evidence that water sorption may lower the Tg to below body temperature (Passerini & Craig 2001), thereby raising the possibility of polylactides being in the rubbery state within the body. The purpose of this study was to investigate the depression of the glass transition temperature (Tg) on dried polylactide films as a function of the quantity of sorbed water by the application of modulated temperature differential scanning calorimetry (MTDSC). Samples of polylactide-co-glycolide (PLGA) 50:50 were used as received and as films. Solutions of the polymer in acetone was prepared at room temperature, then placed in aluminium hermetic pans without lids, dried on a hot plate at 100°C for 1 h and pretreated under various humidity conditions. The quantity of sorbed water was measured by thermogravimetric analysis (performed using a TGA Hi-Res 2950, a dry nitrogen purge and temp. ramp $10°C\,min^{-1}$). MTDSC runs were performed using a TA 2920 DSC, calibrated at $1°C\,min^{-1}$ with indium and n-octadecane for temperature and enthalpy and alumina for heat capacity calibration. Hermetically sealed pans were used throughout. The following thermal procedure was used: isotherm at 10°C for 1 min, ramp at $1°C\,min^{-1}$ from 10°C to 70°C, amplitude ±0.5°C, period 40 s, isotherm at 70°C for 1 min, ramp at $1°C\,min^{-1}$ from 70°C to 10°C. The glass transition temperature was seen in the reversing signal; the change in heat capacity, width of the transition and magnitude of the endothermic relaxation (seen in the non-reversing signal) were also noted. Sorbed water significantly lowered the glass transition temperature of amorphous PLGA 50:50; for example the Tg for PLGA 50:50 films, stored at 85% RH for 1 h, run in hermetic pans, was determined to be $34.83 \pm 4.7°C$ compared with a measured value of $43.57 \pm 0.32°C$ obtained using the film dried without storage at high RH (the corresponding heat capacity changes through Tg are $0.45 \pm 0.04\,J\,g^{-1}°C^{-1}$). Interestingly, the Tg of the films was found to be higher than that corresponding to the powder as received ($35.6 \pm 0.75°C$), an observation that is not explained by differing solvent levels. The relationship between moisture uptake and Tg is discussed in terms of the Gordon-Taylor equation. In addition, we consider the fragility of the system (itself related to the heat capacity change through the transition) as a function of water content, an issue that will have implications for the change in mechanical properties of the film as a function of water content and temperature. Overall, the study not only demonstrates that PLGA films may, in a humid environment, sorb sufficient water to lower the Tg to below body temperature but also presents more fundamental information on the changes in the film's molecular mobility caused by the plasticisation process.

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Drug product analysis through multidisciplinary solid state characterisation

S. D. Ward, M. Perkins, S. J. Ebbens, C. J. Roberts, S. Y. Luk, N. Patel and C. E. Madden

Molecular Profiles Ltd, 8 Orchard Place, Nottingham Business Park, Nottingham NG8 6PX, UK. E-mail: cmadden@molprofiles.co.uk

While challenges still remain for the solid state characterisation of drug substance (e.g., reliable surface amorphous quantification), there are numerous techniques that can be applied to determine physicochemical properties. In comparison, the number of solid state characterisation methodologies applicable to the study of a formulated drug product is greatly reduced. With increasing regulatory guidance and escalating challenges faced for the incorporation of the API into a viable drug delivery system, more sophisticated characterisation technologies are required for evaluation of resultant physicochemical properties. No one technique is capable of elucidating all properties and here we explore, for the first time, the application of high-resolution solid state characterisation methodologies to study the mechanisms of action of drug delivery systems in vitro. In addition to the conventional requirements of identifying and quantifying the composition of components, resolving spatial distribution is a key element in optimising and understanding the mechanism of action in relation to drug release profiles. Here we have combined the use of the chemical mapping techniques of Confocal Raman microscopy and time-of-flight secondary ion mass spectrometry (TOF-SIMS) with the high resolution imaging capability of X-ray microtomography. Two different but equally complex systems have been studied – a multilayered controlled release pellet and a tableted formulation. Non-destructive imaging by X-ray microtomography has been used to probe the 3-dimensional physical structures of both systems in dry and solution immersed conditions. In the dry state, this has provided 3-dimensional quantified information on particle size (in the range 10–55 μm) and layer thickness (range 15–100 μm) as well as physical properties such as cracks and inherent porosity to be determined. Dynamic studies have for the first time revealed 3-dimensional information about the mechanism of action in solution. X-ray microtomography is, however, limited to a spatial resolution of ~5 μm and does not provide direct chemical identification. TOF-SIMS analysis of cross-sectioned regions was therefore used to correlate the microtomography data to the spatial distribution of chemically identified components within the two systems. Through the application of Raman microscopy the chemical form and interactions between components was also correlated to microtomography data under dry and solution conditions. Application of solid state analytical technologies can be used for the in-depth study of drug product analysis. Through careful combination of relevant techniques, issues relating to the final drug form, particle size, chemical distribution and mechanisms of action can start to be resolved aiding formulation problem solving and optimisation early in drug delivery design.

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Characterisation of two multicomponent adenine complexes

P. J. Cox and E. Nixon

School of Pharmacy, The Robert Gordon University, Schoolhill, Aberdeen AB10 1FR, UK. Email: p.j.cox@rgu.ac.uk

Many solid forms of active pharmaceutical ingredients (APIs) can be prepared, including polymorphs, solvates, hydrates, salts and amorphous solids. In addition, crystal engineering can be used to design crystals containing multiple component phases involving an API and other molecules. It is possible for an API and a second substance to crystallise together without a reaction taking place. If both substances can exist separately as solids at room temperature then the multicomponent crystal is known as a cocrystal. Multicomponent crystals may form not only from recrystallisation but also by grinding. Desirable or undesirable properties may then result. Recently, several co-crystals of caffeine have been prepared with a view to enhancing physical stability at various humidities (Trask et al 2005). The aim of this study was to prepare multicomponent crystals of adenine. As adenine is a base, it should be possible to combine it with an acid and adipic acid and salicylic acid were selected for complex formation. The optimum characterisation technique used to analyse the products obtained by recrystallisation was X-ray crystallography. Before X-ray investigations, identification methods used on the samples included simple melting points, microscopic examination, FTIR, DSC and density determinations. Single crystal X-ray data, collected on a Bruker-Nonius KappaCCD diffractometer, were used to determine the previously unknown crystal structures. In both cases the solvent used, methanol, became trapped within the crystal lattice. Multicomponent crystals of adenine:adipic acid: methanol (2:1:2) are triclinic with a = 8.9781 (5), b = 9.9334 (5), c = 14.281 (7) Å, $\alpha = 74.908$ (3), $\beta = 85.357$ (3), $\gamma = 66.786$ (3)°. The five molecules in the asymmetric unit of the crystal are linked together by extensive hydrogen bonding. An attempt to cocrystallise adenine and salicylic acid resulted in a methanolated proton transfer complex where the hydrogen from the carboxylic acid group in salicylic acid transferred to a nitrogen in the pyrimidine ring of adenine. The ortho hydroxy group of salicylic acid is also disordered over both possible ortho positions. The cell dimensions of the resulting monoclinic crystals, space group $P2_1/n$, are a = 7.1636 (2), b = 7.9486 (3), c = 24.7336 (9), $\beta = 91.248$ (2). The ratio of molecules in the crystal is 1:1:1. Again, extensive hydrogen bonding is present and for both multicomponent crystals the molecular geometries were characterised using the PLATON (Spek 1998) computer program. It can be concluded that multicomponent crystals of adenine can be formed by recrystallisation with suitable acids and that the architecture of the products can be characterised by single crystal diffraction.

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An approach to normalise inverse gas chromatography data measured with a range of dispersive probes

M. A. Mohammad, I. M. Grimsey and R. F. Forbes

Drug Delivery Group, School of Pharmacy, University of Bradford, Bradford BD7 1DP, UK. E-mail: i.m.grimsey@bradford.ac.uk

Inverse gas chromatography is a precise and reproducible technique to calculate the surface energetics of pharmaceutical solids by measuring the

retention behaviour of vapour probes injected into a column packed with the powder of interest. To calculate the thermodynamic parameters, knowledge of the free energy of the probe and its interaction area with the surface are required. This data is routinely taken from published sources but due problems have been noted in the determination of the proper values (Voelkel 2004). By using the approach of Schultz et al (1987), the dispersive free energy of the solid (γ_S^D) is derived from the slope obtained by plotting the retention behaviour of a series of linear alkanes. It has been found that the choice of which alkanes are used will give a different value for the dispersive free energy by a factor of up to 20% on the same sample. This error will be compounded in the calculation of the specific free energy calculations ($-\Delta G_A^{SP}$), which is calculated from the deviation of the polar probe from the alkane line. By analysing the retention behaviour from a series of 200 experiments on 30 different samples, it has been found that the difference in the calculated thermodynamic parameters due to the choice of the series of alkane probes can be correlated to which probes are used and is independent of the sample. Calculations based on the geometry of the data plot have allowed a series of "conversion factors" to be determined so that differences in the surface energetic parameters (γ_S^D and $-\Delta G_A^{SP}$) arising from the choice of alkane probes can be calculated and samples analysed with different series of probes can be compared directly. For example, the same material was analysed using the alkane series pentane to octane (C5–C8) and hexane to octane (C6–C8) (Table 1). From this data it would appear that the two measurements were showing a difference in the thermodynamic parameters (especially in the values for γ_S^D and $-\Delta G_A^{SP}$ for acetone and ethylacetate) of the sample. By using the derived conversion tables, the data was recalculated and is shown in Table 2. Now it can be seen that the two measurements on the same sample give equivalent values for the surface energetic parameters.

Table 1 Comparison of the thermodynamic data calculated on the same sample using different alkanes

	γ_S^D (mJ m^{-2})	$-\Delta G_A^{SP}$ Chloroform (kJ mol^{-1})	$-\Delta G_A^{SP}$ Acetone (kJ mol^{-1})	$-\Delta G_A^{SP}$ Ethyl acetate (kJ mol^{-1})	$-\Delta G_A^{SP}$ THF (kJ mol^{-1})
C5–C8	33.83	4.74 (0.03)	6.13 (0.02)	5.01 (0.01)	4.78 (0.01)
C6–C8	37.24	4.89 (0.06)	6.45 (0.02)	5.20 (0.05)	4.96 (0.06)

Table 2 Comparison of the thermodynamic data recalculated using the conversion factors

	γ_S^D (mJ m^{-2})	$-\Delta G_A^{SP}$ Chloroform (kJ mol^{-1})	$-\Delta G_A^{SP}$ Acetone (kJ mol^{-1})	$-\Delta G_A^{SP}$ Ethyl acetate (kJ mol^{-1})	$-\Delta G_A^{SP}$ THF (kJ mol^{-1})
C5–C8	37.1	4.88	6.44	5.19	4.96
C6–C8	37.24	4.89	6.45	5.20	4.96

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The development of temperature controlled force-distance measurements for the analysis and imaging of pharmaceutical materials

L. Dakić, M. Reading and D. Q. M. Craig

School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich NR4 7TJ, UK. E-mail: L.Dakic@uea.ac.uk

The characterization of the adhesion forces associated with pharmaceutical materials is extremely useful for the rational design of solid state formulations, in terms of understanding the interparticulate forces involved in processes such as compaction and gaining insights into the manner by which powder particles interact with each other and powders and compacted surfaces interact with equipment and packaging materials. A very useful means of performing such studies is using force-distance curve (FDC) measurements, whereby the forces involved in introducing and withdrawing a probe from a sample surface may be profiled, allowing a quantitative means of assessing probe–material interactions. A related technique is pulsed force mode (PFM) whereby the sample surface is mapped by modulating the z position of the probe as it is moved over the surface in a raster pattern, allowing identification of species via differences in their pull-off force (Grandy et al 2000). We describe the use of a novel modification of this principle whereby instead of using a standard tip for the measurements we use a thermally controlled probe, allowing us to measure the pull-off profile as a function of temperature on specific regions of a sample. A range of pharmaceutical materials was compressed into tablets and analysed using a TA Instruments 2990 Micro-Thermal Analyzer. A Witec PFM module and a silicon cantilever probe were used for PFM study. Temperature controlled FDC measurements were performed using a Wollaston wire probe, the temperature of which was controlled. FDC measurements revealed differences in the adhesion of materials at elevated temperatures. Low molecular weight drugs (ibuprofen, indometacin) showed an abrupt increase in pull-off forces at temperatures close to their melting points, while the pull-off forces of polymeric materials (PEG 20000, PEG 6000) were considerably lower. Paracetamol, however, showed an unusual increase in adhesion starting from 100°C, well below the melting point of the material (169°C). PFM of a paracetamol tablet revealed two distinctive regions in the 'adhesion' image; regions with higher adhesion are approx. 5–10 μm long and have sharp edges. These are surrounded by an effectively continuous region of lower adhesion. By examining topography images it was noted that lower adhesion regions appear to be granular, while higher adhesion regions appear to be smooth. It is suggested that the compression process has resulted in surface modification of paracetamol resulting in regions of variable adhesion. Possible explanations include a modification in polymorphic form, generation of amorphous material, external contamination of the surface or partial degradation of the surface and studies are ongoing to identify the mechanism involved. The study has demonstrated that controlled temperature pull-off force measurements represent an interesting method of interrogating surfaces. The data obtained has indicated that while many materials behave in a manner commensurate with their bulk thermal properties, this may not invariably be the case. Such unexpected changes in surface properties may be of considerable importance in terms of performance and processing properties. The results suggest that this novel method may be of considerable use in identifying and characterising such changes.

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Correlating drug–binder adhesive strengths measured using Inverse Gas Chromatography with tablet performance

F. Thielmann, D. Burnett[1], K. M. Lusvardi[2] and T. Durig[2]

Surface Measurement Systems, Ltd., London, UK, [1]Surface Measurement Systems, Ltd., Allentown, PA, and [2]Aqualon Division, Hercules Incorporated, Wilmington, DE, USA. E-mail: fthielmann@smsuk.co.uk

Powders often exhibit poor flow and compression behaviour. Granulation can be applied to improve these powder properties. In a wet-granulation process, certain excipients are added as binding agents for this purpose. Controlling the adhesive strength between binders and active drugs is paramount in developing successful pharmaceutical formulations. Poor drug–binder adhesion often leads to insufficient binder spreading and inferior granule and tablet mechanical properties. The goal of this study is to predict drug–binder interactions based on surface energy measurements of the individual formulation components and to correlate results with mechanical properties of the final product. The prediction of drug–binder interactions is based on the determination of the surface energy. The surface energy is directly related to the work of adhesion. It was shown in previous studies that the work of adhesion is a suitable parameter for the description of drug–binder interactions (adhesive strength) (Rowe 1989). The ratio of adhesion to cohesion gives additional information on the thermodynamic "compatibility" of drug and excipients. Surface energy determinations are typically carried out by wetting techniques such as contact angle measurements. However, those have a limited sensitivity and are difficult to perform on powders (Parsons et al 1993). For this reason Inverse Gas Chromatography (IGC) has been used in this study. Surface energies were measured for model drugs (acetaminophen (paracetamol) and ibuprofen) and common binding agents: hydroxypropylcellusoe (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methylcellulose (HPMC). The surface energy values were used to calculate the adhesive strengths for the various drug–binder combinations, which were subsequently compared with tablet strength data. Works of adhesion were calculated for each drug–binder pair from surface energies. For both drugs, the calculated adhesion strengths

with the three binding agents followed the trend of HPC > HPMC > PVP (Table 1). Also the drug–drug works of cohesion are listed in Table 1. As can be seen from Tables 2a and 2b, formulations with HPC show the highest tablet hardness and the lowest friability. This means there is a direct correlation between work of adhesion and tablet hardness and an inverse relationship with the friability. Similar trends were observed when the work of adhesion/cohesion ratio is considered: the higher the ratio the higher the tablet hardness and the lower the friability. Therefore, higher work of adhesion values (in relation to work of cohesion) lead to stronger tablets. IGC surface energy measurements can be used to predict adhesion strengths for different drug-binder systems. The higher the work of adhesion values in relation to the work of cohesion, the stronger the tablets. Adhesion and cohesion values proved to be a good measure for the tendency of particles from different materials to interact at their interfaces in comparison with their tendency of sticking together with a particle from the same material. This concept can also be applied in other areas where dry powder mixtures are of relevance, such as inhalation formulations.

Table 1 Work of adhesion and cohesion (drug–drug) as determined from surface energy measurements

Drug	W_{coh} (mJ m^{-2}) Drug–Drug	W_{adh} (mJ m^{-2})		
		HPC	HPMC	PVP
Ibuprofen	89.17	143.68	124.88	118.17
Acetaminophen	103.28	141.03	121.13	119.72

Table 2a Tablet hardness expressed as crushing force (kP)

Drug	HPC	HPMC	PVP
Ibuprofen	17.3	16.2	15.3
Acetaminophen	14.8	10.7	4.8

Table 2b Tablet friability (%)

Drug	HPC	HPMC	PVP
Ibuprofen	1.1	1.1	1.4
Acetaminophen	0.7	15.9	34.3

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Correlation of polymer energetics and drug release rates

F. Thielmann, D. Burnett[1] and S. Baumgartner[2]

Surface Measurement Systems Ltd., 5 Wharfside, Rosemount Road, London HA0 4PE, UK, [1]Surface Measurement Systems Ltd, 2222 South 12th Street, Suite D, Allentown, PA 18103, USA and [2]Faculty of Pharmacy, University of Ljubljana, Askerceva 7, Ljubljana, Slovenia. E-mail: fthielmann@smsuk.co.uk

Cellulose ether polymers are common matrix compounds in sustained release tablets. It was shown previously by Inverse Gas Chromatography (IGC) that drug release from polymer matrices with a high polarity was faster due to faster polymer swelling and chain relaxation (Baumgartner et al 2004). The goal of this study is to investigate polar and non-polar interactions of the polymers further, as well as the influence of drug, based on surface energy measurements of the individual formulation components and to correlate results with drug release profiles of the final product. IGC is a well-established technique for quickly and accurately measuring the surface energetics for a wide range of solids (Grimsey et al 2002). Dispersive surface energies have been measured by injecting a series of alkanes. Specific interactions were obtained from injections of acetone, acetonitrile, ethyl acetate and dichloromethane. Acid-base numbers have been calculated based on the Gutmann concept (Gutmann 1967). Polymers were hydroxypropyl (HPC), hydroxyethyl (HEC) and hydroxypropylmethyl (HPMC) cellulose. Pentoxifylline was taken as a model drug. The materials were packed into standard columns (0.3 cm i.d., 30 cm in length) and measured at 30°C under infinite dilution conditions. Tablets were prepared by direct compression of a 3:1 polymer–drug mixture. Release rates were determined by USP 26, App. I at 37°C. Results from IGC measurements suggest that HPMC has the highest dispersive surface energy for HPMC, followed by HPC and HEC. Acid-base numbers calculated from specific interactions show the strongest basicity for HEC, followed by HPMC and HPC. The acid numbers show the opposite trend. While the dispersive surface energies show no correlation with the drug release rate, the acid and base numbers show a linear relationship. The higher the basicity and lower the acidity, the faster the release (Table 1). This suggests that hydrophilic basic sites of the polymer are responsible for the interaction with the aqueous medium and that the drug–polymer interactions are less relevant for the release mechanism. Dispersive surface energies increase in the order HEC < HPC < HPMC. Basicity increases in the order of HPC < HPMC < HEC, while acidity decreases in the same order. The trend in the basicity correlates with an increasing drug release rate. This is due to a strong interaction of the highly polar sites on the surface of the polymer with the dissolution medium, water. The specific interactions of the drug pentoxifylline are rather low and do not contribute significantly to the overall release mechanism.

Table 1 Acid and base numbers of polymers and drug release rates (after 8 h)

Sample	Ka	Kb	Drug Release (%), 8 h
HEC	0.07	0.77	75.34
HPMC	0.12	0.68	65.8
HPC	0.18	0.51	54.41

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A viscometric study of the critical concentration of PVP solutions

C. Cararro and A. M. Crean[1]

Ecole Nationale Supérieure de Chimie, Clermont-Ferrand, France, and [1]School of Pharmacy, University College Cork, Ireland. E-mail: a.crean@ucc.ie

Drug-polymer solid dispersions have been formulated as amorphous molecular dispersions to enhance the solubility and hence bioavailability of poorly soluble drugs. Polyvinylpyrrolidone (PVP), due to its stabilising effects on amorphous molecular dispersions, is often the polymer of choice for these drug-polymer solid dispersions. PVP's stabilising effects have been attributed to both molecular mobility and intermolecular interactions (Matsumoto & Zografi 1999). Polymer solution bulk properties, such as viscosity, alter with changes in polymer concentration. Viscometry studies have been used to detect two polymer solution critical concentrations (i.e., critical overlapping concentration (c*) and critical concentration (c**)) (Dondos & Papanagopoulus 1995). c* refers to the concentration separating dilute from semi dilute polymer solutions. Above the c* value, polymer chains lose their individuality due to chain entanglement and viscosity deviates positively from linearity. c** refers to the concentration separating dilute from extremely dilute polymer solutions. At concentrations above the c** value, while polymer chains maintain their individuality in solution during dynamic viscosity measurements collisions between chains or peripheral entanglement may occur, resulting in an apparent reduction in polymer chain hydrodynamic volume. The objective of this study was to investigate whether the critical concentrations of PVP K17 ethanolic solutions can be quantified by viscometric measurements. Ethanolic PVP solutions were prepared at a concentration range of 2–120 mg mL^{-1}. Viscometric measurements were conducted using a U tube viscometer type BS/U size A. Temperature control was achieved by immersing the viscometer in a thermostated water bath (25 ± 0.01°C). Measurements were performed in triplicate. The reduced viscosity increased linearly as the PVP concentration increased between 10 and 120 mg mL^{-1}. The polymer – polymer interaction parameter, b_{ii}, of 0.59 was determined from this linear relationship using the classic Huggins equation. As the PVP concentration decreased below 10 mg mL^{-1}, an increase in the slope of the relationship between reduced viscosity and concentration was observed. Between 2 and 5 mg mL^{-1}, a second linear relationship was observed. The interaction parameter, b_{ii}, calculated for this concentration range was considerably higher, 7.64, indicating a considerable increase in polymer–polymer interaction. c** was determined from the crossover point of these linear relationships. 6.1 mg mL^{-1}was determined to be

the c** for this polymer solvent system under investigation using the viscometer setup described above. Having detected the c** value for PVP alone in ethanol, the second objective of this study was to investigate whether changes in c** can be detected for solutions containing PVP and a model drug, hydrocortisone, known to form amorphous molecular dispersions with PVP (Corrigan & Crean 2002). The data presented will include viscometry results for hydrocortisone PVP ethanolic solutions. A change in the c** value would indicate that intermolecular bonding between hydrocortisone and PVP may have sufficient impact on polymer–polymer interactions. The measurement of c** could therefore assist in elucidating the mechanism of amorphous molecular dispersion formation between drugs and polymers.

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Cellulose derivatives in shampoo formulations

E. S. Farboud and M. Kavousifard

Department of Pharmaceutics, College of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. E-mail: farbod@sina.tums.ac.ir

The original purpose of shampoo is to clean the hair by removing sebum and associated foreign debris. Shampoo products must be safe and non-irritant to the skin and eyes and should be pleasant and convenient to use. To achieve good properties, shampoo formulations should contain ingredients such as primary and secondary surfactants, thickener, perfume, preservative, sequestering agents and so on. In shampoo systems where alternative primary surfactants such as sulphosuccinates or sarcosinates are used, thickening with electrolytes is not successful. In these cases, thickening is normally achieved through the use of external thickeners such as cellulose derivatives. A synthetic detergent base, along with other chemical additives, was chosen as a shampoo formulation. Five different cellulose derivatives – sodium carboxy methyl cellulose (two grades), hydroxy propyl cellulose, hydroxy ethyl cellulose, methyl hydroxy propyl cellulose and two acrylic acid derivatives (Carbopol 1342 and Carbopol 2020) – were chosen as thickening agents in shampoo base and the effects of these thickeners were evaluated on detergency, foam volume, stability, viscosity, pH, surface tension, wetting, conditioning and safety. The results of these tests show that the higher apparent viscosity of thickener containing shampoo obtained using hydroxy ethyl cellulose improves the stability and enhances clarity of shampoo. All the shampoos showed similar foaming characteristics in distilled water as well as hard water. However, in the presence of soil, only the shampoo containing hydroxy ethyl cellulose and sodium carboxy methyl cellulose foamed well. The viscosity profile of shampoos showed pseudoplastic behaviour, which is a desirable attribute in a shampoo formulation. At a low rev min^{-1} these shampoos show high viscosity. On increasing the shear, the viscosity drops, which would allow spreading on the hair. The viscosity-decreasing capacities are related to temperature in all of the shampoos but cellulose derivatives are more related to temperature than acrylic acid derivatives, which is important in the formulation of bath preparations. Some of the results are shown in Table 1.

Table 1 Foam volume and viscosity of shampoos containing cellulose or acrylic acid derivatives as thickeners

Foam volume (mL) after 10 min	Viscosity (poise)			
	60°	40°	20°	
265	50	500	750	Cellulose derivatives
150	500	1250	1450	Acrylic acid derivatives

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An investigation into the behaviour of a fatty acid based formulation in buffer systems: the effect of varying the fatty acid (stearic acid and palmitic acid) ratio

S. Qi, D. Q. M. Craig, S. A. Barker and D. Deutsch[1]

School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich NR4 7TJ and [1]GlaxoWellcome Research and Development, Hertfordshire BR3 3BS, UK. E-mail: d.craig@uea.ac.uk

Stearic acid has been used in pharmaceutical manufacturing for decades. However, BP grade stearic acid contains a range of further fatty acids, including up to 50% w/w palmitic acid. The involvement of "foreign" saturated fatty acids could significantly alter the performance of a fatty acid based formulation. In this study, formulations (spray chilled microspheres) based on pure stearic acid, pure palmitic acid and mixed stearic and palmitic acids (50:50 % w/w and 30:70 % w/w) were prepared and their drug release behaviour in different buffer systems was investigated. It was noted that the fastest drug release appeared for the mixed stearic and palmitic acid formulations in alkaline media and a series of physico-chemical studies were undertaken to explore this phenomenon. DSC and XRPD were utilised for characterising the fatty acid microspheres before and after exposure to alkaline media. A phase diagram of binary mixtures of the two pure components was generated from the DSC profiles. An incongruent melting point of 56.6°C appeared in the 30:70 % w/w mixture of stearic acid and palmitic acid and a melting transition at 58.3°C for the 50:50 % w/w stearic acid and palmitic acid system. After exposure to alkaline media, the mixed fatty acid systems developed a second endothermic transition: at 66.4°C for the 50:50 % w/w system and at 70.1°C for the 30:70 % w/w system, respectively. The XRPD patterns of the mixed systems also showed an additional peak at 22.6° 2 and a series of new peaks under 18° 2 after exposure to alkaline media. The appearances of these peaks were much weaker in the single fatty acid systems than in the mixed systems. In our previous studies, we have shown that these physical and chemical changes correspond to the formation of fatty acid-soaps (Qi et al 2005). To better understand why the mixed fatty acid systems showed stronger interactions with the alkaline media than the single fatty acid systems, the behaviour of fatty acid molecules on a molecular level at the interface of air/alkaline media were investigated using surface pressure-area isotherm measurements. From these studies, it was noted that under a constant surface pressure ($30\,mN\,m^{-1}$) the surface area per molecule of the mixed systems decreased as a function of time. One possible explanation of this observation is chain mismatching of the mixed monolayer of the stearic and palmitic acids. This disruption in the molecular packing leads to lower intermolecular interaction and lower the film stability compared with chain length compatible monolayers. This may also be responsible for the lowered melting point of the mixed fatty acid systems and cause a decrease in their pK_a values. The lowered pK_a values of the mixed systems could be close to the pH value of the media used in this study and increase the likelihood of formation of fatty acid-soaps. In conclusion, it is thought that the formation of fatty acid soaps may be responsible for the observed behaviour of mixed fatty acid microspheres and the difference in behaviour between "pure" and mixed systems.

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An investigation into the recrystallisation behaviour of amorphous paracetamol

S. Qi and D. Q. M. Craig

School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich NR4 7TJ, UK. E-mail: d.craig@uea.ac.uk

Paracetamol is known to exist in three polymorphic forms, including the stable monoclinic form I that has poor tabletting properties, the orthorhombic form II that has improved compressibility and form III that has low physical stability. However, the characterization of the amorphous form paracetamol has not been fully addressed due to the difficulties during sample preparation caused by its thermal instability. The speed of the recrystallization of amorphous paracetamol may be as fast as a few minutes, depending on the storage conditions (Martino et al 2000). Nevertheless, this amorphous drug potentially provides a useful model material by which to study the polymorphic forms generated from the amorphous state, an issue about which little is known. The glassy forms of paracetamol were prepared by slow cooling (cooled at 1, 2, 5, 10 and $20°C\,min^{-1}$) and quench cooling (cooled in liquid nitrogen) of molten paracetamol. The resultant glassy samples were studied using differential scanning calorimetry (DSC) and modulated temperature differential scanning calorimetry (MTDSC). Their recrystallization behaviour during the reheating was investigated using hot-stage microscopy (HSM). The glassy paracetamol produced by slow cooling processes exhibited a glass transition temperature (T_g) around 23°C, two exothermic transitions at 80–85°C and 120–130°C, and a melting transition at 158°C, which matched the reported melting point of paracetamol form II. The relative enthalpy of the exothermic transition at 120–130°C could be significantly increased by using pinhole pans as opposed to hermetic pans. We propose that this transition is related to the polymorphic transformations between metstable forms. The T_g of the quench cooled paracetamol was around 28°C followed by a single exothermic transition. An endothermic transition at 170°C is due to the melting behaviour of paracetamol form I. This indicated that the single exothermic peak between 60–65°C is the recrystallization of monoclinic form I from the amorphous form. Ageing

studies on the quench cooled paracetamol showed that low temperature storage (20–50°C below the T_g) can postpone the complete recrystallization of the amorphous form for up to 2 weeks (studies ongoing). The recrystallization behaviour of the amorphous paracetamol prepared by different methods (in the temperature ranges of 50–70°C, 80–90°C and 90–140°C) were studied using HSM (polarised light mode). Differing nucleation, crystal growth and fusion habits were observed corresponding to the transitions between the amorphous and metastable polymorphs of paracetamol. These transitions can also be presented in terms of light density plotted against temperature from the microscopy images. The study has demonstrated that different thermal histories may have a profound effect on the polymorphic form generated from the amorphous state. The investigation has also demonstrated the utility of using HSM and thermal scanning methods in conjunction to study this issue.

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Application of real time characterisation techniques during Zydis product development

D. Wong, J. Prince, G. Ball, G. Wilson, D. Hassey, R. McLaughlin, I. Haley[1] and C. Edwards[1]

Cardinal Health, Frankland Road, Blagrove, Swindon, Wiltshire SN5 8RU and and [1]Mettler-Toledo Auto Chem, 64 Boston Road, Beaumount Leys, Leicester LE4 1AW, UK. E-mail: Desmond.Wong@cardinal.com

The Zydis dosage form is a fast dispersing tablet designed to disintegrate in less than 10 s and thus dissolves instantly to release the drug when placed on the tongue. The Zydis process involves dispersing the active pharmaceutical ingredient (API) in an aqueous solution of gelatin and mannitol, which is then dispensed into preformed blister pockets. The dispensed aqueous "dispersion" is then frozen and freeze-dried to form a light porous freeze-dried tablet. The API may be dispersed as a suspension or solution and held within the aqueous phase for several hours. Therefore, the ability to monitor API uniformity and potential for morphological changes on line is a significant advantage. Real time particle characterisation is one of several PAT tools being evaluated by Cardinal Health for Zydis product development. This abstract summarised a study on the use of real time analysis to monitor morphological changes, crystal growth, suspension homogeneity and impact of processing conditions, potential physical interactions of excipients and API, for a Zydis "dispersion". For this work, three model Zydis "dispersions" were evaluated using two PAT tools, namely Focus Beam Reflectance Measurement (FBRM) and the Particle Vision and Measurement (PVM) systems. In Example 1, the FBRM tracked the change in the crystal habit of a model drug "A" known to undergo pseudo-polymorphic transformation on prolonged suspension hold and or with an increase in suspension temperature. The data indicated that the particles of the original polymorph dissolved and then transformed into the new pseudo-polymorphic form with new habits. These observations were confirmed by off line microscopy. In Example 2, FBRM and PVM were used to monitor the uniformity of the dispersion and the physical interactions of the API and excipients. The FBRM tracked the particle size and number during the preparation of Zydis suspensions for a model compound "B" with a range of excipients typically used in Zydis formulations. The FBRM was able to quantify the changes to the particle size and particle number as each ingredient was added. The effects of addition of excipients, even in relatively small quantities (e.g. oily flavour, colour pigments, surfactant) were detected. The dispersion and de-aggregation of API particles to reach a stable suspension were also successful detected. The PVM captured images of the dispersion on line, showing clearly the physical interactions of the excipients with each other and with the API. In Example 3, the FBRM tracked the changes that took place as a result of different solid loading of model drug "C", the influence of process conditions on particle dispersion, and stability of the homogenised model suspension while held in an Intermediate Storage Vessel (ISV). In summary, the above examples demonstrated the usefulness of FBRM and PVM in product development by providing real time data for Zydis "dispersion" on events such as changes in crystal growth and habits, physical interactions between the formulation ingredients and the influence on processing conditions on the stability and uniformity of the dispersion.

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Gastro-retentive dosage forms: the characterisation of floating calcium alginate beads

F. Stops, J. T. Fell, J. H. Collett and L. G.Martini[1]

School of Pharmacy and Pharmaceutical Sciences, The University of Manchester, Oxford Road, Manchester M13 9PL and [1]GlaxoSmithKline Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK. E-mail: john.fell@manchester.ac.uk

Gastro-retentive dosage forms have the potential to improve drug bioavailability compared with that from many commercially available immediate release and modified release products. A dosage form, based on freeze-dried calcium alginate beads has been developed and shown to have prolonged gastro-retention in the fed state. The aims of this work were to obtain information regarding the structure, floating ability and changes that occur when the dosage form is placed in aqueous media. Calcium alginate beads were prepared by extruding sodium alginate solution 2% w/w into calcium chloride 0.02 M solution. The precipitated gelled calcium alginate beads were freeze-dried. The formula was modified so that calcium alginate beads containing a model drug, riboflavin, were produced. The characterisation of the calcium alginate beads was divided into five main categories: physical parameters, floating ability, imaging, and release rate of riboflavin from the calcium alginate beads. The weight and diameter of the calcium alginate beads were assessed. The floating ability of the calcium alginate beads was assessed using the resultant weight technique (Timmermans & Moës 1990). The technique considers vertical and gravitational forces exerted by the dosage form, hence providing a quantitative measure of floating ability. The internal and external morphology of the calcium alginate beads was viewed using SEM. Digital photography studied the effect of the aqueous environment on dried calcium alginate beads. Confocal laser scanning microscopy measured the diffusion rate and movement of riboflavin from the calcium alginate beads when the beads were placed in aqueous media. X-ray microanalysis was used to determine the presence of phosphorous and the distribution of riboflavin-5′-phosphate within dried calcium alginate beads. The weight and diameter of the calcium alginate beads varied according to formulation. Calcium alginate beads containing riboflavin were 16.3% larger in diameter, and had a mass 3.2% greater, than placebo calcium alginate beads. The resultant weight technique demonstrated that the calcium alginate beads floated for a time in excess of 12 h, regardless of formulation. SEM showed all calcium alginate beads to be spherical and consist of air filled cavities that enabled floatation. X-ray microanalysis showed the presence of calcium and chlorine, which was expected. The X-ray microanalysis data plot of calcium alginate beads containing riboflavin-5′-phosphate did not show the presence of phosphorus. Only a small part of the riboflavin-5′-phosphate molecule is phosphorous. The absence of phosphorous in the X-ray microanalysis results may be due to insufficient amounts of phosphorous in the calcium alginate bead. Therefore, distribution of riboflavin-5′-phosphate within the calcium alginate beads was not observed. Confocal laser scanning microscopy showed that the movement of riboflavin throughout the bead and rate of riboflavin release from the calcium alginate beads occurred rapidly, (diffusion coefficient $24.70 \times 10^8\ cm^2\ s^{-1}$). Therefore, the drug would not remain in the dosage form long enough to demonstrate prolonged gastro-retention without further formula modifications. Digital photography showed that when calcium alginate beads were placed in aqueous media, air filled cavities remained. The development of a gel barrier, that slows the ingress of the dissolution medium, was also observed. Drug release may therefore occur by erosion and diffusion. The characterisation of calcium alginate beads of different formulations has resulted in obtaining an understanding of the properties of the floating dosage form. The characteristics of the calcium alginate beads make them suitable for further investigation as modified release gastro-retentive dosage form.

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An investigation into the physical properties of a wet granulated formulation at different stages of production

J. P. Pick-Katolik, A.-P. Siamidi and F. Podczeck

Institute of Pharmacy, Chemistry & Biomedical Sciences, University of Sunderland, Chester Road Campus, Sunderland SR1 3SD, UK.
E-mail: jan.pick-katolik@sunderland.ac.uk

The prediction of the properties of granules made by wet granulation is one objective the pharmaceutical industry currently works towards, to optimise products and manufacturing processes and ultimately minimise development times. The aim of this research was to study the physical