Poster Session 2 – Pharmaceutics

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Effect of weak acid solubility on the internal pH and release of a weakly basic drug from pellets

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Weakly basic drugs such as papaverine are soluble in the acidic environment of the stomach but significantly less soluble in the relatively alkaline intestines. To facilitate sustained release they are often formulated with a weak acid modifier to decrease the microenvironmental pH within the dosage form and allow drug dissolution. Cope *et al* (2002) have quantified the pH within the microenvironment of pellets using confocal laser scanning microscopy (CLSM). This method has been used in this study to measure the pH within pellets during dissolution to explore the relationship between weak acid solubility and drug release.

Six acid modifiers were selected with similar particle sizes but different solubilites. Pellets containing 15% w/w papaverine hydrochloride, 15% w/w acid, 20% w/w lactose and 50% w/w microcrystalline cellulose were prepared by extrusion/spheronisation using a 0.036 mM solution of Rhodol Green in water as the binding liquid. Pellets were coated with a 5% w/w Surelease coat. Dissolution was carried out using USP apparatus I at 100 rev min^{-1} in 900 mL of simulated intestinal fluid with 0.1% sodium lauryl sulphate. pH was measured by CLSM using a modified version of the Cope *et al* method (Sutch *et al* 2002).

Dissolution curves were biphasic, with a rapid initial drug release rate followed by a slower second release phase for all acids except fumaric, the least soluble. Dissolution outcome indicators such as Area Under the Curve showed that release of papaverine was related to the solubility of the acid chosen (R^2 = 0.9589, $P < 0.001$).

During dissolution confocal fluorescent imaging showed that in all cases the microenvironment within the pellets initially stayed acidic (pH 3–4) before rising (pH >5.5), presumably as the acid dissolved out. The duration of the microenvironmental pH change was directly related to the acid solubility, with fumaric acid producing the most extended acid environment (227 min below pH 5.5). The time to inflection in the biphasic dissolution curves was also related to acid solubility (R^2 = 0.8828, $P < 0.05$).

During the initial 15min of dissolution CLSM imaging showed that the microenvironment was acidic in all pellet formulations. A strong correlation (R^2 = 0.9793, $P < 0.001$) between percentage of drug released over this timescale and solubility of the weak acid modifier was also seen. Therefore the observed changes in dissolution are not simply due to the production and maintenance of an acid microenvironment. The less soluble acids excipients may hinder the percolation of dissolved papaverine from the pellets, retarding drug release.

Cope, S., *et al.* (2002) *Pharm. Res.* **19**: 1554–1563

Sutch, J., *et al.* (2002) *Variability in the ratiometric determination of pH using confocal laser scanning microscopy, dependant on hydration in microcrystalline cellulose /lactose pellets*. 8th UKICRS Conference, Loughborough, UK

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Ingredient solubility as a predictor of water content for production of pellets by extrusion/spheronisation

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Previous studies have shown the influence of the ingredients' solubility on the amount of water required to produce successful pellets by extrusion/spheronisation. Lustig-Gustafsson *et al* (1999) showed that the amount of water was related to the natural logarithm of the solubility of their model drugs in simple ternary mixtures (drug, microcrystalline cellulose (MCC) and water). In this study we have looked at more complex mixtures, which are more likely to be used in practice, to investigate if the overall solubility holds to a similar relationship.

Pellets were produced by mixing, extrusion, spheronisation, drying and sieving, in which all parameters were kept constant. All formulations contained 50% w/w MCC. The other 50% was made up of fine-grade lactose (solubility 216 g L^{-1}) and a weak acid in various proportions. The acids with their water solubilities are shown in Table 1. The acids were crushed and sieved to produce a similar particle size. The water content was varied over a range to find the optimum water content (OWC) in terms of roundness as determined by digital imaging and the shape factor of Podczeck *et al* (1999).

Formulations containing 25% w/w lactose and 25% w/w acid showed a linear relationship between OWC and natural logarithm of the acid solubility (R^2 = 0.9822, $p < 0.001$, n = 5) (Table 1).

Table 1 Optimum water content for 25% acid 25% lactose pellets

Acid	Solubility (g L^{-1})	OWC (% dry weight)
Fumaric	6.3	57
Adipic	14.4	55
Succinic	45.5	50
Malic	558	45
Citric	643	44

Mixtures containing 10:40 and 40:10 acid-to-lactose were prepared using fumaric, malic and succinic acids. A plot of OWC versus average solubility for all formulations showed a similar trend in terms of solubility but a reduced correlation (R^2 = 0.6714, $P < 0.01$, n = 11). These results suggest that additional properties of the ingredients are influencing their ability to form acceptable pellets.

By multiplying the contributing fraction of the acid and lactose by the average particle size (mean feret diameter) a stronger correlation is produced (R = 0.8181, $P < 0.001$, n = 11) suggesting the particle size as well as the solubility is an important factor although this requires further investigation.

Lustig-Gustafsson, C., *et al.* (1999) *Eur. J Pharm. Sci.* **8**: 147–152

Podczeck, F., *et al.* (1999) *Int. J. Pharm.* **192**: 123–138

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Mapping the pH within the gel layer of a hydrating HPMC matrix tablet

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Cope *et al* (2002) have measured the microenvironmental pH within pellets using dual wavelength fluorescence ratiometry in a confocal laser scanning microscope (CLSM) and derived an equation to calculate pH over the range 3–5.5. In this study we have explored the application of this method to measure the pH within the swelling gel layer of HPMC tablets containing weak acid modifiers.

Tablets (5 mm) contained: 49% w/w HPMC K4M, 1% w/w magnesium stearate, 25% w/w papaverine, a weakly basic drug, and 25% w/w lactose, fumaric or succinic acid. The solubility of papaverine is ten times greater below pH 4 than above pH 5. The tablets were held between two clear Perspex discs to allow tablet imaging from above. In this geometry only lateral swell of the gel layer was possible. The tablets were then hydrated in 5 μM Rhodol Green in simulated intestinal fluid (SIF) and allowed to hydrate. At various time points the tablets were removed from the solution and imaged by a digital imaging system, which provided a macroscopic view of the tablet and then by CLSM to measure pH as in the Cope method. By both imaging methods the gel layer could be seen to expand with time and the tablet core shrink.

A fluorescence concentration gradient from the outside to the inside of the gel layer could be seen. However, as the pH determination method is ratiometric and allows for varying concentrations of fluorophore, the pH could be determined across the

gel layer, despite the presence of this gradient. With this method the spatial pH across the expanding gel layer could be measured and differences in tablets with and without weak acids determined.
The pH within the gel layer of tablets containing no acid remained alkaline (pH > 5.5), except near the tablet core where an acid pH (3–4) was measured. This may be due to the presence of a saturated papaverine solution. The tablets containing acid developed a low pH throughout the gel layer, which would be responsible for the increased solubility of papaverine. Drug release rates from these tablets in SIF was in the rank order succinic > fumaric > no acid.
This method proved capable of quantifying pH from the tablet core to the outer extremities of the gel layer. A pixel-by-pixel comparison of the fluorescent intensity at the two wavelengths was made to produce a visual representation of pH in the gel layer. The spatial distribution of inclusions, which do not take up the fluorophore (e.g. insoluble material and small air bubbles), which nonetheless are important contributors to the structure of the gel layer, are outlined on these images.

Cope, S. *et al.* (2002) *Pharm. Res.* **19**: 1554–1563

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Dissolution study of paracetamol crystallised in the presence of polyvinylpyrrolidone (PVP)

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Many methods have been used to enhance dissolution rates of poorly water-soluble drugs. The methods include, for example, micronization, formation of water-soluble salts of compounds, solid dispersions and spherical crystallization. Chiou *et al* (1976) introduced a unique method to enhance the dissolution rate of poorly water-soluble drugs. The basic method simply involved the crystallisation of drug in the presence of surfactants or hydrophilic polymers. In our previous studies (Garekani *et al* 2000a, b) it was shown that the crystallization of paracetamol in the presence of PVP improved its compaction properties. The aim of this study was to investigate the dissolution properties of paracetamol crystallised in the presence of different grades of PVP.
Crystallization was carried out by adding a solution of paracetamol (5 g/12 mL) in hot ethanol to 50 mL water at 3°C containing 0, 0.1, 0.3 or 0.5% w/v PVP of molecular weights of 2000, 10 000 or 50 000. After 15 min, the precipitated crystals were collected by filtration. The dissolution profiles and the aqueous solubility of obtained crystals were determined. The amount of PVP present in the paracetamol crystals was measured by photometric analysis of PVP-iodine complex. The contact angle between water droplet and paracetamol surface was measured using Padday equation ($\cos\theta = 1 - Bh^2$). Particle size of crystals was determined using scanning electron micrographs.
Crystallization of paracetamol in the presence of PVP caused a marked enhancement in its dissolution rate. With increasing the molecular weight or the concentration of PVP in crystallization medium, the obtained crystals exhibited faster dissolution profiles. The percentage of paracetamol dissolved within the first two minutes of dissolution test was increased from 13.4% for untreated paracetamol to 79.2% for paracetamol crystallised in the presence of 0.5% PVP 50 000. Differential scanning calorimetry and X-ray powder diffraction experiments showed that paracetamol particles crystallised in the presence of PVP did not undergo structural modifications. The enhancement of dissolution was attributed to adsorption of PVP onto the surfaces of paracetamol crystals, which increased their wettability. This was confirmed by measuring the contact angle which decreased from 62.8° for untreated paracetamol to 0° for paracetamol crystallised in presence of 0.5% PVP 10 000 or 50 000. Decrease in crystal size of paracetamol obtained in presence of PVP was another reason for the higher dissolution rate. There were no significant differences between the solubility of untreated paracetamol and samples crystallized in the presence of PVP. It was shown that the solubility of untreated paracetamol in the solution containing PVP increased. However, the amount of PVP in the paracetamol particles crystallised in presence of PVP was far below that required to produce a considerable concentration in dissolution medium to increase the solubility of paracetamol.

Chiou, W. L., Chen, S. J., Athanikar, N. (1976) *J. Pharm. Sci.* **65**: 1702–1704
Garekani, H. A., *et al.* (2000a) *Int. J. Pharm*, **208**: 87–99
Garekani, H. A., *et al.* (2000b) *Int. J. Pharm.* **208**: 101–110

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Solid dispersion of Eudragit RS and propranolol hydrochloride: effect of particle size, compaction pressure and plasticizer addition on drug release

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Particle size of polymer, the compaction pressure and presence of insoluble or soluble additives are among factors affecting drug release from inert matrices (Dabbagh *et al* 1996). It has been shown that the use of solid dispersion (SD) systems is valuable in production of inert matrices (Pignatello *et al* 2001; Sadeghi *et al* 2003). However, the effect of factors mentioned above has not been thoroughly investigated on drug release from these systems. The objectives of this study were to investigate the effect of particle size, compaction pressure and plasticizer addition on the release of drug from Eudragit RS matrices prepared by SD technique.
To prepare SD systems, weighed amounts of drug and polymer (1:3 ratio) dissolved separately in ethanol. Drug solution was added to polymer solution and mixed. The resulting solution was oven dried at 50°C. The dried thin films were ground and the size fractions of 300–350, 250–300, 125–250, 90–125 and < 90 μm were collected. Flat faced tablets equivalent to 80 mg drug were compressed at 10 kN compaction force. To investigate the effect of compaction force, size fraction of 125–250 μm was compressed at 5, 10, 20 or 30 kN. To prepare SD systems containing plasticizer the required amount of each plasticizer (5% or 10% with respect to polymer weight) namely diethylphtalate (DEP) or thriethylcitrate (TEC) was added to polymer solution and the above procedure was repeated. The size fraction of 125–250 μm was compressed at 10 kN compaction force. The crushing strengths and dissolution profiles of the matrices were determined.
The results showed that drug release was slowed down upon reduction of particle size from 300–350 to 125–250 μm. However, further reduction of particle size did not profoundly affect drug release. The crushing strengths of matrices prepared from different size fractions of SD system (from large to small fraction) were 5.1 ± 0.6, 7.9 ± 0.5, 11 ± 0.5, 8.1 ± 0.7 and 7.5 ± 0.7 kg, respectively. While the 300–350 μm and 125–250 μm size fractions produced the softest and the hardest tablets respectively, there were no significant differences between the crushing strengths of 250–300 and 90–125 or < 90 μm size fractions. The crushing strengths of matrices prepared at compaction forces of 5, 10, 20 or 30 kN were 2.9 ± 0.2, 11 ± 0.5, 12.4 ± 0.8 and 13.6 ± 0.6 kg, respectively. There were significant differences between crushing strengths of matrices prepared at 5 kN compaction force with those compacted at higher forces while crushing strengths of matrices compacted at higher forces were not significantly different. Matrices compacted at 5 kN showed rapid release profile however the release profiles for matrices prepared at other compaction forces were super imposable. Incorporation of 5% plasticizer did not affect the crushing strengths and also release profiles while 10% plasticizer addition retarded drug release and helped tablets to retain their shape throughout the dissolution testing.

Dabbagh, M. A., *et al.* (1996) *Int. J. Pharm.* **140**: 85–95
Pignattello, R., *et al.* (2001) *Int. J. Pharm.* **218**: 27–42
Sadeghi, F., *et al.* (2003) *S.T.P. Pharma Sci.* **13**: 105–110

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Estimation of critical relative humidity of water (%cRH) for amorphous indomethacin using isothermal microcalorimetry

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It is necessary to understand the physical instability of the amorphous form of substances, due to the tendency for such materials to crystallize into the more stable crystalline form. Among the factors influencing the conversion of amorphous to crystalline form, are temperature and humidity. It is known that molecular mobility increases considerably at the glass transition temperature (Tg), which accelerates the transition to the crystalline state. In this study we are proposing that isothermal microcalorimetry can be used to reveal the %cRH, which could be equivalent to the point where Tg is reduced to the experimental temperature (T°C). Isothermal microcalorimetry (TAM) coupled with an RH perfusion unit fitted with mass flow controllers (Thermometric, Sweden) was used for this purpose.

Amorphous indomethacin was obtained by quenching and was used as a model substance; around 30–40 mg was placed in the steel ampoule of the perfusion unit. Relative humidity (% RH) of the chamber of the steel ampoule was ramped using the mass flow controllers at the rate of 3% RH per hour from 0–95% RH. The resultant heat flow was recorded, with a water bath temperature of 25°C. Mass changes in the sorption process accompanying the RH ramp were measured using DVS (SMS, UK) using the same ramp rate and temperature.

The thermogram obtained by ramping the humidity from 0–95% RH showed a sharp exothermic peak with an onset at ca. 70% RH. The mass change due to sorption obtained using DVS showed increased rate of water vapour uptake at around same % RH. This sharp exothermic deflection could be due to rapid uptake of water vapours as supported by the DVS results, however, the TAM responses showed a sharp rise and fall (a complete peak) superimposed on the gradual rise in exothermic response. This peak would not be expected if the sample were simply absorbing water, which would give rise to a gradual exothermic response. Consequently, the TAM is revealing a physical transition in the sample at ca 70% RH which is not evident from the gravimetric sorption data. The response seen in the TAM at ca. 70% RH is not a crystallisation event, as an equal and opposite response was obtained when sorbing and desorbing at 85% RH, implying that the recorded event is reversible, where as it is known that crystallization is an irreversible event. The absence of crystallization for the time scale of the study is also supported by lack of crystallization for amorphous indomethacin at 68% RH and 30°C for 20 days (Andronis *et al* 1997).

It can be concluded that the %cRH for amorphous indomethacin can be obtained using isothermal microcalorimetry, which reveals an event other than an increased rate of water sorption, and as such has a clear advantage over gravimetric technique. It is expected that the response is related to relaxation of the sample (or a portion of the sample) as Tg is lowered to T, which can be expected to relate to the stability of the amorphous form.

Andronis, V., *et al.* (1997) *J. Pharm. Sci.* **86**: 346–351

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The release of diclofenac sodium from tableted pellets coated with Aquacoat® plasticised with 30% w/w Myvacet or Surelease E-7-7050

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Tableting of polymer-coated pellets can cause rupturing of the polymer coat (Altaf *et al* 1998). Cushioning excipients are used to cushion against these affects (Bodmeier, 1997). However, the polymer coat itself needs to be flexible and ductile enough to withstand compaction. Addition of plasticiser increases film flexibility and ductility. The aim of this study was to examine drug release from compressed pellets coated with Aquacoat plasticised with 30% w/w Myvacet or Surelease E-7-7050 (aqueous system containing 15% w/w dibutyl sebacate as plasticiser). Diclofenac sodium (DN) was the model drug.

Pellets (1–1.7 mm) manufactured by extrusion-spheronisation, contained 86.7% Avicel PH-101 (FMC), 5% Polyvinylpyrrolidone (K90, BASF) and 8.3% DN B.P. Pellets were coated with Aquacoat (FMC) containing 30% w/w Myvacet (Honeywill & Stein), plasticiser mixed for 18 h, or Surelease E-7-7050 (Colorcon). Pellets were coated at a film coating level of 25% w/w theoretical weight gain and were mixed 60:40 with 97% Avicel PH-102 (FMC), 2% Explotab (Penwest) and 1% magnesium stearate (BDH). These were then compressed at 10 or 30 kN using a Manesty single punch tablet machine with 7 mm flat faced punches. The release of DN (7.5 mg) from uncompressed and compressed pellets (n = 5 for each coating and at each compaction force) was measured using British Pharmacopoeia Method I (B.P. 1998) in water at 37°C; baskets were rotated at 100 rev min^{-1}.

Table 1 Effect of compaction on the % release of DN from Aquacoat or Surelease coated pellets at 1, 6 and 12 h

Film coat type	Force (kN)	1 h	6 h	12 h
Aquacoat	0	1	16	52
	10	24	53	85
	30	27	65	100
Surelease	0	2	6	13
	10	33	100	100
	30	72	100	100

Results indicated that uncompressed Surelease-coated pellets release DN slower than uncompressed plasticised Aquacoat-coated pellets. However, when compressed at either of the compaction forces the Surelease-coated pellets released DN faster than compressed, plasticised Aquacoat-coated pellets. This faster release of DN from compressed Surelease-coated pellets, may be effectively related to rupturing, observed by Electron Microscopy, of the Surelease coat with lower levels of plasticiser. The Aquacoat coat plasticised with 30% w/w Myvacet was sufficiently flexible and ductile to withstand the compaction process especially at 10 kN. It has been shown polymer coated pellets may retain control of release following compaction. Further optimisation of plasticiser in aqueous dispersions should additionally increase the flexibility and ductility of films they produce especially during compaction.

Altaf, A. A., Hoag, S. W., Ayres, J. W. (1998) *Drug. Dev. Ind. Pharm.* **24**: 737–746

Bodmeier, R. (1997) *Eur. J. Pharm. Biopharm.* **43**: 1–8

British Pharmacopoeia (1998) London: Her Majesty's Stationary Office. 1, Appendix XII D

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The rheological and drug release characteristics of novel HEC gel networks

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Cellulose ether derivatives have been extensively used in the pharmaceutical industry to produce topical drug delivery vehicles with suitable mechanical and rheological characteristics (e.g. ease of removal from a container, ability to withstand shearing stresses experienced in-vivo) (Banerjee *et al* 2001). Although the rheological properties of cellulose derivatives have been previously reported (Van Santvliet *et al* 1999), there is a notable lack of investigations describing the physical properties of hydroxyethylcellulose (HEC). More interestingly, there have been no reports describing the correlation between the rheological, mechanical and drug release properties of HEC and the significance of polymer interactions on the structure, drug release properties and ultimately, clinical efficacy.

HEC gels were prepared by dissolving the required mass of HEC in phosphate buffer saline (PBS) with the aid of mechanical stirring. Dynamic and continuous shear rheology was performed on a Carri-Med CSL^2-100 rheometer, as previously reported (Jones *et al* 2000). In-vitro drug release studies were performed using a Caleva 7ST dissolution apparatus in conjunction with paddle stirrers (25 ± 2 mm from the surface of the gel, 50 rev min^{-1}). Gel formulations (5 g) were placed in dissolution tanks containing 1 L of PBS with samples being removed at pre-defined intervals. The concentration of metronidazole was determined using ultraviolet spectroscopy (λ_{max} = 320 nm). The effects of polymer concentration, metronidazole concentration and oscillatory frequency on the drug release and rheological properties of HEC gel networks were statistically investigated using analysis of variance with an associated post-hoc test (Tukey's HSD). $P < 0.05$ denoted significance.

Table 1 The effect of metronidazole addition on the storage (G') and loss moduli (G") of formulations containing 10% w/w HEC

Met concn (% w/w)	G' (Pa)	G" (Pa)
0	7375.00 ± 186.90	2088.47 ± 37.21
0.5	5815.67 ± 417.21	1465.12 ± 114.08
1.0	5764.07 ± 267.75	1321.42 ± 71.99
2.0	6992.38 ± 312.64	1785.23 ± 72.33

Each value is the average ± s.d of five replicates

The storage modulus (G'), loss modulus (G") and dynamic viscosity (η') of all gels were significantly increased as the oscillatory frequency increased whereas tan δ decreased. These responses were in accordance with the Maxwell model for viscoelastic materials. Furthermore increases in the HEC concentration resulted in a significant shift in the rheological response of the gels. HEC (3% w/w) exhibited fluid-gel transition behaviour whereas HEC (5, 7 and 10% w/w) were characterized by gel behaviour; effects that were ascribed to increased entanglements. The addition of 0.5% metronidazole significantly decreased G', G" and η', whereas further addition (1.0%) had no effect. Partial recovery of the structure was observed at 2% (Table 1). These effects were attributed to the interaction of metronidazole and HEC, which was dependent on the physical state of the drug. When solubilised (0.5%), metronidazole hydrogen bonded to polymer chains significantly disrupting polymer/polymer interactions. At 2% the presence of solubilised and suspended drug had destructive and constructive effects, respectively, the overall effect governed by the HEC concentration. Decreased release rates of metronidazole were observed as HEC concentration increased, for example, HEC 3% released 88.02 ± 1.24% whereas 10% w/w HEC released 37.02 ± 0.35% of total drug loading (2% w/w). HEC (3%) systems were subject to a large degree of erosion, whereas HEC (5–10%) had release exponents indicative of anomalous release mechanisms. In conclusion this study may aid in the development of novel HEC based drug delivery platforms but more importantly provides a description of the rheological and drug release properties of previously unreported systems.

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Jones, D., *et al*. (2000) *J. Controlled Release* **67**: 357–368
Van Santvliet, L., *et al*. (1999) *J. Pharm. Sci.* **9**: 99–105

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Thermal behaviour of ethyl cellulose above the glass transition temperature

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The thermal behaviour of ethyl cellulose, a commonly used hydrophobic polymer that is used for the manufacture of controlled release dosage forms, has been reasonably well studied, particularly in terms of its glass transition temperature (Tg). However, the behaviour above Tg is less well understood. It has been suggested that ethyl cellulose undergoes oxidative degradation at temperatures above 150°C (Dubernet *et al* 1990; Guyot & Fawaz 1998). In contrast, Brown & Tipper (1978) suggested that the polymer undergoes pyrolysis by a radical-induced chain scission mechanism at temperatures between 268°C and 320°C. Our preliminary studies have indicated that the thermal profile is highly dependent on the experimental conditions used, hence the aim of the present study is to investigate the nature of the > Tg behaviour using differential scanning calorimetry (DSC), modulated temperature differential scanning calorimetry (MTDSC) and thermogravimetric analysis (TGA), in particular identifying the influence of experimental conditions on the observed profile.

DSC was performed using sealed and pin-holed aluminum pans. The samples were run at a rate of 2°C, 5°C and 10°C min^{-1}, from 20°C to 250°C and subsequently quenched back to 60°C from 230°C and heated again to 250°C. MTDSC was performed for both sealed and pin-holed pan at 2°C min^{-1} with a modulation of ± 0.212°C over 40 s. TGA was performed using 10 mg of sample in open aluminium pans.

The DSC results showed that the glass transition temperature of ethyl cellulose was between 120°C and 130°C, depending on the ramp rate. We also noted a thermal event at circa 175°C that Dubernet *et al* (1990) ascribed to exothermic oxidative degradation when the samples were run in sealed pans. In contrast to their findings, however, an endothermic peak immediately after the exothermic peak was observed, suggesting that two processes may be occurring simultaneously. The endothermic peak was found to be repeatable on cycling, strongly suggesting that this event is not due to degradation. We also noted that the exothermic peak was not found in pin-holed pans under a nitrogen atmosphere, suggesting that the exotherm is due to oxidation but that the endotherm is an independent event. MTDSC studies indicated that the exothermic peak was non-reversing (i.e., was kinetically constrained). The reversing heat flow showed that the heat capacity of ethyl cellulose varied considerably with temperature, probably explaining the difficulty in obtaining a good baseline for this material. TGA was performed under both nitrogen and air. The data demonstrated that weight loss occurred at a lower temperature if the samples were run under air. We conclude that there is a previously unreported transition that occurs over the same range as the oxidative degradation. Given the reversible nature of this transition, it is logical to suggest that it is a reflection of the fundamental physical structure of the ethyl cellulose sample.

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Dubernet, C., *et al*. (1990) *Int. J. Pharm.* **64**: 99–107
Guyot, M., Fawaz, F. (1998) *Int. J. Pharm.* **175**: 61–74

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Preparation, characterisation and evaluation of pH-responsive prednisolone microparticles

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Effective drug targeting to site-specific regions of the gastrointestinal tract is a focus of current research with the aims of reducing drug dosage, increasing therapeutic response and minimising systemic side effects. Recently the colon has been acknowledged as an increasingly important site for drug delivery for the treatment of local diseases and delivery of peptides and proteins (Basit 2000).

Due to their small size pH-responsive microparticles may offer several advantages over conventional enteric-coated systems. Gastric residence time should be reduced resulting in a faster and more reproducible onset of drug action, particles should spread out over the length of the intestine reducing irritation and giving a more reproducible drug release profile, particle dissolution and drug release should be rapid once the pH threshold is reached.

Three acrylic polymers have been used in this study for their ability to target different regions of the gastrointestinal tract. Eudragit L100-55 dissolves at pH

> 5.5 and can be used for duodenal targeting, Eudragit L100 dissolves at pH > 6 and is therefore able to release drug in the jejunum/ileum and Eudragit S100 will dissolve at pH > 6.8 and has been used for targeting the ileum/colonic region.
Prednisolone was chosen as a model drug as it is used to treat acute exacerbations of asthma and inflammatory bowel diseases. The chosen method of micro-encapsulation was the emulsification-solvent evaporation technique, adapted from Lorenzo-Lamosa *et al* (1997). Briefly, 3 g of polymer and 0.4 g of prednisolone were dissolved in 20 mL acetone/10mL ethanol and the resulting solution was emulsified into 200 mL liquid paraffin containing 1% Span 85. Solvent evaporation was completed overnight and particles were filtered through sintered glass, washed 3 times with 50-mL portions of *n*-hexane and dried under vacuum. Particles were characterised by scanning electron microscopy. Prednisolone encapsulation efficiency was calculated by dissolving 50 mg samples in phosphate buffer. Drug release studies were performed using Apparatus II of the British Pharmacopoeia 2001 at gastric and intestinal pH.
L100-55 particles had excellent morphology being spherical, non-porous and in the size range 100–200 µm. L100 and S100 microparticles of size 50–100 µm had similar surface characteristics but tended to exist as large aggregates. Prednisolone encapsulation efficiency was approximately 100% for all polymers. All particles exhibited pH-responsive release in-vitro. L100-55 particles released 5% of drug after 2 h in acid and approximately 100% of drug after 15 min in pH 6.8 buffer. Eudragit L100 particles behaved similarly. S100 particles released approximately 0% in acid, 15% after 6 h at pH 6.8 and 100% after 3 h at pH 7.4. The slower than expected release of S100 particles is possibly due to the particle aggregates.
In conclusion, L100-55 particles have acceptable size, morphology and pH-responsive release characteristics. The morphology of L/S100 particles may be improved by careful manipulation of disperse phase solvent or surfactant.

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Development RGD peptide-anchored liposomes for tumour targeting

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Many molecules specifically expressed by tumour endothelium cells have been proposed as target molecules for tumour vasculature targeting. The αvβ3 integrin has been identified as a target molecule on angiogenic endothelium. It can interact with various RGD (Arg-Gly-Asp) sequence containing extracellular matrix components. Peptides containing this RGD sequence inhibit angiogenesis by inducing apoptosis in endothelial cells in tumour and inflammatory sites. RGD peptides are being widely exploited to deliver cytotoxic molecules to the tumour endothelium (Schraa *et al* 2002). Ligand targeting using small peptides offers advantages over the use of large protein molecules such as antibodies that include ease of preparation, potentially lower antigenicity, and increased stability (Forssen & Willis 1998). It was therefore envisaged that RGD peptide anchored liposomes could be designed and guided towards the tumour vasculature expressing avidly αvβ3 integrins with high affinity for RGD containing peptide, which could selectively and preferentially present chemotherapeutic agent at the tumour site. The present study was aimed at developing 5-fluorouracil (5-FU) loaded and RGD peptide, cRGDFV (cyclo(Arg-Gly-Asp-D-Phy-Val)) anchored liposomes for their selective and preferential presentation at tumour site and assessing their targetabilty.
Liposomes were prepared by reverse phase evaporation method using egg yolk PC, cholesterol and phosphatidylethanolamine (7:3:0.7 molar ratio). The emulsions were extruded through polycarbonate membrane of 0.2-µm pore size using Nucleopore filtration cell to obtain more homogenous liposome population. Entrapment efficiency, size and stability were determined and preparation with highest entrapment efficiency vis-à-vis good stability was anchored with cyclic peptide, cRGDFV. Process variables like lipid:cholesterol ratio and incubation time were optimized. In-vitro drug release rates were determined for different formulations. The stability of the preparations was determined at different storage temperatures. The cyclic peptide anchored liposome bearing 5-FU was administered intravenously to BALB/c mice bearing B16F10 tumour implanted subcutaneously at $10\,mg\,kg^{-1}$. The tumour volume and growth delay of the tumour were taken as parameters to assess the antitumour efficacy. Experimental and spontaneous lung metastases assays were performed to ascertain the antimetastatic effects of the formulations.
The average size of unilamellar liposomes prepared was 210 ± 5 nm. Entrapment efficiency of the 5-fluorouracil was found to be $9 \pm 1\%$. cRGDFV anchored liposomes bearing 5-FU were found to be appreciably stable. Administration of the cRGDFV anchored liposomes bearing 5-FU resulted in effective suppression of tumour growth and more than 2-fold prolongation of survival times compared to plain liposome bearing 5-FU and free drug. Results indicate that cRGDFV anchored liposomes bearing 5-FU are significantly ($P < 0.01$) more active against primary tumour and metastasis than the conventional liposomes formulation and free drug. Thus RGD peptide anchored liposomes prove their worth as an ideal carrier for cancer treatment.

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Characterisation of freeze-dried and solvent cast drug delivery systems

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Freeze-dried wafers and solvent cast films of sodium carboxymethylcellulose (CMC) and sodium alginate (ALG) hold promise as drug delivery systems capable of adhering to moist surfaces. In this study the mechanical and dissolution properties of CMC and ALG formulations for delivery of paracetamol were investigated.
Wafers and films were prepared by freeze-drying or drying in an oven (45°C, 6% RH), aqueous solutions of CMC (2 g/100 mL) (Blanose 7H4X, Hercules, UK) and ALG (1–5 g/100 mL) (Protanal LF 10/60, FMC Biopolymer, UK).
The mechanical properties of the wafers were determined using a Texture Analyser TAXT2I (Stable Microsystems, UK) by compressing to depths of 0.2–3 mm with a stainless steel probe. The effects of speed, depth of compression and polymer content on the resistance of the wafers to compression and relaxation were investigated.
Dissolution studies were performed in a diffusion cell (Thapa *et al* 1999) at 37°C, in which the formulation was just wetted on the underside by distilled water in the receptor compartment. At given intervals, 5 mL of solution was sampled, replaced with fresh distilled water and drug release measured by UV spectroscopy at 242 nm.
The resistance of the wafers to compressive forces increased with depth of compression and polymer content. Higher depths of compression resulted in a greater resistance and after compression a lower recovery of original shape (Table 1) as a result of reduction in porosity when compressed to greater penetration depths and more intimate contact of the polymer chains.

Table 1 Effect of compression depth on resistance and recovery of ALG wafers (2% w/w solution, 0.2 mm s^{-1})

a		b	a − b
Depth of compression (mm)	Resistance to compression (N)	Relaxation distance (mm)	Compaction index (mm)
0.20	1.85 (0.27)	0.19 (0.01)	0.01 (0.01)
0.40	3.82 (0.24)	0.36 (0.01)	0.04 (0.01)
0.80	9.95 (0.01)	0.61 (0.01)	0.19 (0.01)
1.00	17.06 (2.11)	0.71 (0.01)	0.29 (0.01)
2.00	30.44 (0.15)	1.05 (0.07)	0.95 (0.07)
3.00	41.62 (0.05)	1.08 (0.01)	1.91 (0.01)

Means (s.d.)

During dissolution experiments both the wafers and films absorbed water from the receptor compartment forming a thick swollen gel from which the drug diffused. The t_{50} values for wafers containing 0.25, 0.5, 1.0, 1.5, 2.0 and 2.5 mg paracetamol were 88, 70, 96, 75, 69 and 70 min, respectively, and those for the films were 120, 110, 130, 104, 92 and 104 min. The wafers showed a higher rate of release because their porous nature provided more channels for drug diffusion than the more dense films.

The study showed that the resistance to compression of the wafers was directly proportional to their polymer content. The drug loading did not have significant effect on the release profile and the amount of polymer present appears to be the main controlling factor.

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The use of micro-thermal analysis for the detection of compression-induced recrystallisation of amorphous indomethacin

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The use of amorphous drugs and excipients has attracted considerable recent interest, particularly in terms of the favourable dissolution profile shown by glassy active ingredients due to the absence of a requirement to overcome a lattice energy barrier. However, comparatively little is known with regard to the effects that processing may induce in such metastable materials. Indeed, while it is known that, for example, compression into tablets may alter polymorphic forms or indeed induce the formation of amorphous material from the crystalline state, very little is known with regard to the effect of compression on amorphous drugs. In this investigation we describe the novel use of micro-thermal analysis, used in conjunction with modulated temperature DSC, as means by which the effect of compression on an amorphous model drug (indomethacin) may be monitored.

Amorphous samples were prepared by heating indomethacin above its melting point (160°C), then transferring the molten material to an aluminium heat sink held at ambient temperature, allowing rapid cooling and formation of the amorphous phase, followed by gentle milling of the resultant glassy material. DSC experiments confirmed that the material was still in the amorphous state. The powder product was then compressed using a Specac 13 mm die in a 25 ton ring press for 180 s. Modulated Temperature DSC experiments were performed using a TA Instruments Q1000 DSC operating in T4P modulated mode, which compensates for the pan masses and the thermal characteristics of the DSC cell used by the use of a third thermocouple. The instrument was calibrated for cell constant with indium, heat capacity with sapphire and temperature with n-decane, indium and tin. Experiments were performed at 2°C min^{-1} from 0 to 200°C with an applied modulation of ± 0.212°C over 40 s. Nitrogen was used as the purge gas at a constant flow rate of 30 mL min^{-1}. Local thermal analysis experiments were performed using a TA Instruments μTA 2990 Micro-Thermal Analyzer, calibrated for temperature using nylon-6. The programmed temperature was ramped from –50 to 300°C at 10°C s^{-1}.

The amorphous material showed a single deflection at circa 70°C, indicative of > Tg softening of the material, with MTDSC studies showing the glass transition, the softening (seen in the phase angle) and recrystallisation peaks, followed by melting. The difference between the two sets of data are due to much faster heating rates used for the micro-TA that prevent recrystallisation occurring within the timeframe of the experiment. The samples compressed at 2 and 4 tons show an initial sensor deflection at circa 70°C, characteristic of amorphous material, followed by a further more marked negative deflection at 164°C, characteristic of crystalline material (Royall *et al* 2002). The corresponding MTDSC data also showed that both crystalline and amorphous material are present in the samples, indicating that the compression process is converting the glassy drug back to the crystalline state. However, these studies also indicated that the polymorphic form to which the amorphous indomethacin reconverted was also dependent on the compression force used. Overall, the study has shown that compression of amorphous materials may result in their recrystallisation and that micro-TA represents a novel and potentially highly useful means of detecting such conversions.

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In-line high-pressure particle size reduction of poorly soluble drugs to enhance oral bio-availability of drugs delivered by freeze dried fast dispersing dosage form (Zydis)

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Many drugs are poorly water-soluble and as a consequence are slowly or poorly absorbed from the gut. Particle size reduction is a well known technique used to improve the dissolution rate and bio-availability of such drugs. However, size reduction methods available are either unable to reduce the mean particle size to the nano-size range (jet milling) or are prohibitively expensive or complex (super critical fluid particle design). Many of these methods also have the disadvantage that the process requires the size reduction to be carried out as a separate processing step, often away from the main site of manufacture. In some cases this may require the addition of potentially undesirable stabilising excipients to prevent the aggregation of the drug particles following size reduction. Such stabilising excipients may be incompatible with the active ingredient or with other required excipients.

It has been found that the unique manufacturing process used to prepare the Zydis freeze dried fast dispersing dosage form is particularly well suited to particle size reduction to the nano-size range using an in line high-pressure homogeniser. The Zydis manufacturing process routinely includes a suspension processing stage during which the high-pressure homogenisation can be incorporated. Also, the Zydis base formulation contains a structure forming excipient which prevents the aggregation of the size reduced particles by a process of Steric Stabilisation.

Table 1 shows that a period of re-circulation of a non-steroidal anti-inflammatory drug suspension through a microfluidiser, during the wet stage of the Zydis process, has allowed for the mean particle size (Dv,0.5) be reduced to within the nano-particulate size range (< 1 μm).

Table 1 Effect of microfluidiser re-circulation time and pressure on the particle size of a non-steroidal anti-inflammatory drug

Sample Point	Microfluidiser re-circulation time and Pressure	Mean particle size[a] (μm)
Initial	None	10.83
A	5 min at 30 psi	8.70
B	A+ 5 min at 50 psi	4.39
C	B + 15 min at 70 psi	1.25
D	C + 15 min at 75 psi	0.93
E	D + 15 min at 80 psi	0.80
F	E + 5 min at 85 psi	0.78

[a] D(v,0.5) measured using laser light scattering (Malvern Mastersizer S)

This process has had no adverse effect on the ease of processing or on the finished product quality. Dissolution testing of Zydis tablets containing a sedative drug that has been size reduced by this method, has shown a substantial increase in the rate of dissolution compared with the non-size reduced control formulation. Indeed after 5 min of dissolution testing the formulation containing the size reduced sedative drug (mean = 1.45 μm) released 75% into solution compared with only 24% from the non size reduced formulation (mean = 12.95 μm).

It is anticipated that product produced in this manner could improve the variable or poor absorption observed with many drugs that exhibit dissolution rate limited absorption.