emulsions of various molecular weights. Liposomal formulations of TTO had large particle sizes (>10 μm), which is believed to result from the formation of a visible precipitate within the formulation. TLC analysis of the precipitate indicated that it was an amalgam of several TTO components, in addition to phosphatidylcholine and cholesterol. Whereas the trigger for precipitation is unclear, it may result from the differential solubility of individual TTO components within both the bulk aqueous medium and organic solvent (chloroform) used during the preparation of liposomes. Percentage encapsulation of PVA (EE%) for liposomal TTO-PVA emulsions indicated that 1.0% w/v $PVA_{30–70kDa}$-TTO emulsion showed the highest PVA EE% of 78.5%, compared with all other concentrations and molecular weights of liposome-encapsulated polymer.

Conclusions In conclusion, a stable, low-viscosity delivery vehicle of PVA-emulsified TTO which can be encapsulated into liposomes has been developed. These chimaeric delivery systems may be able to provide prolonged and sustained release of anti-microbial natural products for treatment of a variety of bacterial, fungal and viral infections.

Takeuchi, H. et al (1998) *Int. J. Pharm.* **164**: 103–111

Material Science

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An investigation into the thermal behaviour of different grades of hydroxypropyl methylcellulose for the preparation of amorphous dispersions by spray-drying

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Objectives Paracetamol is known to form a low-stability amorphous phase (Sheng et al 2008) hence there is considerable potential benefit in developing means by which such drugs, with a low glass transition temperature (T_g), may be stabilized. The dispersion of drugs in hydrophilic polymers with a relatively high T_g is a practical approach to enhancing both the dissolution rate and stability of amorphous drugs (Bruno and George 1997). In this study, hydroxypropyl methylcellulose (HPMC) was chosen as the model polymer and five grades of such polymer – HPMC A, B, C, D and E – were explored for the variation in their thermal behaviour as a means of stabilizing amorphous paracetamol within a spray-dried solid disperse system.

Methods Each grade of HPMC raw material and their corresponding spray-dried products were characterized for T_g and moisture content, using modulated-temperature differential scanning calorimetry (MTDSC) and thermogravimetric analysis (TGA), respectively. Dispersions with a paracetamol/HPMC ratio of 1:1 (w/w) were prepared by spray-drying and characterized afterwards in comparison with equivalent physical mixtures via thermal techniques and X-ray powder diffraction (XRPD). All spray-drying processes in this study were performed with the same inlet temperature of 110°C and a pump rate of approximately 5 mL/minute.

Results It was found that water contents of HPMC A and B were dramatically increased after spray-drying while those of HPMC C, D and E were all decreased. Curves obtained by TGA demonstrated that all spray-dried HPMC products had a lower water-loss temperature than their corresponding raw materials, which is in good agreement with DSC findings. In terms of raw materials, HPMC B failed to show a marked T_g. However, a glass transition at 149.9, 159.9 and 158.8°C, each with an enthalpic relaxation in the non-reversing heat flow, was obtained for HPMC C, D and E. A comparatively higher T_g at 187.1°C without relaxation was shown for the HPMC A raw material. Further studies on the drug-loaded systems showed a melting response for paracetamol for all samples. However, a paracetamol recrystallization peak at 66.7°C was found exclusively for systems containing HPMC C. In addition, the XRPD patterns produced by this sample showed partially amorphous character.

Conclusions Different grades of HPMC have different thermal behaviours due to the changes in polymer molecular weight, substitution type, viscosity, T_g, moisture content, etc., resulting in the variation in stabilizing effects on drugs within solid dispersions. In particular, all findings in this study are indications that HPMC C is a promising polymer for inhibiting the crystallization of paracetamol within solid dispersions.

Bruno, C. H., George, Z. (1997) *J. Pharm. Sci.* **86**: 1–12
Sheng, Q. et al (2008) *Eur. J. Pharm. Biopharm.* in press

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The stability of biodegradable polyesters and polyester-co-lactones utilized for drug delivery

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Objectives Although it is desirable for biodegradable biomaterials to degrade after administration, depending on how they are stored such materials are also prone to degrade prior to use. The aim of this study was to investigate the stability of a library of biodegradable polymers under various environmental conditions to establish optimal storage conditions and provide an estimation of shelf life. This information will contribute to existing studies on these polymers, which have recently shown promise for drug-delivery applications (Kallinteri et al 2005).

Methods Polymers were synthesized by a combination of enzyme-catalysed condensation and ring-opening polymerization of divinyl adipate with either glycerol or butanediol and with and without pentadecalactone. All materials were characterized by nuclear resonance spectroscopy, infrared spectroscopy and gel-permeation chromatography (GPC) (Gaskell et al 2008). Poly(glycerol adipate) (PGA), poly(glycerol adipate-co-pentadecalactone) (PGA-co-PDL), poly(butanediol adipate) (PBA) and poly(butanediol adipate-co-pentadecalactone) (PBA-co-PDL) were used to investigate the effect of temperature (4, 25 and 40°C) and humidity (0, 25 and 75% relative humidity) on the polymer structure over a 6 month period according to published guidelines (Mathews 1999). Samples of polymer were removed at 20 day intervals for 3 months and then after 6 months of storage, and compositional and physical changes of the polymers were monitored by GPC and infrared spectroscopy.

Results Polymer degradation was observed to increase with temperature. At 4°C there was less than a 5% decrease in molecular weight over 6 months compared with up to a 50% decrease at 40°C. Similarly, at all temperatures, polymer degradation was observed to accelerate with increasing humidity. However, this was much more noticeable at 25 and 40°C. Under the same environmental conditions, low-molecular-weight polymers degraded more quickly than those with a higher molecular weight and, for a comparable molecular weight, those in a solid form degraded less than liquid polymers. PBA and PBA-co-PDL demonstrated longer estimated shelf lives at both 4 and 25°C than PGA and PGA-co-PDL. This is probably due to the presence of hydroxyl groups on the polymer backbone, which increase the hydrophilic character of these polymers. This leads to an increase in degradation by hydrolysis compared with those without backbone hydroxyl groups.

Conclusions These results indicate that increasing temperature and/or humidity increases polymer degradation, suggesting that the degradation of these polymers occurs by random chain scissions induced by thermolysis and hydrolysis of labile ester bonds. Hence, to minimize degradation, storage at 4°C, preferably under a dry atmosphere, is advised. Minimization of degradation is crucial, both when evaluating these polymers for potential and in actual use in drug-delivery applications. Further studies will determine how the presence of chemical moieties conjugated to the polymer backbone via the free hydroxyl groups affects degradation of both the backbone and conjugate ester bonds.

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Mathews, B. R. (1999) *Drug Dev. Ind. Pharm.* **25**: 831–856

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The study of the effect of photodegradation products on the phase transitions in crystalline and amorphous nifedipine using differential scanning calorimetry

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Objectives To study the use of differential scanning calorimetry (DSC) to analyse the influence of photodegradation products on the phase changes in nifedipine. In addition, to investigate the effect of the UV irradiation on solid–solid phase transitions. The study was conducted by comparing various exothermic and endothermic processes (glass transition, solid–solid transition, crystallization and melting) of crystalline and UV-irradiated nifedipine.

Methods DSC experiments were carried out using a Mettler Toledo DSC823^e with a sample size in the range of 6–8 mg. All experiments were analysed in the temperature range 10–210°C and performed using sealed pans and following thermal cycles: heating/cooling/reheating at 5, 10, 20 and 40° min^{-1}. An irradiated sample was prepared by exposing a thin bed of nifedipine to UV irradiation in a UV chamber Spectroline CC80 for 114 hours.

Table 1 DSC results showing onset temperatures for the observed processes in the untreated and the irradiated nifedipine samples at different heating rates (SDs in parentheses, n = 3)

Heating rate (°C/minute)	First heating		Second heating			
	Endo (°C)	Endo (°C)	*T*g relax (°C)	Exo (°C)	Exo (°C)	Endo (°C)
Untreated sample						
5	–	173.4 (0.1)	45.4 (0.1)	96.2 (0.4)	114.5 (0.5)	171.9 (0.1)
10	–	173.0 (0.1)	44.8 (0.1)	100.1 (0.1)	115.2 (1.4)	171.4 (0.6)
20	–	173.1 (0.5)	48.2 (0.1)	109.1 (1.0)	133.1 (1.4)	172.0 (0.4)
40	–	173.1 (0.2)	50.3 (0.1)	119.1 (0.2)	131.9 (0.6)	171.1 (0.3)
Irradiated sample						
5	70.8 (0.2)	159.2 (0.1)	37.5 (0.1)	–	112.5 (0.2)	154.7 (0.1)
10	69.8 (0.2)	155.3 (0.4)	38.5 (0.5)	–	120.4 (1.4)	156.9 (0.7)
20	70.9 (0.5)	157.2 (0.2)	40.4 (0.2)	–	124.0 (2.2)	160.0 (1.5)
40	73.3 (0.5)	155.6 (0.1)	40.6 (0.6)	–	–	162.1 (0.1)

Endo, endothermic; Exo, exothermic.

Results A summary of the results obtained in this study is presented in Table 1. Experimental results for nifedipine untreated sample are in alignment with the previously published values (Keymolen et al 2003, Groof et al 2007). The first endothermic peak, which appears in all irradiated samples at around 70°C, is due to melting of the nitroso degradation product. The melting point of the irradiated sample is lower than for the untreated sample, which is due to the conversion of Form I to Form II during the irradiation of nifedipine. Finally, on second heating the glass transition temperature (T_g) in the irradiated sample is lower than the one observed for the untreated sample. In addition, the solid–solid (Form II to Form I) phase transition is missing and the melting process is at a significantly lower temperature than the irradiated sample, which is due to the melting of the unstable Form II.

Conclusions Results presented here show how DSC can be used to study the influence of degradation products on the phase transitions in amorphous nifedipine generated from irradiated samples. Furthermore, this study revealed that degradation products inhibit some phase-transition processes and lower the T_g and melting point in nifedipine. In addition, irradiation is responsible for the conversion of the more stable crystalline form into the less stable one (Form I to Form II). Further work involving liquid chromatography-mass spectrometry and X-ray diffraction is required to fully characterize and link the influence of particular degradation products with phase-transition processes.

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Pharmaceutical Technology

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Improvement of dissolution profile of gliclazide through co-inclusion in urea

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Objectives The present work aimed to exploit urea co-inclusion compounds to improve the dissolution profile of gliclazide (GLC). GLC, a second-generation sulphonyl urea, is characterized by poor aqueous solubility and, hence, by a low dissolution rate in water. This also causes inter-individual variation in its bioavailability. Hence, increasing the solubility of GLC – a Biopharmaceutical Classification System (BSC) class II drug – in aqueous media is of pharmaceutical interest for obvious reasons.

Methods Urea is a well-known adductor for linear compounds and GLC, a highly substituted cyclic organic compound, is not known to form an adduct with urea under any known conditions. Hence, a modified technique employing the use of a rapidly adductible endocyte (RAE) (Thakral and Madan, 2008) was successfully employed for inclusion of GLC in urea. Formation of urea inclusion compounds was confirmed by Fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC) and X-ray diffraction. The minimum amount of RAE required for adduction of GLC in urea was estimated by modified Zimmerschied calorimetric method (Zimmerschied et al 1950, Madan 1994). Urea-GLC-RAE inclusion compounds containing varying proportions of guests were prepared and their thermal behaviour studied by DSC. The inclusion compounds were analysed for content uniformity. Drug as well as its urea co-inclusion compounds was subjected to dissolution studies in phosphate buffer, pH 7.4.

Results The minimum amount of RAE required for adduction of GLC in urea was found to be 0.988 grams per gram of drug. Thermal analysis of various urea-GLC-RAE inclusion compounds revealed that, as the proportion of GLC in inclusion compound increases, the stability of the resulting inclusion compound decreases. Whereas the pure drug demonstrated a dissolution efficiency of approximately 0.26 after 60 minutes of dissolution, its urea co-inclusion compounds exhibited rapid and instantaneous release of included drug upon addition of contents to dissolution medium. However, this immediate drug release in the dissolution medium was followed by a subsequent fall in the amount of drug contents in solution. As GLC is known to have limited water solubility, the initially released drug molecules subsequently tend to crystallize out of the dissolution medium in excess of its solubility, owing to non-sink conditions prevailing in the dissolution medium. Since GLC is a lipophilic moiety and is known to permeate rapidly through biological barriers, a concentration build-up at the actual site of dissolution may not actually be achieved *in vivo*. Thus complete dissolution followed by rapid permeation of the drug may be expected *in vivo*.

Conclusions The inclusion compounds were found to exhibit high content uniformity and improved dissolution profile as demonstrated by increased dissolution efficiency for GLC dissolution. Hence, urea co-inclusion compounds can be exploited in the development of improved pharmaceutical formulations of low-dose drugs.

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Development and characterization of carvedilol-loaded solid lipid nanoparticles

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Objectives Carvedilol is an anti-hypertensive drug with poor oral bioavailability ranging from 25 to 35% due to the first-pass metabolism. Therefore, the aim of this study was to improve the oral bioavailability and to avoid high first-pass metabolism of carvedilol by making carvedilol-loaded solid lipid nanoparticles.

Methods Carvedilol-loaded solid lipid nanoparticles (SLNs) were prepared by dispersing a warm oil-in-water (o/w) microemulsion in cold water. For this purpose, stearic acid was heated to 70°C to melt completely. Carvedilol was dissolved in molten stearic acid. A warm-water solution of sodium taurocholate, poloxamer and ethanol was then added to obtain an optically transparent system. Then the hot microemulsion was immediately dispersed in cold water (2–3°C), under mechanical stirring, to get SLNs at a 1:15 microemulsion/water (v/v) ratio. The SLN dispersion was washed twice with filtered water by 0.45 μm diaultrafiltration with a TCF2 system (Amicon, Danvers, MA, USA) using a Diaflo YM 100 membrane (cut off 100000 Da) to take out the majority of the co-surfactant in microemulsion. A portion of the washed dispersion was freeze-dried to obtain dry products for the quantitative estimation. SLN were characterized for particle size, shape, entrapment efficiency and crystallinity of the lipid and drug. *In vitro* release studies were performed in phosphate buffer, pH 6.8, using a Franz diffusion cell.

Results A differential scanning calorimetry (DSC) thermogram of the lyophilized drug-loaded SLNs did not show the melting peak of crystalline carvedilol around 119.9°C, indicating the presence of carvedilol in SLNs in an amorphous state. The method used for preparing SLNs – the microemulsion method – may be responsible for conversion of the drug from crystalline to amorphous form as the rapid quenching of the microemulsion does not allow the drug to crystallize. X-ray diffraction patterns were in good agreement with the results established by DSC measurements. It was clear that in the drug-free and drug-loaded SLNs the less-ordered crystals were in a majority, thereby providing more space for drug loading. From the X-ray pattern there was other information that clearly showed that the state of the model drug carvedilol changed from crystalline to amorphous when incorporated into SLNs. Transmission electron micrographs revealed that the particles had a diameter of less than 200 nm and that the surface was smooth. Entrapment efficiency was found to be 68–72%. Drug release was found to be 72% in 48 hours.