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Three-dimensional imaging of multicomponent pharmaceutical compacts using scanning thermal microscopy (SThM) with localised thermomechanical analysis (L-TMA)

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There is a recognized need to develop methodologies whereby complex materials and products may be characterised in a spatially resolved manner. To date, very little is known with regard to the spatial distribution of components within complex samples such as pharmaceutical compacts. We present a novel method of mapping the three-dimensional distribution of tablet components using microthermal analysis in scanning thermal microscopy (SThM) and localised thermomechanical analysis (L-TMA) modes. Previous work in this area (Royall et al 1999) has indicated that microthermal analysis may identify the two components via a series of point L-TMA studies. However at that stage of the technique development it was not possible to actually map the two components. We describe a novel approach whereby we believe that both 2- and 3-dimensional mapping is possible. Tablets of paracetamol, HPMC and 50:50 mixes of the two were prepared and the materials characterised in scanning and localised modes using a TA Instruments 2990 Microthermal Analyzer with an Explorer AFM head and Wollaston wire thermal probe. Topography and thermal conductivity images were obtained in contact mode with the probe temperature held at 100°C. L-TMA measurements were performed at a heating rate of 20°C/s. L-TMA studies of the pure components indicated markedly differing thermal responses, with the paracetamol showing a sharp melting at 161°C, accompanied by a probe pull-in effect. HPMC showed the initial thermal expansion, followed by some softening above 200°C, which is probably related to thermal decomposition. The thermal image of a mixed compact showed two phases to be present. By comparing the pixel intensity histograms of the images, it can be seen that the topography images show a monomodal distribution of pixels with no systematic differentiation between the two materials. However, thermal conductivity images show a bimodal distribution, indicating that the thermal image can discern between the two phases. This is further supported by L-TMA studies on selected areas of the image, whereby the contrast seen in the thermal images is shown to correspond to the presence of the two components. Three dimensional imaging using a grid of L-TMA measurements is presented, utilising the distinct thermal responses of the two components. Nine 400 μm long lines were scanned with 50 μm between lines, giving a total of 153 L-TMA profiles. The depth of probe penetration through the paracetamol was plotted, thereby allowing the underlying HPMC profile to be imaged and, by subtraction, the paracetamol distribution to be mapped. It proved possible to obtain three 3-dimensional images for the sample surface; the topography, the paracetamol distribution and the HPMC distribution. The maximum depth probed by the technique is currently limited to 10 μm, which is the maximum z-range of the scanner. The study has therefore indicated that the Microthermal Analyzer may image complex samples not only in two dimensions via thermal conductivity but also in three dimensions by penetration profiling. We see this approach as being a useful novel method whereby not only systems such as tablets but also film coats and other surface layers may be characterised.

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The use of temperature controlled pulsed force mode AFM technique for the detection of amorphous domains on pharmaceutical compacts

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There is a consistent interest within pharmaceutical development in the phenomenon of accidental generation of amorphous material during processing, as this may

result in significant changes in the quality and performance of the final dosage form. The amount of amorphous material generated is often very small (< 1% w/w) and is usually located on the material's surface. Pulsed force mode atomic force microscopy (PFM-AFM) offers the possibility to directly visualize the surface of the material, allowing identification of species via differences in their pull-off force. In this study we demonstrate the use of PFM-AFM for *in situ* visualisation of amorphous domains located on the tablet surface. Furthermore, we employ this technique for the study of the recrystallization behaviour of amorphous drug at elevated temperatures. Indometacin (Sigma), supplied as a γ polymorph, was compressed into tablets and analyzed using a TA Instruments μTA 2990 Micro-Thermal Analyzer equipped with a TM Microscopes Explorer AFM and a Wollaston wire probe. A Witec PFM module and a silicon cantilever probe 1950–00 (Veeco) were used for the PFM-AFM study. The probe was subjected to a modulation frequency of 600 Hz and an approximate amplitude of 120 nm. Amorphous domains were introduced onto the tablet surface by performing a localised thermal analysis (LTA) experiment at 25°/s. Molten indometacin was quench cooled, creating a crater of amorphous material approximately 30 μm in diameter. A subsequent LTA at the same location confirmed the presence of a glassy indometacin. A transition at 60°C was detected, which is higher than the glass transition detected by DSC (43°C); the reason for this lies in the fact that microthermal analysis is more sensitive to softening processes than to the T_g itself (Royall et al 2001). A PFM-AFM image of the crater region revealed that amorphous indometacin showed higher pull-off force values than its crystalline counterparts. The craters were then imaged using the PFM-AFM technique and a variable temperature AFM stage at 25, 30, 40, 50, 60 and 70°C. With increasing temperature, surface recrystallization was detected and mapped. On cooling to room temperature, the region was rescanned and no significant change in the material's properties was observed, thereby demonstrating that the observed effects were a function of the sample structure rather than a simple temperature effect. The crystalline structure of indometacin in the crater region was confirmed by performing further LTA experiments, showing a transition at 159°C corresponding to the melting of the γ form. The study has demonstrated the ability to create highly localised micron-sized regions of amorphous material in an otherwise crystalline indometacin compact. PFM-AFM has allowed direct visualization and mapping of the amorphous phase. Furthermore, recrystallization of the amorphous phase as a function of temperature was studied using this technique. Variable temperature PFM-AFM therefore appears to be an exciting research tool for the study of small regions of amorphous materials generated on surfaces.

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Dynamics in sugar glasses

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It has long been known that simple carbohydrates may offer protection to some specialist species of plants, fungi and insects against the effects of dehydration by forming glasses. Carbohydrate glass formation may also be exploited in pharmaceutics for the preservation of drugs and therapeutic proteins during freeze-drying and storage. To better understand the stability of the glass and the mechanisms involved in the cryopreservation process it is extremely useful to have an understanding of the molecular dynamics of the glass forming material. Here we describe the use of solid state ^{13}C NMR spectroscopy as a means of assessing the whole-molecule motions of a model glass forming material, methyl rhamnoside, with a particular view to deriving novel information on mobility that may be related to recrystallisation phenomena. The dynamics of the systems are important since they may affect the ability to stabilise a drug. Methyl rhamnoside (methyl-α-L-rhamnopyranoside) was selected as the model for the study since it has been well characterised in previous studies. A proton NMR study of the molecular motions of methyl rhamnoside in both the crystalline and glassy state has been carried out and has shown that the dominant relaxation pathways (in both the laboratory and rotating frames) are via rotation of the methyl and methoxy groups (Tang et al 2004). The hydroxyl groups were found to give a comparatively weak relaxation pathway. However, as the motions of the whole sugar molecules remain uncharacterised, a solid state ^{13}C NMR method has been developed to address this. Samples of methyl rhamnoside glass were prepared in sealed solid state NMR rotors by heating the crystalline material past the melting point followed by cooling. Samples were heated for the minimum time possible for total amorphiscity to be reached. The liquid sugar was quickly cooled to −17°C to quench any thermal degradation reactions and form the glass. Verification of the amorphous state was obtained using ATR-FTIR. Using advanced dynamic Solid-State NMR methods such as the CODEX (Azevado et al 1999) pulse sequence, molecular motions were measured in both the crystalline and the glassy material over a temperature range of 263–343 K. The resulting spectra indicated reorientational motions on a time scale as long as two seconds. The methyl rhamnoside glass proved to be a useful model for the study and demonstrated the practicability of characterising motions in carbohydrate glasses, but in practice its glass transition temperature (290 K) is too close to room temperature to be suitable for stabilising pharmaceutics. A study of the non-reducing disaccharide trehalose is currently underway and a parallel study of sucrose is planned for comparison.

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Enhanced release of model drugs from PEG-modified silicone elastomers

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Due to its flexibility and biological inertness, silicone elastomer is routinely used in the manufacture of a wide range of medical and controlled-release drug delivery devices (Shastri 2003). However, the highly hydrophobic nature of conventional silicone elastomers also limits the utility of such systems (e.g., only relatively hydrophobic molecules such as steroids can usefully be released from silicone elastomers). From both a medical device and a drug delivery perspective, there is currently much interest in developing novel silicone elastomer biomaterials that have enhanced hydrophilicity as a result of modifications made to either the entire elastomer system or only its surface. In this study, vinyl functionalized PEG (mono allyl, mono methyl terminated poly(ethyleneglycol), AMPEG 450) was used to covalently modify the hydrophobic character of a linear poly(methylhydrosiloxane) prior to preparation of the corresponding silicone elastomer. In this way, the hydrophobic silicone polymer was functionalized with poly(ethyleneglycol) side-chain grafts, while simultaneously undergoing a platinum-catalysed addition-cure crosslinking reaction with a vinyl-terminated poly(dimethylsiloxane). The main objective of this study was to investigate the release of three model drugs (fluoxetine hydrochloride, AZT, and testosterone) from these systems with a view to evaluating the release characteristics compared with conventional silicone elastomer systems. AMPEG 450 was added to the poly(methylhydrosiloxane) in sufficient quantity to theoretically react with 25% of the available silicon-hydride moieties using well-established chemistries. Fluoxetine hydrochloride, AZT and testosterone were incorporated into the modified silicone materials at various loadings (1, 5 or 10% w/w). Control samples were also prepared containing no AMPEG 450. The matrix-type, silicone elastomer rods thus prepared were placed into sample flasks containing release medium (acetate buffer 0.02M for fluoxetine HCl and AZT release; ethanol:distilled water (10:90 v/v) for testosterone release) and placed in an incubator at 37°C and 60 rpm. The ability of the model drugs to be released *in vitro* from the silicone matrices was analysed by HPLC using a UV detector (El-dawy et al 2002; Radwan 1995). Triplicate samples were analysed for each formulation. Release data demonstrated that the pegylated silicone elastomers facilitated enhanced release of all model drugs investigated compared with the control. Table 1 details the daily release from silicone which contained 10% w/w drug loading. Also, the silicone samples modified with AMPEG 450 increased in weight when placed in release medium due to swelling of the silicone caused by influx of the release medium. The order of decreasing cumulative release for the model drugs was as follows: testosterone > AZT > fluoxetine HCl. The significantly higher release of testosterone from this system may be explained by the fact that testosterone is the most hydrophobic of the model drugs, and the modified silicone systems, despite having been pegylated, still retain a degree of hydrophobicity. In conclusion, silicone modified

Table 1 Summary of daily release of fluoxetine hydrochloride, AZT and testosterone (10% w/w) from pegylated silicone elastomers and control silicone elastomers

Matrix	Drug	Release (μg)		
		Day 1	Day 7	Day 14
Control	Fluoxetine HCl	143.8 ± 25.5	115.4 ± 5.9	40.4 ± 1.9
Pegylated	Fluoxetine HCl	250.2 ± 30.3	152.7 ± 6.3	88.2 ± 7.0
Control	AZT	928.8 ± 5.0	417.4 ± 45.8	214.3 ± 23.7
Pegylated	AZT	1449.5 ± 72.8	519.7 ± 32.4	301.2 ± 42.7
Control	Testosterone	313.2 ± 3.4	588.7 ± 18.0	632.2 ± 24.8
Pegylated	Testosterone	315.5 ± 14.0	671.9 ± 62.7	760.5 ± 44.9

with AMPEG could potentially be used in medical devices to provide enhanced release of drugs that might not otherwise be effectively released from conventional silicone elastomer systems. Future work will investigate the release characteristics of silicone modified with different quantities of AMPEG and different molecular weights of AMPEG.

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Photochemical characterisation of novel porphyrin-impregnated anti-adherent biomaterials

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Photodynamic therapy (PDT) has several uses including antimicrobial applications using photosensitising agents in solution (Merchat et al 1996). In a novel approach to the problem of infectious endophthalmitis, this study examined the potential of porphyrins, well established photosensitisers, attached to the surface of an intraocular lens (IOL) biomaterial to prevent bacterial colonisation of the IOL. Infectious endophthalmitis arising from bacterial colonisation is a rare but potentially sight-threatening condition. Light activation causes the porphyrin to generate highly reactive singlet oxygen, a cytotoxic species leading to cell death due to peroxidative damage (Taylor et al 2002). In this study, the cationic porphyrin tetra-4-N methylpyridinium porphyrin (TMPyP) was bound via electrostatic attraction to the surface of anionic copolymers of varying compositions of 2-hydroxyethyl methacrylate (HEMA) and methacrylic acid (MAA) via direct adsorption from solution, by dipping prehydrated samples in a 100 mcg/mL TMPyP solution for 60 s, blotting with medical tissue to remove excess porphyrin solution, and repeating until the samples were dipped a total of five times. The study aimed to characterise the physicochemical behaviour of the porphyrin-impregnated copolymers. Initial transient absorption measurements (excitation 532 nm, 10 ns pulse) were carried out to determine if the triplet state lifetimes showed sensitivity towards molecular oxygen. The results of this study are shown in Table 1 below. It is clear that all samples showed a significant increase in lifetime when oxygen was removed from the system suggesting that the porphyrin triplet state had undergone energy transfer with oxygen to produce singlet oxygen. Singlet oxygen production was then investigated using a liquid-nitrogen cooled Judson InGaAs detector. Blocking filters were employed to separate the singlet oxygen emission at 1270 nm from other interfering emissions in the NIR range. As with the transient absorption experiment, the samples were excited at 532 nm with low energy (1 mJ) pulses to prevent sample burning. The results showed that each of the copolymers ranging from 70% HEMA to 100% HEMA was capable of producing singlet oxygen. The quantum yield of singlet oxygen for each of the samples was comparable with the quantum yield for TMPyP in solution, indicating that the efficiency of singlet oxygen generation was not adversely affected by incorporation into a copolymer material. The variation between copolymer samples was not significant. However the 90% HEMA 10% MAA did appear to produce the greatest yield of singlet oxygen. This sample has therefore been taken forward for microbiological studies.

Table 1 Showing the lifetimes of the triplet state of the porphyrin for a range of copolymer compositions

Composition	Lifetime τ/mcs
70% HEMA – Air	176.2
70% HEMA – O_2 Free	892.2
80% HEMA – Air	362.5
80% HEMA – O_2 Free	740.9
90% HEMA – Air	1152.3
90% HEMA – O_2 Free	1617.7
100% HEMA – Air	768.7
100% HEMA – O_2 Free	1034.9

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The effect of particle size and deformation mechanism on the consolidation behaviour of mixtures of microcrystalline cellulose and lactose monohydrate

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Research has shown that the compaction of powder mixtures is a complex process, dependent on a number of variables including material physical properties and compression parameters (e.g. punch velocity) (Fell 1996). Inconsistent experimental methodologies used by researchers mean that results in this area are at times conflicting. The following piece of work was performed in an attempt to understand better the consolidation behaviour of powder mixtures. The materials studied were microcrystalline cellulose (MCC), a plastically deforming material, and lactose monohydrate (LM), which deforms by either plastic deformation or fragmentation depending on particle size (Roberts & Rowe 1987). The grades used were Avicel PH101 and PH200 (FMC Corp, median particle sizes of 64 and 230 μm), and Pharmatose 450M and 80M (DMV UK, median particle sizes of 18 and 244 μm). Binary mixtures were produced by mixing combinations of MCC and LM at various volume fractions (% v/v). Particle size analysis was performed by means of laser diffraction using a dry dispersion method on a Sympatec particle size analyser and the mean deformation pressure (P) of each mixture was determined at both 0.1 and 300 mm s^{-1} using a compaction simulator (Table 1). Graphs of P versus composition for Avicel PH200/lactose 450M mixtures were linear indicating that both materials deform plastically at the particle sizes tested (the brittle-ductile transition of lactose monohydrate is approximately 27 μm). This was further confirmed by the notable effect of punch velocity on the mean deformation pressures. In contrast, mixtures of Avicel PH200 and lactose 80M showed a different relationship. Linearity was maintained at low volume fractions of LM but as 75% v/v was approached, a negative deviation was apparent. This was attributed to MCC preventing fracture of lactose 80M until a critical volume fraction where previously isolated LM particles start to make contact. Point to plane contacts between LM particles under compressive force caused fracture to occur and the mean deformation pressure to reduce. Similar results were observed with mixtures of Avicel PH101 and the two lactose grades, however in these instances the smaller grade MCC provided greater protection of the lactose 80M due to the formation of a continuous network of MCC particles, even at low volume fractions. It was therefore apparent that, under these circumstances, larger volumes of LM are required before particle-particle contact can be made and therefore fracture can occur. Computer generated packing simulations will be run to help understand the pre-compaction architecture of these mixtures. These results illustrate the complexity of the tablet forming process. For mixtures of microcrystalline cellulose and lactose monohydrate particle size is important for determining both the architecture of the system and the overall consolidation behaviour.

Table 1 Mean deformation pressures (MPa) of binary powder mixtures of MCC and LM (n = 3)

Volume fraction of MCC (% v/v)	Avicel PH200 + Pharmatose 450M Speed (mm s^{-1})		Avicel PH200 + Pharmatose 80M Speed (mms^{-1})	
	0.1	300	0.1	300
0	136.4	147.2	106.1	123.5
25	105.8	132.6	78.4	105.5
50	83.8	113.3	80.5	103.8
75	70	93.4	68.2	91.5
100	56	76	56	76

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The characterization and dissolution properties of griseofulvin solid dispersions with HPMCAS

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Solid dispersions have always been viewed as a potential approach by which to improve the dissolution profile of poorly soluble drugs and subsequently their bioavailability. These formulations could be used to molecularly disperse the drug in polymers and hence to improve the physical stability of the amorphous form and the dissolution rate of the drug (Chiou & Riegelman 1971). In our experiments, griseofulvin, which is a class II drug, was used as a model due to its poor solubility in water. Solid dispersions of griseofulvin and HPMCAS (Hydroxypropyl Methylcellulose Acetate Succinate) were prepared by spray drying. HPMCAS is a cellulose based polymer with three different grades (HPMCAS L, M & H) differing in their acetyl and succinoyl group contents. The highest content of acetyl groups is found in the H grade while the succinoyl group content is the highest in the L grade. Griseofulvin (2.5 g) and HPMCAS (2.5 g) were dissolved in a mixture of 190 ml acetone and 85 ml water and subsequently spray dried using a system pressure of 25 kg/hr, atomizing pressure of 2.5 kg/hr and inlet and outlet temperatures of 65°C and 45°C, respectively. The size range of the prepared particles was 1–5 μm (assessed using scanning electron micrographs). Using x-ray powder diffractometer it was shown that the particles were physically stable for more than 22 weeks when stored at 75% RH and at 30°C compared with the spray dried griseofulvin which crystallized totally within 24 h at ambient conditions. The possibility of hydrogen bonding between the drug and the polymer was studied using FTIR. The results showed a shift in the peak of the carbonyl group of the cyclohexene of griseofulvin from 1662 cm^{-1} to 1647 cm^{-1}. This indicates that the carbonyl group was hydrogen bonded to the hydroxyl group in the HPMCAS which could explain the extended stability of the drug. The dissolution studies were undertaken with about 20% of the saturated solubility of griseofulvin in pH 6.8 (which was measured and found to be 14.2 μg/ml) using 900 ml of a phosphate buffer (pH 6.8) to maintain sink conditions. The results showed that the dissolution rate of the dispersion increased significantly when compared with the crystalline drug. These formulations were able to release more than 90% of the drug in less than 20 min while the same amount of the crystalline drug (no carrier) was dissolving in more than 7 h in the same media. The wettability of these formulations was assessed using contact angle measurements. The different formulations were pressed into disks and a microsyringe was used to drop a microdrop on the disk surface as explained previously by Buckton & Newton (1986). The droplet was just attached to the surface and the contact angle was measured visually using computer software (IMAGEJ). The results showed that there is a correlation between the wettability of the drug and the dissolution rate. These results indicate the importance of the interaction between the polymers and the drug to keep it in the amorphous state. Moreover, the dissolution properties of griseofulvin could be significantly improved via the association with HPMCAS.

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Synthesis and characterisation of a novel anti-adherent polymer blend for medical device coatings

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Medical devices are responsible for many nosocomial infections (Darouiche 2001). These device-associated infections are responsible for an increase in morbidity and cost of hospital stay. To overcome this limitation materials have been modified by two main strategies: surface modification of a material to reduce bacterial adherence and incorporation of antimicrobials into the device (Wu & Grainger 2006). The most promising method of producing an anti-adherent material has been through surface modification with poly(ethylene oxide) (PEO) (Kingshott & Greisser 1999). The aim of this work was to increase the anti-adherence of poly(methyl methacrylate) through blending with Pluronic, amphiphilic non-ionic polymers with a central hydrophobic segment of poly(propylene oxide) and lateral hydrophilic segments of poly(ethylene oxide), and to investigate the drug release capabilities of these novel polymer blends. Polymers were prepared by dissolving Pluronic F127 (PF127) at defined concentrations (20, 30 40 and 50% w/w) into MMA prior to polymerisation. Polymerisation was initiated using 1% benzoyl peroxide (w/w). The adherence of *E. coli*, and *S. epidermidis* to the polymers was investigated after 4hr exposure to the micro-organism in vitro. The ability of these polymer blends to control drug release was investigated using rifampicin. Rifampicin loading was achieved via the equilibrium partitioning technique and release was carried out into Tris buffer under sink conditions. The contact angle of the material was investigated using the captive bubble technique on a FTA 200 contact angle analyser. The studies show that the incorporation of PF127 into pMMA greatly reduces the level of adherence of both the micro-organisms studied compared to the pMMA control (Table 1). This is due to the presence of PEO on the surface of the material as shown by the reduction in contact angle of the materials, corresponding to an increase in surface hydrophilicity. Drug loading of rifapmicin into the polymer blends was greatly increased by incorporation of 30% F127 or greater into pMMA (Table 2). Subsequent release from these materials occurred at a reduced rate in comparison to pMMA and the PF127 20% blend. These materials may prove to be beneficial in the medical device field as anti-adherent materials with good drug delivery capabilities.

Table 1 Contact angle and bacterial adherence at 4 h (pMMA PF127 blends)

Polymer	*E.coli* adherence (%)	*S. epi* adherence (%)	Contact angle (%)
pMMA	100	100	56.3 ± 4.2
20%	0.35 ± 0.09	0.22 ± 0.11	51.8 ± 3.9
30%	0.26 ± 0.16	0.11 ± 0.04	48.4 ± 1.7
40%	0.09 ± 0.02	0.07 ± 0.02	40.1 ± 2.3
50%	0.12 ± 0.02	0.12 ± 0.01	33.5 ± 3.1

Table 2 Rifampicn loading and release from pMMA PF127 blends

Polymer	Rifampicin loading (mcg/cm^2)	Rifampicin released at 24 h (%)
pMMA	5.7 ± 3.6	95.2 ± 4.7
20%	113.7 ± 20.83	90.4 ± 5.2
30%	992.8 ± 50.9	42.3 ± 4.0
40%	2267.3 ± 174.2	39.1 ± 1.9
50%	2090.9 ± 79.4	43.7 ± 1.6

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Novel complexation hydrogel: characterisation and drug release

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Poly(Methacrylic acid) (pMAA) is a pH-responsive hydrogel. Previously, pMAA has been grafted with poly(ethylene oxide) (PEO) (Madsen & Peppas 1999). These materials exhibit pH-dependent behaviour due to the formation of interpolymer complexes. Hydrogen bonding occurs at low pH between the unionised carboxylic group of pMAA and the ether oxygen of PEO. Above the pK_a of pMAA, the carboxylic group is ionised and the hydrogen bond dissociates. In this investigation pMAA was blended with Pluronic, a triblock copolymer consisting of a poly(propylene oxide) block flanked by two PEO chains, to develop and characterise a novel polymer blend. Polymers were prepared by dissolving Pluronic (PF127) (10, 20, 30 and 40% w/w) into MAA prior to polymerisation. Polymerisation was initiated using 1% benzoyl peroxide (w/w). Swelling was investigated by soaking dried polymer discs in buffer at pH 7.2 and pH 4. Swelling index was calculated as the ratio of the swollen weight to the dry weight. Mechanical properties of the materials were investigated after soaking at pH 4 and pH 7.2 using a TA.XT Texture Analyser. The ability of these polymers to control drug release was investigated. Rifampicin loading was achieved via the equilibrium partitioning technique and release was carried out at pH 4 and pH 7.2. The effect of polymer composition on material properties was statistically evaluated using a one-way ANOVA ($P < 0.05$ denoting significance). At pH 4 a decrease in swelling index with increasing PF127 content was observed (Table 1). This is due to the formation of hydrogen bonds restricting water uptake. At pH 7.2 increased swelling was observed with increasing PF127 as the

Table 1 Mean (±s.d.) equilibrium swelling index of pMAA PF127 blends at pH 4 and pH 7.2

Polymer	Swelling Index pH 7.2	Swelling Index pH 4
pMAA	6.06 ± 0.63	1.30 ± 0.15
10%	6.27 ± 0.55	0.94 ± 0.03
20%	6.77 ± 0.36	0.54 ± 0.02
30%	7.62 ± 0.69	0.39 ± 0.01
40%	9.25 ± 0.96	0.44 ± 0.09

Table 2 Mean (±s.d.) percentage cumulative rifampicin released at 72 h (pH 4 and pH 7.2)

Polymer	% Rifampicin released (pH 4)	% Rifampicin released (pH 7.2)
pMAA	19.39 ± 0.94	100.87 ± 4.69
10%	13.48 ± 0.66	99.49 ± 4.02
20%	12.11 ± 0.99	97.60 ± 3.86
30%	9.22 ± 0.56	95.25 ± 1.84
40%	8.54 ± 0.48	88.98 ± 3.52

complexes dissociate with the ionization of MAA and water uptake increased due to hydrophilic PEO. The mechanical properties reflect this; at pH 4 an increase in PF127 content results in increased ultimate tensile strength (UTS) and Young's Modulus (E) of the material. pMAA and PF127 30% showed 0.80 ± 0.05 and 3.85 ± 0.39 MPa (UTS), and 0.78 ± 0.08 and 5.94 ± 0.83 MPa (E), respectively. At pH 7.2 PF127 is detrimental to the mechanical properties. MAA PF127 40% had the lowest values of UTS (0.38 ± 0.06 MPa) and E (1.06 ± 0.19 MPa). Rifampicin release rate was found to be reduced from the networks at pH 4 in comparison with pH 7.2 due to the decrease in mesh size of the hydrogel associated with decreased swelling (Table 2). An increase in PF127 resulted in a decrease in rifampicin released. It was concluded that polymer composition and pH had a significant effect on the hydrogel properties due to formation and dissociation of interpolymer complexes between pMAA and PF127.

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Hydroxylpropyl β-cyclodextrin (HP-β-CD): a porogen and a protein stabiliser

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Porous microspheres can be employed as tissue engineering scaffolds or as delivery systems for biotherapeutics. Various methods have been used to fabricate porous microspheres. However, it is often difficult to control the porosity of these systems and to control the stability of encapsulated protein. Previously, hydroxypropyl-β-cyclodextrin (HP-β-CD) had conferred conformation stability to bovine serum albumin (BSA) (Kang & Singh 2003). This study's objective is to investigate the use of hydroxypropyl-β-cyclodextrin (HP-β-CD) as a porogen and a protein stabiliser. A solvent evaporation (double emulsion) method was used to encapsulate a model protein, BSA (MW 66,550), into Poly (DL-lactide-co-glycolide) (PLGA) microspheres. Two ratios of HP-β-CD: BSA (1:5 and 5:5) were homogenised with PLGA 50:50 4A in dichloromethane. The w/o emulsion was further homogenised in a polyvinyl alcohol (PVA, 13–23kDa) solution (0.5% w/v) forming a w/o/w emulsion. Microspheres were formed by evaporation and harvested by centrifugation. The sizes of the microspheres were measured via laser diffraction. Characterisation of surface morphology was determined using scanning electron microscopy (SEM), stability using SDS polyacrylamide gel electrophoresis (SDS PAGE) and encapsulation efficiency and release kinetics using total protein assay (BCA). Control microspheres containing HP-β-CD or BSA were also prepared. By using a low concentration of PLGA (5% m/v), porous spherical microspheres 20–40 μm in size were prepared. SDS PAGE experiments of formulation #2 indicated that HP-β-CD had acted as a stabiliser of BSA. Scanning electron micrographs of formulations (#'s 1–2) had demonstrated that when the concentration of HP-β-CD was increased, the porosity was also increased. The pores of the microspheres in formulation #1 were partially covered by a layer of polymeric skin covering. In contrast, formulation #2 was composed of microspheres with clearly visible pores. Control microspheres (HP-β-CD and BSA) were non-porous in nature. By increasing the HP-β-CD: BSA ratio from 1:5 to 5:5, the encapsulation efficiency was reduced from 93.2% to 61.0%, respectively, and the rate of release of BSA was increased. BSA was completely released within 14 days and 1 day respectively (Table 1). Protein aggregation may be reduced by the shielding of the hydrophobic residues of BSA within the hydrophobic core of the HP-β-CD (Kang & Singh 2003). Hydrophilic HP-β-CD: BSA complexes may increase the rate of diffusion of internal aqueous phase droplets through to the outer phase, resulting in an increase in porosity when the HP-β-CD concentration was increased. By increasing the porosity, the rate of degradation of microspheres and the rate of protein diffusion from the microspheres were increased. In conclusion, HP-β-CD may find application as a porogen and a protein stabiliser for fabrication of porous microspheres. By varying the ratio of HP-β-CD:BSA, control over porosity, encapsulation efficiency, release kinetics and stability of the encapsulated protein were achieved.

Table 1 Morphology, encapsulation efficiency and release kinetics of formulations #1- #2 (n = 3)

Formulation (HP-β-CD: BSA ratio)	Morphology	Encapsulation efficiency (%)	Time for complete BSA release (days)
#1 (1:5)	Semi-porous	93.2 ± 0.2	14 ± 1.89
#2 (5:5)	Porous	61.0 ± 4.0	1 ± 0.79

Data are means ± s.d.

Kang, F., Singh, J. (2003) *Int. J. Pharm.* **260**: 149–156

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Solid state characterisation of formulated drug products

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Controlled release formulations typically employ polymers to release an active ingredient in a pre-designed manner. As such the structure, location and stability of such layers within a controlled release product are crucial to its performance in-vivo. While numerous techniques exist for the study of excipients and active pharmaceutical ingredients, solid state characterisation of the formulated product remains challenging. Here we describe the physiochemical characterisation of a controlled release formulation through the use of X-ray micro tomography (SkyScan, 1172) providing structural characterisation and Raman microscopy (Witec CRM200) providing spatial and chemical identification of components. Employing these techniques in combination enables cross-correlation of structural features with chemical identification and mapping. X-ray micro tomography is a non-invasive technique capable of successfully probing 3-dimensional structure. Furthermore, it is capable of discriminating between the components within the formulation on the basis of material and elemental density. For the controlled release product studied here, three defined layers are clearly observed and these are inferred to be an exterior coating, an active layer and the sugar/starch core. In addition, porosity and average layer thickness can be determined. In the case of this particular formulation pores can be observed in all layers of the pellet, which may have implications for the formulation performance. While the micro-CT images are able to resolve the internal structures of pellets the assignment of these layers is by inference using the proposed structure. Using cross-sectional analysis and Raman microscopy it is possible to chemically identify and spatially locate the components within the formulation. Chemical analysis clearly discriminates the exterior coating from the active layer, as structurally observed by X-ray micro tomography. More importantly chemical mapping reveals that none of the active ingredient is incorporated into the coating. The use of Raman microscopy in solid dosage form can also provide information regarding the form of an API and ensure that no changes in the physical form have occurred during processing. Solid-state characterisation techniques can provide an insight in to the structure and chemistry of a formulated product. Micro-CT is a non-invasive technique providing a global view of the formulation giving an indication of pellet volume, coating thickness, coating integrity and porosity. This non-invasive methodology can be successfully combined with the Raman microscopy to chemically and structurally characterise formulations.

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Impact of lactose polymorphism on salbutamol sulphate-lactose interactions in DPI formulations

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Lactose is the most common carrier used in DPI formulations. It is a well established fact that drug–lactose interactions significantly affect processability (e.g. powder flow and content uniformity) as well as drug dispersion (e.g. fine particle fraction). For this reason it is important to understand the polymorphic behaviour of lactose in detail since different polymorphic forms can cause a variation in drug–lactose interactions due to their different surface energies. So far the attention of most researchers was focused on the amorphous to crystalline ratio since the amorphous phase is less stable

and more energetic. However, even crystalline lactose can occur in different polymorphs and mixtures of these forms can appear in different ratios and therefore affect drug-lactose interactions. The binding strength between two solids can be determined by the materials' surface energy. Inverse Gas Chromatography (IGC) is a well-established technique for quickly and accurately measuring the surface energetics for a wide range of solids (Domingue et al 2003). Unlike in wettability experiments this can be done with a very high reproducibility and sensitivity. In this study, the energetic properties of pure alpha lactose anhydrous (stable form), pure alpha lactose monohydrate, and standard as well as purified beta lactose (all supplied by Baker) have been investigated using finite concentration IGC. Mixtures with salbutamol sulphate have been prepared followed by in-vitro tests with the Next Generation Impactor (NGI). The dispersive and specific contributions of the surface energy were obtained for the different lactose polymorphs as well as for the drug. From these values, the work of adhesion and cohesion was calculated for each drug-lactose pair. These numbers were then correlated with the fine particle fractions (FPF) from the in-vitro tests. There is a nearly linear correlation between dispersive and specific surface energies and subsequently with the work of adhesion to cohesion ratios predicted from the IGC experiments. The data suggest that there is an increase in FPF with decreasing surface energy and work of adhesion, most likely due to a decrease in the required detachment force for drug dispersion. Different crystalline polymorphs of lactose can have a strong impact on in-vitro performance of salbutamol sulphate—lactose DPI formulations. Higher surface energies and work of adhesion/cohesion ratios can be directly correlated with decreasing fine particle fractions. IGC surface energy experiments are a valuable method for predicting drug-excipient interactions in DPI formulations.

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Determination of the amorphous content in excipients and drugs

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The presence of amorphous materials in drugs and excipients can be desired or undesired, depending on the application. Amorphous phases can have advantages effects like increase solubility. However, amorphous materials are inherently metastable, thus stability and shelf life can be decreased. For this reason the knowledge of the amorphous content is important. Dynamic Vapour Sorption (DVS) is a well-established gravimetric method for the determination of vapour sorption properties. Various methods have been described in the literature (Saleki-Gerhardt et al 1994; Mackin et al 2002), mainly using a humidity-induced crystallisation to quantify the amorphous content. However, since not all materials fully crystallise it is desirable to measure the amorphous content based on a change in uptake of vapour. This requires a test vapour that does not induce any morphology changes. For the current study lactose was investigated as an example for a common excipients and octane was identified as an appropriate vapour. The samples were initially preconditioned in dry air at 25°C. Then, the samples were exposed to different partial pressures of octane (0–95% p/po) at constant temperature while monitoring the change in mass. For the quantification of the amorphous content a reference curve was established using physical mixtures of spray-dried amorphous lactose and crystalline alpha-lactose monohydrate. The uptake at 95% p/po was then plotted versus the amorphous fraction in the reference mixtures. Since octane vapour does not induce any crystallisation in either sample the amount adsorbed increases with increasing amorphous content. The introduction of amorphous material due to mechanical processing was investigated for alpha-lactose monohydrate. Samples were milled for different durations and the octane uptake was measured at 95% p/po. The amorphous content was obtained from the calibration curve. As milling time increased, there was a steady increase in amorphous content until it maxed out at 14% amorphous after 60 min of milling. A novel method was established for the determination of low levels of amorphous content based on organic vapour sorption. First, a calibration curve was ascertained using samples of known amorphous content. This allowed determination of amorphous contents of alpha-lactose monohydrate samples exposed to different milling times. This method could be applied to a wide range of drugs and excipients without the limitations of other gravimetric methods.

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A comparison of powder flow assessment techniques

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Assessment of powder flow is an important step during pre-formulation studies and batch control in the pharmaceutical industry. Currently a number of methods are used within industry for this purpose; however, these methods are not without their limitations, consequently new methods are currently being developed. We have compared two methods recently developed, the Powder Flow Analyser (PFA) (Stable Microsystems, UK) that studies powder flow under the influence of force using a mechanical blade, and the Aeroflow (Amherst Process Instruments MA) powder avalanching technique (MTA), with two established British Standard indicators (BSI) the Angle of Repose (AOR) and Tapped density (Hausner ratio (HR)). The powder flow analyser comes with four pre-programmed test setups, 2 of which were chosen – the cohesion Test and the Power Flow Speed Dependence (PFSD) tests, as measures of powder behaviour over a range of induced flow rates. Six samples of lactose and five samples of mannitol were characterised using all the techniques. The aim of the experimental work was to ascertain the reliability and reproducibility of the new techniques in comparison to those already established. From the correlation of the AOR and the HR a benchmark value of $R^2 = 0.7955$ was obtained. When the mean time to avalanche (Aeroflow) was compared with the AOR and HR, R^2 values of 0.8377 and 0.6324 respectively were obtained. However, results for the Cohesion Test using the Cohesion Index (CI) only showed a partial correlation with the AOR and poor correlation was found with HR. The standard deviations were also compared and the AOR, Mean Time to Avalanche (MTA) and the CI possessed high standard deviations. The AOR also struggled to provide accurate assessment of more cohesive powders. Analysis of the initial results showed further experimental work was required. Both the PFA vessel and programming was modified and a standard filling procedure was devised. The second batch of powders gave a benchmark value of $R^2 = 0.8585$, the correlation between the AOR and the MTA also showed a slight increase ($R^2 = 0.8491$) but correlation decreased with HR ($R^2 = 0.5874$). When the CI was compared with the BSI, poor correlation was found, even when using the standard vessel and test parameters. The standard deviations obtained, however, were significantly lower those with AOR and MTA. The results for the modified test vessel and programming were assessed and a new index devised which gave R^2 values of 0. 766 and 0.6852, respectively, for the AOR and Hr. A second index for flow measurement was also obtained from the PFSD test using the modified vessel and programming, giving R^2 values of 0.7984 with the AOR and 0.7565 with the Hr. Both the Aeroflow and the PFA gave better correlation with lactose than with mannitol. The MTA gave better differentiation for free flowing powders while the PFA was better with cohesive powders. Overall while the Aeroflow gave better correlation with the BSI than the PFA, the PFA gave more reproducible results after modification.

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A calorimetric investigation of hydrogel swelling and drug release

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Hydrogels, a commonly used drug delivery system, are comprised of a cross-linked polymer network. In water the dry hydrogel (zerogel) will swell and hydrate, increasing in volume but retaining its geometry; importantly, the cross-links prevent complete dissolution of the polymer, which means that hydrogels can be removed from solution and dried. Hydrogels are loaded with drug by swelling them in a concentrated drug solution. The drug diffuses into the polymer network before the hydrogel is removed and dried. Subsequent drug release also occurs by diffusion. Knowledge thus of both the swelling characteristics of the hydrogel, as well as the interactions (if any) between the polymer, the drug and the solvent system are essential in order to ensure the best hydrogel is selected for a specific drug and/or release profile. With the premise that all of these events will have a thermal signal, here the use of solution (ampoule-breaking) calorimetry as an assay technique was assessed. Two hydrogels were prepared; cross-linked PEG400 and PEG1500, which were synthesized by chemically cross-linking poly(ethylene glycol) 400 and 1500 with diisocyanate and hexanetriol. Small cylinders of hydrogel were cut using a cork borer, which enabled the geometry and mass of the samples to be consistent between experiments. Experiments were conducted using the 2265 micro-solution ampoule (Thermometric AB) at 25°C. Starting with simple swelling, hydrogels (ca.10 mg) were introduced into buffer (pH 7.8) and the power-time data recorded. The data were subsequently analysed by a modified form of the Ritger & Peppas (1987) model: q_t/Q=kt^n where q_t is the heat released up to time t, Q is the total amount of heat released (and hence q_t/Q is a term analogous to the fraction of swelling), k is a constant and n is a parameter the value of which indicates the mechanism of swelling. Thus, by plotting log q_t/Q versus log t linear relationships were obtained, the slope of which gave the value of n directly. The n values were 0.55 and 0.7 for PEG400 and 1500, respectively. It was also noted that the response of the PEG1500 hydrogel was clearly biphasic while that of PEG400 was monophasic. We believe that this difference reflects a difference in the amorphous state of the hydrogels (PEG400 being above its glass transition at 25°C, PEG1500 being below its glass transition). The interaction with drugs was then investigated using three model drugs; metronidazole, diclofenac sodium and salicylic acid. The

power-time data for the polymer alone were subtracted from the power-time data for the hydrogel swelling in drug solution. Heats of interaction varied in magnitude; salicylic acid > diclofenac sodium > metronidazole and were shown to correlate with drug dissolution results. In summary, it appears that solution calorimetry has the sensitivity to detect both hydrogel swelling (and changes in mechanism) and drug-polymer interactions and thus has the potential to be a powerful tool for the study of hydrogels.

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Raman spectroscopic analysis of chlorhexidine–myristic acid interaction in methacrylate biomaterials

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The use of methacrylate polymers as biomaterials is often limited by bacterial infection and biomaterial formation. Bacterial infection of polymethylmethacrylate (PMMA) bone cement for prosthetic hip replacements can lead to loosening of the implant, often requiring removal and replacement of the implant (Atkins et al 1998). Attempts have been made to prevent infection by incorporating antimicrobial agents into the matrix of the cement. However, the diffusion of the antimicrobial agents from the cement is often limited. Drug diffusion may be controlled by the use of ion-pairing agents. These offer a way to alter the physicochemical properties of the diffusant. In this study, the interaction of the ion-pairing agent, myristic acid on the antimicrobial agent, chlorhexidine, was examined using Raman spectroscopy (Jones et al 2000). Methacrylate samples were prepared by free-radical polymerization of methyl methacrylate using 2,2′-azo-*bis*-isobutyrylnitrile (AIBN) as the initiator and heating at 60°C for 18 h. Chlorhexidine base (CHX) alone or chlorhexidine base and myristic acid (MA) in a 1:2 ratio were dissolved in the monomer mixture before heating. In both cases, the concentration of chlorhexidine in the reaction mixture was 1%. Raman spectra were recorded using 785-nm excitation and accumulated for 1000 s. Spectra for chlorhexidine base, chlorhexidine dihydrochloride pure PMMA and PMMA + MA were also collected. The Raman spectra of all the polymer samples were dominated by bands from the PMMA and only the strongest CHX bands ca. 1650 cm^{-1} were visible as small peaks in the raw data. Subtraction of the 100% PMMA spectra allowed more CHX and MA bands to be distinguished. The CHX bands in the CHX/PMMA spectra were similar to those of the spectra of chlorhexidine base, while those of the CHX/MA/PMMA samples resembled those of the dihydrochloride salt of the drug, implying protonation of CHX by MA in the polymer. However, the CHX bands were significantly shifted and broadened in the polymer compared with the crystalline samples. The strongest CHX band shifted from 1568 cm^{-1} (FWHM 17 cm^{-1}) to 1555 cm^{-1} (FWHM 45 cm^{-1}) in the polymer without MA. A smaller effect was also observed in the presence of MA. This implies there is a significant interaction between the drug and the polymer. Consistent with this, is the observation that the sharp polymer band at 814 cm^{-1} (which lies in a region free from interference from CHX and MA bands) cannot be removed from spectra of the mixed samples by subtraction of a pure PMMA spectrum. Subtraction leaves a derivative-like residual which is characteristic of a small shift in band position which is not apparent in the raw data which shows the same position ± 1cm^{-1}. The Raman spectra indicate that chlorhexidine base does not undergo any ionization when incorporated into the PMMA. However, when myristic acid is added, protonisation of chlorhexidine occurs and interaction of the drug with the ion-pairing agent occurs. This may account for the observed effects of myristic acid on the release of chlorhexidine from this polymer.

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Isothermal methods to investigate the structural relaxation of amorphous materials

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DSC is commonly used to assess the relaxation of amorphous materials, but involves heating a sample, which can accelerate the relaxation and/or degrade the sample. Thus, isothermal techniques may offer more reliable data. This study investigated the use of two isothermal techniques; solution calorimetry (SC) and inverse gas chromatography (IGC) for characterisation of the structural relaxation of amorphous lactose. Amorphous lactose was prepared by spray drying as previously described (Chidavaenzi et al 1997), and stored in a dry desiccator. Sieved amorphous lactose (<425 μm) was aged at 50 and 65°C at 0% RH. Periodically, samples of amorphous lactose were collected for enthalpy of solution, dispersive surface energy and enthalpy recovery measurements. Enthalpies of solution (n = 3) were determined on a Thermometric 2225 Precision Solution Calorimeter (Thermometric AB, Sweden) as previously described (Hogan & Buckton 2000). Dispersive surface energy measurements (1 column, n = 4) were carried out by IGC (SMS, UK) as described by Newell et al (2001). Enthalpy recovery data (n = 3), glass transition temperature and heat capacity change at glass transition were determined by Step-Scan Differential Scanning Calorimetry (SSDSC) on a Pyris-1 DSC (Perkin Elmer Instruments, UK) using a heating rate of 5°C/min, a step of 1°C and an isothermal period of 30 s. The extent of relaxation was calculated for each set of data and the relaxation time (τ) and stretching parameter (β) were determined by fitting the data using non-linear regression analysis to the Kohlrausch-Williams-Watts (KWW) equation using Origin (Microcal Inc). For the enthalpy of solution data, the enthalpy relaxation was calculated by subtracting the enthalpy of solution at time zero from each enthalpy of solution measurement. The extent of relaxation was calculated from the previous data taking the enthalpy of solution at day 17 as the enthalpy relaxation at infinite time. A similar procedure was used for the dispersive surface energy data. Enthalpy recovery determined by SSDSC was used to determine the extent of relaxation considering enthalpy recovery at day 17 as the enthalpy relaxation at infinite time. The relaxation parameters obtained from the fitting of the data to the KWW equation are represented in Table 1. The τ and β obtained from the three techniques show some variation. This could be due to the different experimental conditions used for each technique. For example, SC samples had to equilibrate at 25°C for almost 1 h before the enthalpy of solution was determined, while SSDSC runs were carried out immediately after the sample was removed from the aging conditions. In addition, as IGC probes the surface of the material, τ and β obtained from the dispersive surface energy measurements characterise the structural relaxation of the surface, while both SSDSC and Solcal data will reflect the structural relaxation of the whole sample. τ^{β} values obtained from the three sets of data are closer and show the same trend; amorphous lactose annealed at a higher temperature shows a smaller τ^{β}, reflecting the higher molecular mobility of this sample.

Table 1 Relaxation time constants (τ and β) evaluated from StepScan DSC, Solution Calorimetry and Inverse Gas Chromatography data according to aging conditions

Ageing conditions	τ (days)	β	τ^{β} (days)
SSDSC			
50°C 0% RH	283.5	0.6	35.5
65°C 0% RH	584.0	0.2	2.8
SC			
50°C 0% RH	2.8	0.9	2.6
65°C 0% RH	2.1	0.6	1.6
IGC			
50°C 0% RH	6.9	~1	6.5
65°C 0% RH	4.4	~1	4.2

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