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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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.

Conclusions Microemulsion technique is suitable for producing SLNs of 60–200 nm. Lipophilic drugs like carvedilol can be successfully loaded in stearic acid. DSC and X-ray diffraction analysis showed the amorphous state of carvedilol in SLNs. *In vitro* release of carvedilol followed Higuchi equations better than first-order equations. This system is most suitable for exploiting the lymphatic transport pathway in improving the oral bioavailability of carvedilol.

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The effects of drug solubility parameter and concentration on the rheological properties and adhesive performance of drug-in-adhesive transdermal patches

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Objectives To study the effects of drug solubility parameter and concentration on the rheological properties and adhesive performance of acrylic pressure-sensitive adhesive (PSA) transdermal patches.

Methods Drug-in-adhesive patches were made by incorporating model drugs into acrylic PSA (DuroTak 87–900A, National Starch and Chemical, NJ, USA) transdermal patches. The six model drugs employed, together with their total solubility parameters (δ), calculated according to the Hoftyzer and Van Krevelen method (Van Krevelen 1990), were lidocaine hydrochloride monohydrate (δ = 19.3), amitriptyline hydrochloride (δ = 20.4), sumatriptan succinate (δ = 22.1), diclofenac sodium (δ = 23.8), nicotinic acid (δ = 25.7) and thiamine hydrochloride (δ = 30.8). Three levels of drug loading were used, namely 5, 10 and 20% w/w. Placebo patches containing no drug were also prepared for testing. After coating on to a polyester foil, all test preparations were dried at 40°C for 2 hours. A Bohlin Gemini 200 Advanced Rheometer (Malvern Instruments, UK) was used for all rheological testing. An amplitude sweep was first carried out to determine the linear viscoelastic region of each material under test. Rheological behaviour (in terms of elastic modulus, G' and loss modulus, G'') was then characterized via frequency sweeps at 32°C (ω decreasing from 100 to 0.1 rad/seconds). The adhesive performance of each patch was then evaluated. The rheological criteria for acceptable PSA tack and peel properties have previously been established (Chu 1991). Specifically, for good tack and peel performance, Chu identified $G'_{100}/G'_{0.1}$ (G'(at ω = 100 rad/seconds)/G'(at ω = 0.1 rad/seconds)) ratios of approximately 5–300, together with $G'_{0.1}$ values (G' at ω = 0.1 rad/seconds) of approximately 2×10^4–4×10^4 Pa. One-way analysis of variance tests with Scheffe *post-hoc* analysis were performed (using SPSS version 15) for elastic (G') and loss modulus (G'') at 0.1 and 100 rad/seconds with a significance level $\alpha = 0.05$ and sample number n = 3.

Results The drugs within each transdermal patch were found to be present in suspension form, implying that no drug was completely soluble in the adhesive. $G'_{100}/G'_{0.1}$ ratios ranged from 10.9 to 26.6 (placebo = 11.7). $G'_{0.1}$ values ranged from 1.6×10^4 to 3.7×10^4 Pa (placebo = 1.84×10^4 Pa). No patch showed a significant deviation from the Chu criteria. For drug-loaded adhesives, $G'_{0.1}$ values tended to increase with increasing drug concentration.

Conclusions The acrylic polymer employed proved to be a versatile PSA in accommodating drugs with differing solubility parameters and concentrations when compared with the placebo. All patches exhibited adequate pressure-sensitive adhesive properties in terms of the Chu criteria. Hence, changes in drug solubility parameter and concentration did not significantly affect their adhesive performance. These findings will be of interest to the pharmaceutical industry specializing in transdermal patches and, in particular, to the manufacturers of drug-in-adhesive transdermal patches.

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Novel application of hydrotropic solubilization to formulate syrup (liquid oral solution) of water-insoluble drug

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Objectives The term hydrotropy has been used to designate the increase in aqueous solubility of various poorly water-soluble compounds due to the presence of a large amount of additives. In the present investigation, the poorly water-soluble drug gatifloxacin was selected as a model drug for formulating its liquid oral solution (syrup) with the help of urea, as a model hydrotropic agent. Urea is almost non-toxic. The use of hydrotropy was explored in developing the syrup of gatifloxacin to give a quick onset of action and better bioavailability in comparison with a suspension.

Methods The solubility of gatifloxacin in 10 M urea solution (a hydrotropic solution) at room temperature was 8.183% (the solubility in distilled water was found to be only 0.728%). To develop a model syrup (solution) formulation of gatifloxacin, 2% w/v gatifloxacin (for 200 mg/10 mL), 48% w/v urea, 20% w/v sucrose and 2% w/v sodium benzoate (preservative) were used. The pH of this syrup was found to be 8.72. Syrup was colourless. The drug content of gatifloxacin syrup was determined spectrophotometrically at 333 nm. The prepared syrup was subjected to various physical and chemical stability studies.

Results Freeze-thaw cycle testing revealed that there was no precipitation and no turbidity in syrup after seven alternating cycles at 4 and 40°C. The residual drug contents after 6 months at room temperature and at 40°C and 75% relative humidity (RH) were 98.54 and 93.01%, respectively. The residual drug content after 1 month at 55°C was found to be 95.52%. The syrup turned deep yellow during the second month at 55°C and was discarded; further studies at 55°C were discontinued. The possible production of ammonia at the higher temperature of 55°C might have destabilized the syrup during the second month. Although gatifloxacin syrup was found to be quite stable at room temperature and at 40°C/75% RH, its stability can be further improved by use of appropriate formulation additives and by use of optimum pH.

Conclusion Like gatifloxacin syrup made by use of urea (a hydrotropic agent) there is good scope for other poorly water-soluble drugs to be developed as syrups (in solution form) by use of suitable hydrotropic agents. Solutions have better bioavailability than corresponding oral suspensions. Therefore, if chemical stability remains unaffected, it is better to develop solutions than suspensions. Also, solution-type dosage forms are more physically stable than suspensions. Suspensions also have their own problems, like cake formation and crystal growth. The proposed techniques would be economical, convenient and safe. The developed formulations would be definitely cheaper than marketed formulations, which employ costly additives/excipients. Further, the proposed hydrotropic agent is known to be safe; hence toxicities and safety-related issues will not raise concern, suggesting suitability and feasibility for large-scale industrial manufacture.

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Application of fluidized hot-melt granulation as a novel granulation technique for processing poorly water-soluble active pharmaceutical ingredients

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Objectives The purpose of this work was to determine the feasibility of fluidized hot-melt granulation (FHMG) as a novel process for the granulation of commonly used pharmaceutical powders and to investigate the potential application of FHMG to enhance the dissolution property of poorly water-soluble active pharmaceutical ingredients (APIs).

Methods A low-melting point copolymer of polyoxyethylene-polyoxypropylene (Lutrol® F68 Poloxamer 188) was used as the hydrophilic polymer carrier for a model poorly water-soluble API (mefenamic acid). Hot-melt method was used to produce the solid dispersions at various drug loadings and the solubility of drug in polymer matrix was investigated by different techniques. The drug–polymer solid dispersions were then used as meltable binders for the FHMG process. Granules produced by FHMG were pressed into tablets and tablet properties, such as uniformity of drug content and drug-release profile, were evaluated, compared with the tablets produced by direct compress technique. The stability of the formulation produced by solid dispersion was investigated after 3 months of storage.

Results Solubility investigations by different techniques showed good correlations with each other. Hot-stage microscopy, hyper-differential scanning calorimetry (DSC) and Raman spectroscopy illustrated the solubility of drug in the molten state of the polymer matrix while Raman spectroscopy and powder X-ray diffraction indicated the solubility of the drug in a solid-state matrix. The granules prepared by FHMG showed excellent flowability during tablet pressing. The dissolution rate and percentage of drug release of the poorly water-soluble API were significantly increased by using the solid dispersion as a binder in the FHMG process. Furthermore, the drug-content uniformity of dosage forms, especially lower-dosage forms, was improved a lot by using this novel granulation technique.

Conclusions The solubility of drug in molten or solidified polymer was successfully investigated by various techniques. Raman spectroscopy was developed as a novel tool to measure the solubility of drug in polymer. The application of solid dispersions in the FHMG process is an effective procedure for pharmaceutical manufacture to improve drug-content uniformity, dissolution rate and hence the bioavailability of poorly water-soluble drugs.

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Characterization of wax granules containing paracetamol produced by a hot-melt spray system

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Objectives Paracetamol of different particle-size ranges was incorporated into glyceryl monostearate (GMS) granules with the anticipation of producing a sustained-release oral delivery system from a hot-melt solid dispersion (Habib 2001). Subsequent characterization of these formulations indicated that drug release was dependent on particle size but not as anticipated by Noyes-Whitney (Martin et al 1983).

Methods 10% w/w of ball-milled paracetamol of various particle-size ranges (53–250 μm) was incorporated into separate batches of GMS granules. An agitated spray system was used, at 80°C, to transform bulk molten wax/drug mixture into small droplets dispersed in a carbon dioxide atmosphere. The sprayed droplets were cooled in the gaseous atmosphere on descent and collected as granules for analysis. The resultant particle-size distribution (PSD) of granules was characterized by sieve analysis and dissolution performance of the formulations was determined using US Pharmacopoeia (USP) XXII apparatus 2. All dissolution testing was automated and performed at a paddle speed of 50 rpm, using 1000 mL distilled water maintained at a temperature of 37°C. Statistical analysis was undertaken using two-way analysis of variance and f_2 statistical tests. Drug/excipient compatibility was investigated utilizing differential scanning calorimetry (DSC). Samples of individual components as well as each drug/excipient combination were weighed directly into unpierced aluminium pans (1–2 mg) and scanned from 20 to 200°C, with a heating rate of 20°C minute^{-1}, using a Mettler DSC, model 844e.

Results For all three batches of sprayed paracetamol granules the majority of the resultant granules were within the 250–500 μm size range. Statistical comparison of the PSD obtained for the three paracetamol granule batches indicated that there was no significant difference in the PSD (two-way analysis of variance; $P > 0.05$). Therefore, the overall PSD of the sprayed granules is independent of the drug particle size used during formulation. Mean drug-release profiles for paracetamol sprayed granules indicate that as the particle size of the active ingredient in the granules decreased below 90 μm the rate of drug release significantly decreased (f_2 value < 50). The decrease in dissolution rate may be due to small particle reaggregation of paracetamol into larger particle sizes, thus decreasing the drug particle surface area and resulting in a slower drug release rate. All paracetamol binary mixtures appeared compatible with GMS, as there were no significant shifts in the drug/excipient endotherms from DSC analysis, indicating the thermal stability of the mixtures and stability of ball-milled paracetamol.

Conclusions The particle size of the hydrophilic drug incorporated into sprayed granules did not significantly affect the PSD or the thermal properties of the granules. Drug-release rate from the resultant product appears to be under the control of the initial particle size of paracetamol used but not as anticipated by Noyes-Whitney. Its impact of dissolution performance is subject to ongoing investigation.

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Thermal investigation into the interaction of cetostearyl alcohol and a cetostearyl alcohol/sodium lauryl sulphate mixed emulsifier with liquid paraffin

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Objectives In previous work, mobile nanoemulsions were prepared by the ultrasonication of liquid paraffin (LP) in water macroemulsions containing the mixed emulsifier (ME) sodium lauryl sulphate (SLS) and cetostearyl alcohol (CSA; Kim et al 2007). It was shown that the lamellar gel networks, formed when the ME interacts with water (ternary system), were not present in freshly prepared nanoemulsions. In these systems, the endotherm associated with the lamellar phase was absent and replaced by a prominent, broad unidentified endotherm between 50 and 60°C. The aim of this work was to identify the nature of this endotherm to gain a better understanding of nanoemulsion microstructure. To this end, the interactions of the ME and its components in oil were investigated.

Methods LP mixtures (10 g) containing SLS (0.1–1% w/w), CSA (0.1–10% w/w) or ME with a CSA/SLS ratio of 9:1 (0.1–16.6% w/w) were prepared by heating each mixture to 75°C in a water bath and then cooling to 25°C. For comparison a nanoemulsion containing 4% ME in LP was prepared by ultrasonication as described previously (Kim et al 2007). The samples were examined microscopically (crossed polars) using a Polyvar microscope (Leica, Germany), rheologically using a Carrimed CSL100 rheometer (TA Instruments, UK) and by differential scanning calorimetry (DSC) from 10 to 80°C at 10°C/minute (DSC 822^e, Mettler Toledo, UK).

Results SLS did not interact with LP. Lower concentrations (0.1–0.5%) of either CSA or ME formed clear solutions in LP, whereas higher concentrations showed evidence of interaction as they formed either structured fluids (1% w/w) or semisolid ointments (5 and 10% w/w). However, the small quantity of SLS in the ME (< 1% w/w) appears to change the nature of this interaction. Although both excipients formed semisolid mixtures with complex flow properties and similar apparent viscosities (range 0.14–0.41 Pa·s (ME) and 0.14–0.48 Pa·s (CSA)), the flow curves for the CSA systems showed large yield values. Microscopically the ME and CSA systems showed differences in crystalline appearance. The nanoemulsion immediately after preparation showed one broad endotherm at 50–60°C. A similar endotherm was present in the LP/ME systems (containing SLS), but not in the LP/CSA systems. This indicates that the nanoemulsion endotherm may be due to interaction of ME in the bulk oil as well as at the oil/water interface. It was previously assumed that most of the emulsifier would be located at the vastly expanded oil/water interface. The low-temperature endotherm (30–40°C) present in both the ME and CSA systems is due to the interaction of CSA in LP and is not present in either nanoemulsions or macroemulsions.

Conclusions The nanoemulsion contains structural elements in the oil phase. The microstructures of these elements are currently being investigated using small-angle neutron scattering.

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Osmotic effects on release from coated pellets: impact of substrate core composition

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Objectives To study the impact of the osmotic pressure of the release medium on drug release from pellets coated with ethylcellulose/poly(vinyl alcohol)-poly-(ethylene glycol) (PVA-PEG) graft-copolymer blends. To determine the importance of the type of starter core, comparing drug-layered (i) microcrystalline cellulose (MCC) cores, (ii) sugar cores and (iii) sugar cores sealed with an ethylcellulose layer.

Methods Diltiazem hydrochloride, a freely water-soluble model drug, was layered on to MCC cores, sugar beads and sugar beads that had been seal-coated with ethylcellulose (Aquacoat ECD). 25–30% coating levels of 90:10 ethylcellulose/PVA-PEG (i.e. an aqueous ethylcellulose dispersion (Aquacoat ECD, triethylcitrate) and PVA-PEG graft-copolymer) were applied to the drug-loaded beads in a fluidized bed coater (Wurster insert). The coated pellets were subsequently cured for 1 day at 60°C and drug release was measured in 0.1 M HCl and phosphate buffer, pH 7.4, using the US Pharmacopoeia (USP) 30 paddle apparatus (UV drug detection). To adjust osmolarity of the release medium, appropriate amounts of sodium chloride were added.

Results Drug release from sugar pellets was less sensitive to changes in the osmotic pressure of the release medium than release from MCC pellets, irrespective of the coating level and type of release medium. For instance, drug release after 4 hours in 0.1 M HCl decreased from 69 to 40% and from 84 to only 6% when osmolarity was increased from 0.2 to 3.5 osmol in the case of sugar and MCC starter cores respectively (25% coating level). In phosphate buffer, pH 7.4, the corresponding 4 hour release dropped from 73 to 42 and from 77 to only 7% on increasing the osmolarity from 0.28 to 3.58 osmol. The decrease in the release rate with increasing osmolarity of the surrounding bulk fluid can at least partially be attributed to the external osmotic pressure counteracting water uptake by the pellets, limiting dissolution and subsequent release of the drug. The fact that pellets containing sugar starter cores are less sensitive to changes in the osmolarity of the release medium might at least partially be explained by the fact that the sugar cores exhibit a higher osmotic pressure than the MCC cores. This assures a minimum water penetration into the devices at all the investigated osmolarities of the release media. Sealing the sugar starter cores with an ethylcellulose layer makes the drug-layered beads behave similarly to the MCC pellets.

Conclusions The sensitivity of drug release from coated beads to the osmolarity of the dissolution media strongly depends on the type of starter core. Osmotically active sugar starter cores result in less sensitivity compared with MCC cores, which are osmotically much less active.