous solid dispersion of griseofulvin. Polymers exhibit various conformations and sizes in different solvents. In a bad solvent the polymer will tend to be more compact where spherical structures called polymeric globules can form, while in a good solvent the polymer will be in an expanded conformation. The formation of polymeric globules may also occur as a result of increasing the polymer concentration. This leads to increased polymer chain entanglements (Huang et al 1999). We have sought to prepare stable solid dispersions of amorphous actives by spray drying. This study was designed to correlate the stability of an amorphous solid dispersion with different concentrations of the solids in solution before spray drying.

**Methods** Solid dispersions of griseofulvin, poly(vinyl pyrrolidone) (PVP) and poly(2-hydroxypropyl methacrylate) (PHPMA) (2:1:1) were prepared by spray drying with a Niro Micro system in a nitrogen atmosphere. Griseofulvin:PHPMA:PVP (2.5 g:1.25 g:1.25 g) were dissolved in a mixture of acetone/water (185/85 mL) and then spray dried (chamber nitrogen flow, 25 kg/h; atomizing flow. 2.5 kg/h; inlet/outlet temperatures, 65/45 °C). The same volumes of solvent and the same ratio of solids were used to prepare additional dispersions that had lower absolute weights of solids (i.e. griseofulvin was decreased to 1.25 g, 0.63 g and 0.31 g). The heat of recovery was measured using a step-scan module using Pyris 1 DSC after first being annealed at 60 °C for 3, 6, 15, 18 and 20 h. The size of the polymeric globules before spray drying was measured using photon correlation spectroscopy.

**Results** The size of the spray-dried particles was in the range of 1–5 $\mu$m with the particle size appearing to decrease as the amount of solids in solution for spray drying was decreased (SEM). The measured enthalpy of relaxation positively correlated with increased amounts of griseofulvin. Since the enthalpy of relaxation can be an indication of the ability of an amorphous dispersion to remain amorphous (Hancock & Zografi 1997), these data suggest that smaller particles may prolong the amorphous form for this griseofulvin formulation. Photon correlation spectroscopy indicated that PHPMA (1.25 g) globules were larger (32.8 nm) in acetone/water (185/85 mL) than in acetone (270 mL) alone (16.4 nm). Since PVP is not soluble in acetone alone, it was not possible to obtain the analogous comparative measurements, however the use of water in these spray dry solutions may serve to reduce polymer-polymer entanglements.

**Conclusions** These results suggest that the formation of small particles may have potential to increase the stability of the amorphous form by reducing the relaxation of the material on storage. Variation in concentration and the use of water may serve to decrease polymer-polymer entanglements to improve polymer interactions with the drug in the solid dispersion.

Hancock, B. C., Zografi, G. (1997) *J. Pharm. Sci*. **86**: 1–12
Huang, D., et al (1999) *Macromolecules* **32**: 6675–6678

## 46
## Variation of dissolution rate of spray-dried solid dispersions from different solvents

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**Objectives** To evaluate the dissolution rates of griseofulvin dispersions that have been prepared by spray drying from methanol-acetone and water-acetone solutions. We are developing spray-drying processes to prepare solid dispersions that are capable of prolonging the amorphous form. The effect of the solvent has been described for microparticles that are prepared by solvent evaporation (Pekarek et al 1994). However, this has not been as extensively studied for solid dispersions that have been prepared by spray drying.

**Methods** A solid dispersion of griseofulvin, poly(vinyl pyrrolidone) (PVP) and poly(2-hydroxypropyl methacrylate) (PHPMA) (2.5 g: 1.25 g:1.25 g) was prepared by spray drying with a Niro Micro system in a nitrogen atmosphere using acetone/water (185/85 mL). A second dispersion was prepared from acetone/methanol (150/150 mL) with the same ratio of components; griseofulvin: PHPMA:PVP (2 g:1 g:1 g). The spray drying parameters were: chamber nitrogen flow, 25 kg/h; atomising flow, 2.5 kg/h; inlet/outlet temperatures, 65/45 °C. The dissolution rate was studied at different loadings of the solid dispersion (3%, 6%, 12% and 24%) in 200 mg tablet (pH 6.8 and at 37 °C). The heat capacity change was measured using Pyris 1 DSC. The solution viscosities were measured using a U-tube viscometer at 25 °C. The evaporation rate was measured for the solutions (10 mL) at 65 °C (± 0.1 °C) and constant nitrogen gas flow (5 L/min).

**Results** To avoid PVP precipitation, it was necessary to use a lower relative volume of acetone in the presence of methanol than with water. Smaller particles were obtained from acetone-methanol than from acetone-water (SEM). The viscosity of the spray drying solution was lower for acetone-methanol (0.554 cP) than for acetone-water (1.39 cP). There was a significantly higher evaporation rate for the acetone-methanol solution. It would be expected a dispersion derived from the lower viscous solutions that had a faster rate of evaporation would give smaller particles. The dispersions that were prepared from acetone-methanol also displayed a faster dissolution rate. This difference became more significant with increased loadings of the solid dispersion within the tablet. Particles derived from acetone/methanol displayed a Tg = 105 °C, those from acetone/water had Tg = 85 °C. No change in Tg was observed after annealing at 60 °C for 20 h. This suggests that any residual solvent is tightly bound within the solid and that the lower Tg was not due to plasticizing residual solvent.

**Conclusions** Utilising methanol instead of water in a mixed solvent system with acetone to fabricate spray-dried griseofulvin dispersions produced smaller particles with an improved dissolution rate. An increased Tg for the solid dispersion derived from acetone/methanol indicated that the interactions in the particle changed and that the molecular mobility is retarded.

Pekarek, K. J., et al (1994) *Nature* **376**: 258–260