Poster Session 1 – Pharmaceutics

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An investigation into the subambient behaviour of aqueous mannitol solutions

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The subambient behaviour of mannitol solutions is of considerable relevance to the preparation of freeze dried formulations in which it is commonly used as an excipient. However, it tends to crystallise during the process which can cause problems (Williams & Dean 1991; Izutsu *et al* 1993). In this study the properties of 3% w/v mannitol solutions were investigated using differential scanning calorimetry (DSC), cold stage microscopy (CSM) and X-ray diffraction (XRD) in order to identify the subambient structural transformations undergone by this system.

The effects of annealing at –30°C were investigated by DSC (TA Instruments DSC 2920) by cooling (10°C min^{-1}) to –30°C before annealing for time periods between 10 and 80 min before further cooling (10°C min^{-1}) to –60°C and reheating (2°C min^{-1}) to 0°C. To investigate annealing during reheating, samples were cooled (10°C min^{-1}) to −30°C and held for 30 min before further cooling (10°C min^{-1}) to −60°C and reheating (2°C min^{-1}) to the required annealing temperature (range –40°C to –25°C) then annealing (30 min) before reheating. SM was performed (Linkam BCS 196 biological cryostage, Olympus BX50 microscope, X10 magnification, differential interference contrast) using temperature protocols mimicking those used in the DSC studies as was XRD (Bruker D8 X-ray diffractometer with Cu tube radiation source and PSD).

Upon reheating a small endotherm followed by an exotherm were observed (−29°C and −24°C, respectively) using DSC. Increasing annealing time (to 40 min) at −30°C upon cooling caused simultaneous increased thickness of an excluded band (CSM) and subsequent increase in enthalpies of both transitions (Table 1). XRD revealed that initially there was no detectable crystalline mannitol but that after 6 min this had begun to appear in the β form. Heating to –30°C before cooling and reheating had no effect on either transition, prior heating to –25°C reduced the exotherm enthalpy while prior heating to –20°C removed it completely. These observations corresponded to the growth of an excluded phase (CSM) and the appearance of β-mannitol (XRD).

Table 1 Effect of annealing at −30°C on the reheating transitions

Anneal time (min)	Endotherm enthalpy (J g^{-1})	Exotherm enthalpy (J g^{-1})
0	1.30 (0.33)	2.84 (0.20)
10	2.40 (0.08)	2.97 (0.56)
20	2.43 (0.12)	3.38 (0.30)
30	3.01 (0.14)	3.62 (0.28)
40	3.40 (0.43)	4.17 (0.40)
50	2.45 (0.42)	3.26 (0.14)
60	1.67 (0.24)	3.29 (0.30)
80	1.55 (0.70)	2.23 (0.69)

The combined use of DSC and CSM and XRD provide a powerful means by which subambient behaviour may be assessed. Cooling and annealing have a profound effect on the structure and thermal behaviour of aqueous mannitol solutions.

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Calculating the surface energy of the individual crystal faces of paracetamol

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It has been previously demonstrated that the overall surface energy of a powdered drug sample is dependant upon the shape of the individual crystals (York *et al* 1998; Trowbridge *et al* 1998) and by inference, the proportion of the exposed crystal faces and the chemistry of the groups exposed at these faces. Previously the link between the change in surface energetics and the proportion of the dominant crystal face has been qualitative. In this work, a quantitative approach has been taken to directly relate the changes in surface energy of paracetamol crystals with the shape of the crystals and the proportional areas of individual crystal faces and to calculate the surface energetics of the individual faces.

Paracetamol crystals were formed by crystallisation from aqueous solution. By altering the conditions, the crystal habit can be altered from a needle shape at low supersaturation ({110} dominant}) to a more plate like shape at higher supersaturation ({001} dominant) (Finnie *et al* (1999)). Using image analysis, the three major crystal faces of paracetamol ({001}, {201} and {110}) were identified and their relative proportion calculated. The surface energy of the crystals was measured by Inverse Gas Chromatography by injecting a series of probe vapours under the conditions of infinite dilution. By choice of the probes, the surface energy can be split into its dispersive, acidic and basic components.

The total value of each component of the surface energetics (E) of crystals of a particular habit can be expressed as a sum of the proportion individual faces (p_{001}, p_{201}, p_{110}) multiplied by the contribution from each particular face (e_{001}, e_{201}, e_{110}). This can be equated to the actual surface free energy of that face.

e.g. $E = p_{001}\, e_{001} + p_{201}\, e_{201} + p_{110}\, e_{110}$

From surface energy measurements on crystals of different shapes, the acidic, basic and dispersive properties of each crystal face was calculated using matrix analysis. The results are shown in Table 1.

Table 1 Crystal face properties

Crystal face	Dispersive surface free energy (mJ m^{-2})	Acidic surface free energy (as measured by THF) (kJ mol^{-1})	Basic surface free energy (as measured by chloroform) (kJ mol^{-1})
{001}	59	7.9	0.5
{201}	16	0.8	0.9
{110}	55	7.0	0.2

These show that the {001} face has the highest dispersive and acidic components of the surface free energy, but the {110} face is only slightly less energetic. The {201} face, on the other hand, is significantly less energetic in terms of the dispersive and acidic component, but has the highest basic component (although this is low for all three faces).

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059
Improved stability and release profile of vitamin C multiple emulsion

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Multiple phase emulsions are increasingly used as alternatives to simple emulsions in personal care products. One of the major advantages of these emulsions over simple emulsions is slow and controlled release of their ingredients. Other favorite cosmetic characteristics of multiple emulsions include occlusivity (in o/w/o emulsions), aesthetics and consumer acceptance.

Vitamin C (ascorbic acid) has been widely used in formulations of skin care products. Due to its effects on collagen biosynthesis, it is considered as moisturizing and anti-aging active ingredient. Instability problems such as oxidation susceptibility have made incorporating vitamin C in topical formulations a challenging issue.

The formulation method was a two-step process. We have formulated o/w/o emulsions to investigate vitamin C stability and its release profile. By using different surfactant type and ratio, volume ratio of phases, multiple phase emulsions containing vitamin C were prepared. Different parameters and formulation factors such as temperature of phases, duration and speed of mixing were evaluated. Some of the experimental variable parameters have been summarized in Table 1.

Based on our results, more stable emulsions were prepared from non-ionic siliconized surfactants, sorbitan derivatives and co-surfactants such as polyglyceryl derivatives. Temperature of phases was adjusted at 60–65°C and phases were mixed at 1300 rev min^{-1} for 45 min. Paraffin was used as an internal and external phase. Physical stability was determined by microscopic examination, centrifugation and incubating emulsions in different temperatures. Vitamin C in-vitro release studies from o/w and o/w/o emulsions were conducted using Franz diffusion cell (at room temperature). The removed samples were analysed for vitamin C using spectrophotometeric method. The results showed that about 60.138% of vitamin C released from o/w emulsions in the first four-hour period, whereas at the same time only 14% of vitamin C released from o/w/o emulsions. It appears that in multiple emulsions and simple emulsions the profile of release follows zero-order and first-order kinetics, respectively. Our data indicate that incorporating vitamin C in multiple emulsions significantly increased its stability possibly attributed to reverse micelle formation of surfactants (and/or co-surfactants), which entrapped vitamin C inside the micelles surrounded by hydrophilic heads of surfactant. Moreover, vitamin C was released from multiple emulsions in a zero-order slow- and controlled-release manner.

Table 1

Emulsion	pH	Viscosity	HLB	Droplet size
O/W/O multiple emulsion	3–4	760–4500 cps	3–10	1–30 μ
W/O simple emulsion	3–4	760–4500 cps	3–6	1–30 μ

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The effect of L-amino acid structure on cloud point and drug release from hydroxypropyl methylcellulose (HPMC) matrix tablets

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HPMC matrices are exposed to amino acids in-vivo as food digestates. This may lead to a change in integrity of hydrophilic matrix tablets through an interaction with HPMC. This study reports the potential for HPMC interaction with food components using L-amino acids in a model system. The effect of L-amino acids on drug release from HPMC matrices is investigated and a quantitative structure activity relationship (QSAR) between amino acid molecular properties and HPMC solution behaviour is proposed.

Tablets (300 mg, 10 mm), comprising HPMC USP type 2208 (Methocel K4M) 20%, chlorpheniramine maleate 20%, magnesium stearate 1.5% and lactose Ph. Eur to 100% w/w were prepared by direct compression. Drug release studies were undertaken in USP23 apparatus 1 at 37°C, 100 rev min^{-1} in 900 mL 0.125 M L-amino acid solutions. Cloud point temperature (50% reduction in light transmittance) concentration gradients (Δ_{CPT}) were determined on a temperature-ramp turbidimeter using HPMC 1%w/w solutions containing L-amino acids up to maximum solubility. QSARs utilising ordinary and partial least squares methods were performed in order to probe the influence of molecular parameters on the potency of the amino acids to reduce or raise cloud points.

Significant differences in $T_{50\%}$ values (time to 50% drug release) were observed between dissolution media containing L-amino acids. The $T_{50\%}$ values for Ser, Ala, Gly, Val and Phe media were 69, 82, 89, 96 and 132 min, respectively. There was a significant correlation between $T_{50\%}$ and Δ_{CPT} ($R^2 = 0.995$, $P < 0.05$). Cloud point studies on an extended range of L-amino acids revealed a lyotropic series in which Δ_{CPT} was negative for aliphatic but positive for aromatic (Phe, Try, Trp) amino acids. Grouped into hydrophobic (Ala, Cys, Gly, Phe, Pro, Trp, Tyr, Val) and hydrophilic (Arg, Asn, Asp, Glu, Gln, His, Lys, Ser, Thr) types, a significant QSAR ($R^2 = 0.942$, $Q^2 = 0.883$, $P < 0.05$) was obtained for a combined term of dipole moment and molecular weight (Mw) which predicted the cloud point activity of hydrophobic L-amino acids (Table 1), but not hydrophilic L-amino acids. This suggests that a relationship using simple molecular parameters can describe the correlation with HPMC cloud point where hydrophobic interactions predominate.

Table 1 The predictive relationship between combined dipole and Mw for hydrophilic L-amino acids

L-amino acid	Actual Δ_{CPT} (°C/M)	Predicted Δ_{CPT} (°C/M)	Cross-validated Δ_{CPT} (°C/M)
Ala	−18.2	−30.3	−32.4
Cys	−6.8	−18.4	−18.5
Gly	−21.5	−37.3	−42.2
Phe	+25.7	+10.5	+9.1
Pro	−14.7	−15.4	−15.5
Trp	+45.5	+21.7	+13.5
Tyr	+40.4	+19.0	+15.1
Val	−11.8	−15.0	−15.1

L-amino acids have the potential to influence drug release in HPMC matrices with the ramifications that in-vitro or in-vivo exposure to amino acids could result in changes in release rate, through putatively a mechanism of altered HPMC solution behaviour.

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An investigation into the thermal and analytical techniques used in the development of lyophilised protein pharmaceuticals

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Freeze-drying (lyophilisation) is a unit operation in which a solvent, usually water, is frozen and then sublimed in a vacuum (Pikal 1990). It is commonly used in the vaccine and pharmaceutical industries when there are stability issues with the active ingredient, typically proteins, when in solution (Carpenter *et al* 1997). In this study modulated temperature DSC (MTDSC), freeze-drying microscopy (FDM), DTA and freezing resistance analysis (FRA) were used to evaluate the frozen excipient solutions with regard to glass transition (Tg′) and collapse temperatures (Tc). The formulations were freeze-dried in a laboratory scale freeze-dryer, using a common cycle based on the above characterisations. MTDSC was used to study the Tg of the products, while TGA was used to determine moisture contents. These excipient mixtures were then included in formulations of a model

protein, lactate dehydrogenase, which were then freeze-dried in the same freeze-dryer, using a cycle that was devised on the basis of the data obtained in the above studies. The success of the developed protocol was then measured in terms of the retained protein activity, Tg and moisture content.

The solutions were analysed using MTDSC (TA Instruments DSC 2920), and a *Lyotherm* (Biopharma Technology Ltd) consisting of both DTA and FRA, to determine thermal events. Freezing and freeze-drying behaviour of the samples were observed by FDM (*Lyostat2* Biopharma Technology Ltd) in order to determine the temperature range over which collapse took place. Table 1 shows a comparison between solution Tc and Tg′ values of a selection of excipients; dextran (70 k), dextran (9500), PEG (1000), PEG (10 k) and mannitol-glucose. Portions (1 mL) of the solutions were dispensed into freeze-drying vials, partially stoppered and freeze-dried (VirTis Genesis 12EL freeze-dryer). Resulting lyophiles were analysed using MTDSC and TGA. Reconstituted samples were analysed for retained protein activity.

Table 1 Showing comparison of Tc and Tg′

Excipients 2%	MTDSC (Tg′)	Microscopy (Tc range)	FRA	DTA
Dex 70 k	−1.2	−11.4 to −9.1	−5.0	−10.0
Dex 9500	−11.64	−12.4 to −10.9	−28.0	−30.0
PEG 1000	−20.33	−28.5 to −21.6	−14.0	−25.0
PEG 10 000	−10.76	−19.0 to −16.3	−18.0	−15.0
Man-1% glu	−25.19	−42.0 to −26.4	−14.0	−26.0

In conclusion, there is some correlation between Tg′ and collapse range of the solutions studied, with the different techniques being more appropriate for some samples than others. However structural differences between excipients mean that correlation between thermal softening and physical collapse is much better in the case of the high molecular weight polymers. Thermal stabilisation by the excipients will not always ensure protection of the protein. Work is ongoing to find a more optimal balance for this model protein between these desirable properties.

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Microscopic characterisation of a complex multiparticulate drug delivery device

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Film coating is an ideal process for the production of sustained release (SR) multiparticulate dosage forms. Ethylcellulose is the most widely used water insoluble polymer in barrier film coating. Application of water-based dispersions of ethylcellulose (latex systems) is common practice in the pharmaceutical industry and is the method of choice for film coating.

The influence of some parameters such as drug solubility, coating equipment, coating process and core characteristics on drug release from aqueous ethylcellulose dispersion coated pellets has been reported in the literature. Homogenous film formation around the pellets during coating is critical for the successful application in SR systems. Consequently, methods that can spatially characterise the chemical and physical properties of such systems are of great interest. In this study the microscopic structure of the applied films has been examined. In addition, the possible migration and partitioning of soluble components into the film during the coating process was investigated using time-of-flight secondary ion mass spectroscopy (TOF-SIMS), optical microscopy and scanning electron microscopy (SEM).

Pellets were loaded with diclofenac sodium and two polymeric modified release coatings. A seal coat and a top coat were also applied. The modified release films were an enteric polymer system (Acryl-EZE) and an ethylcellulose based slow release system (Surelease). Drug release from the beads was determined by dissolution methods. Optical microscopy and SEM provided information on the pellet size, individual layer thickness and pellet morphology. TOF-SIMS imaging under high vacuum was used to acquire a mass spectrum from the surface of beads to identify the chemical composition of the surfaces. Retrospective analysis of the spectral data produced high-resolution images of the spatial distribution of components and any possible cross migration of the coating components. Optical and SEM images of the coated beads revealed uniform films with differing morphology around the cores. These layers were observed to vary in thickness from ~ 10–45 μm. TOF-SIMS images confirmed the differences in the layer order of the controlled release pellets and the integrity of each layer. The results did not show any indication of migration of the drug molecule into the modified release layers.

To conclude, this study has demonstrated that TOF-SIMS analysis combined with other complementary analytical tools can have considerable value for the characterisation and understanding of complex heterogeneous modern dosage forms.

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Characterisation of polymorphic behaviour using Thermally Stimulated Current (TSC) spectroscopy

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TSC is a general term applied to the measurement of current that originates from the relaxation of molecular dipoles that are displaced by the application of static electric fields. This technique has been used extensively for the characterisation of polymeric materials (Vanderschueren & Gasiot 1979) but seldom for pharmaceutically-relevant small molecules.

Application of an electric field to a system causes any dipoles (with enough thermal energy) present (permanent or induced) to align themselves in the direction of the field. The polarisation temperature should be sufficient to allow the complete orientation of all relevant dipoles. Once the polarisation is complete and with the field still being applied, the system is rapidly cooled so that the polarisation is ''frozen in'' the system. The electric field is then removed and the system heated at a constant rate. At a defined temperature, the dipoles acquire enough energy to start to relax back to their original position; during this process, current is generated and measured. The temperature and magnitude of these processes may be used both to detect thermal events and to obtain information on molecular mobility and relaxation behaviour.

TSC experiments were carried out using a TSC/RMA 9000 spectrometer (Setaram, France). Liquid nitrogen was used as a coolant and high purity helium as the chamber gas. As a model system, we used caffeine (Sigma, MO). Caffeine exists in two enantiotropic polymorphic forms, Form I and II, that are unstable and stable at room temperature respectively. Transformation from one form to the other occurs at 141 ± 2°C (Bothe & Cammenga 1979).

A marked transition was detected in Form II at 139°C (α-process). Additional transitions in Form II are seen around 91°C (β_1-process) and at −8°C (γ-process). Form I showed transitions around 107°C (β_2-process) and at −8°C (γ-process). Corroborative DSC studies indicated that the α-process represents the main solid-to-solid phase transition from one crystalline form to another. The γ-process is a second solid-state transition, which may correspond to side group movement in caffeine molecules. It may be inferred that the molecular sub-unit giving rise to the γ-process is oriented similarly in both polymorphic forms as the temperature of transition was consistent. Conversely, the β_1 and β_2 processes were observed at different temperatures, hence while they are likely to arise from the same relaxation mechanism, the molecular sub-units responsible probably exist in different environments in the two polymorphs. This may be a result of different degrees of hydrogen bonding in the different polymorphs (Nieuwenhuyzen 1999). Further work is ongoing to confirm this interpretation, using supportive techniques such as X-ray diffraction and NMR. However, the above data indicate that TSC may, at the

most basic level, indicate differences between polymorphs but may also be able to provide information on molecular mobility differences between polymorphs.

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Dynamic vapor sorption and near infrared spectroscopy for the analysis of co-spray-dried catalase/trehalose powders

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The hydration layer surrounding proteins is lost in the final stages of drying processes (Prestrelski *et al* 1993). This can result in denaturation of the protein structure and hence loss of activity (Arakawa & Timasheff 1982). Stabilising additives such as carbohydrates are used to protect proteins from denaturation during drying. It is accepted that the stabilising additive must be amorphous to confer such stability, although the mechanism of stabilisation is a matter of debate (Arakawa *et al* 2001).

The aim of this project is to study the near infrared spectra of a model protein, catalase, on exposure to high relative humidity following spray drying with a known stabilising additive, trehalose. It aims to try to elucidate the mechanism of carbohydrate-protein stabilisation upon desiccation.

Catalase from bovine liver (Sigma, UK) was spray-dried with trehalose in different ratios using a Buchi 191 Mini Spray Dryer. Samples were stored over phosphorus pentoxide. The water sorption behaviour of the co-spray-dried formulations was examined gravimetrically using a Dynamic Vapor Sorption analyser (DVS, Surface Measurement Systems, UK). Samples were exposed to 0% relative humidity (RH) for 8 h, 75% RH for 10 h and then 0% RH for 6 h. Near infrared (NIR) spectra (1100–2500 nm) were simultaneously collected every 900 s via a fibre optic probe (Foss NIRSystems).

NIR spectra to represent equivalent physical mixes of catalase and trehalose for comparison with the spray-dried formulations were prepared by combining proportional percentages of the 100% spray-dried catalase and trehalose spectra. The spectra of 'physical mix' and spray-dried equivalent formulations were compared using the VISION software (Foss NIRSystems) and by visual assessment.

DVS data show that formulations with an excess of trehalose (% w/w) took up moisture at high RH and mass loss was shown, indicating crystallisation of the carbohydrate in the sample. Spray-dried formulations containing an excess of catalase showed moisture uptake but no mass loss at high RH. NIR spectra of these formulations indicate that trehalose crystallisation did not occur, suggesting an interaction between the catalase and trehalose.

Distinct differences were observed between NIR spectra of the 'physical mix' and spray-dried formulations. In formulations with a lower ratio of trehalose to catalase, the peaks at approx. 1450 nm and 1934 nm believed to be characteristic to the formation of trehalose dihydrate were absent in the spray-dried spectrum but present in that of the equivalent 'physical mix'. The absence of these peaks in spray-dried formulations is indicative of an interaction between the catalase and trehalose during the spray drying process.

DVS/NIRS data and the 'physical mix'/spray-dried NIR spectral comparison suggest an interaction between catalase and trehalose upon spray drying. Ongoing work aims to fully analyse the NIR spectra to determine the exact nature of this interaction.

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Isothermal crystallisation of PCL-PLA blends

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Both poly(caprolic acid) (PCL) and poly(lactic acid) (PLA) are used for biomedical implants in various forms, such as periodontal membranes (e.g. Wake *et al* (1996)) and orthopaedic fixation devices (e.g. Daniels *et al* (1990)). These polymers are widely used for drug delivery applications. Blending PLA into PCL offers a route to optimising the properties to meet end use specifications. However, depending on the miscibility of the polymers, the T_g and crystallisation rate of the PCL may be altered by this addition of PLA. This abstract presents the data for the effect caused by increasing the proportion of PLA on the isothermal crystallisation parameters. PCL and PLA were solvent blended using chloroform and then isothermal crystallisation experiments were carried out by differential scanning calorimetery (DSC). At a rate of $20^{\circ}C\,min^{-1}$, 10 mg of polymer blend was heated from –50°C to 200°C, then cooled back down to –50°C. This cycle was repeated twice, to remove all thermal history from the polymer, and also to provide information on the crystallisation temperature (T_c) of the PCL and blends. For the isothermal crystallisation experiments, the sample was heated at 80°C for 5 min, then rapidly cooled, at a rate of $60^{\circ}C\,min^{-1}$ to 20, 25, 30 or 35°C and was held at this temperature for up to 10 min.

As the PLA content increases, the crystallisation rate constant (K_n) increases, indicating that the addition of PLA increased the crystallisation rate of PCL (Table 1). The Avrami values (n) provide an indication of the shape of the crystallites being formed (Table 2). In general, $1 \leqslant n \leqslant 2$, indicating 2D crystallite growth for the PCL. However, as PLA is added to PCL $2 \leqslant n \leqslant 3$ indicating a change to 3D crystallite growth.

Table 1 Crystallisation rate constant (K_n) as a function of isothermal temperature and PLA addition

Isothermal temperature	100% PCL	80% PCL 20% PLA	60% PCL 40% PLA
20°C	4.00×10^{-3}	3.33×10^{-2}	3.68×10^{-2}
25°C	1.30×10^{-3}	1.99×10^{-2}	2.55×10^{-2}
30°C	3.00×10^{-4}	1.12×10^{-2}	2.75×10^{-2}
35°C	8.00×10^{-5}	5.90×10^{-3}	1.70×10^{-3}

Table 2 Avrami number (n) as a function of isothermal temperature and PLA addition

Isothermal temperature	100% PCL	80% PCL 20% PLA	60% PCL 40% PLA
20°C	1.43	1.48	1.44
25°C	1.49	1.55	1.30
30°C	1.59	1.77	1.72
35°C	1.69	2.08	2.43

These results indicate that by blending in PLA with PCL, it is possible to control the crystallisation processes of PCL. This is particularly useful as when these biomaterials are placed into the body, it is the crystalline component of the material which can result in adverse tissue reactions and drug aggregation phenomena. By developing an understanding of the crystallisation behaviour, this information can be used to optimise the crystallisation of biomaterials, ensuring it is suited to its associated application.

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