Table 1 Network parameters of 2:1 ratio of 20% PMVE/MA and PEG (10000, 1000 and 200 Da) crosslinked hydrogels

Network Parameters	PMVE/MA:/PEG, 2:1		
	10000	1000	200
EWC (%)	78.57	58.90	39.47
M_c **(g/mol)**	1203.15	980.63	453.33
χ	0.7313	0.7880	0.8121
q	0.1446	0.1774	0.3838
ϕ	0.69	0.86	0.94

Furthermore, NMR and ATR-FTIR studies showed the presence of peaks in the ester region, suggesting that etherification occurs between PMVE/MA and PEGs.

Conclusions NMR and ATR-FTIR studies showed the presence of ester linkage between PMVE/MA and PEGs. Hydrogels of PMVE/MA crosslinked with PEG 10000 showed a significantly higher degree of swelling, followed by PEG 1000 and PEG 200 crosslinked hydrogels. Therefore, PMVE/MA–PEG 10000 hydrogels could possibly be used for rapid delivery of drugs, due to their low crosslink density. In addition, moderately crosslinked PEG 1000 or highly crosslinked PEG 200 hydrogels could be used in controlling drug-delivery rates.

New Scientist Session "Pharmaceutical Sciences: Where are We Going?"

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Intelligent anti-infective biomaterials

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Objectives One of the predominant problems with the use of urinary medical devices is the development of device infection: beginning with bacterial adherence, developing with the formation of biofilm and with the symptomatic end point of encrustation. Catheter encrustation can cause pain upon removal and increases the frequency with which catheters must be removed; this is particularly problematic for patients requiring long-term catheterization. Serious consequences include septicaemia, pyelonephritis and shock (Lawrence and Turner 2005). Approaches to overcoming this problem include the incorporation of antibiotics into the device to combat infection and also the modification of the device surface so that it is not as susceptible to infection. This work attempts to join these two approaches together in a synergistic manner, with a device surface that is inherently resistant to infection through intelligent *in vivo* reactions and which is also impregnated with antibiotics.

Methods Polymers were mixed with suitable plasticizers to enable processing with a twin-screw extruder. Different drug loadings of different anti-bacterial agents were then mixed with the polymer/plasticizer formulations. Formulations were stored in a desiccator for 24 hours prior to processing. The formulations were then extruded with varying concentrations of anti-bacterial agent. The samples were suspended in release medium appropriate to the *in vivo* conditions. Samples were then filtered using 0.45 μm syringe filters and analysed using UV spectroscopy to determine their drug-release properties.

Results The different polymers demonstrated an intelligent response, with one polymer demonstrating drug release in conditions mimicking infection, and the other demonstrating drug release in conditions mimicking both the healthy state and an infected device.

Conclusions These polymers are suitable for further investigation as a novel responsive anti-infective medical-device coating, providing actions to both prevent and treat medical-device infection.

Lawrence, E. L., Turner, I. G. (2005) *Med. Eng. Phys.* **27**: 443–453

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Novel approaches to characterizing phase separation and drug distribution across hot-melt-extruded solid dispersions containing poorly water-soluble drugs

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Objectives To investigate the phase-separation behaviour of hot-melt-extruded (HME) solid dispersion formulations containing a poorly water-soluble drug. Novel approaches are introduced to characterize the phase-separation behaviour and map the drug distribution in the HME formulations at a micrometre to sub-micrometre scale of resolution. These approaches include local thermal analysis (LTA) using nano-thermal tips, photothermal microspectroscopy (PT-MS) and Fourier-transform infrared (FTIR) photoacoustic spectroscopy (PAS).

Methods Felodipine was incorporated into EUDRAGIT® E matrices using hot-melt extrusion. The drug/polymer ratios of the HME formulations were between 10/90 and 70/30. Pulsed-force mode atomic force microscopy (PFM-AFM) was performed to identify phase separation in the formulations. After the PFM-AFM imaging, LTA measurements were carried out at selected locations to further identify the thermal properties of each sampling point. PT-MS measurements were carried out by interfacing an FTIR spectrometer with an AFM equipped with a Wollaston probe; these experiments were performed at different locations across the surface and the cross-section of the HME strands. The photoacoustic spectra were taken using a Bruker IFS 66/S spectrometer fitted with a photoacoustic cell. The PAS spectral depth profiling of the HME samples was obtained using step scans at different frequencies.

Results The PFM-AFM imaging revealed phase separation in the solid dispersion of miscible felodipine and EUDRAGIT® E after hot-melt extrusion. Particles could be seen in the HME formulations with drug/polymer ratios at and above 30/70. The LTA measurements performed on the particles and the surrounding areas indicated the presence of different phases in the HME formulations. The thermal behaviour of these separated phases varied with the drug/polymer ratio of the HME solid dispersion. The PT-MS results demonstrated the differences in the drug concentration and distribution on the surface and at the cross-section of the HME strands with drug/polymer ratios at and above 30/70. To further investigate the depth profile of the drug distribution of the HME formulations, photoacoustic step-scan measurements were performed. Three different frequencies were applied in the step-scan measurements to allow the evaluation of the drug distribution at three different layers in depth from the surface of the HME strands. Combining these results with the PT-MS and conventional attenuated total reflectance (ATR)-FTIR results, the drug distribution of the formulations with phase separation was mapped on a micrometre scale.

Conclusions In this study, phase separation was observed in a miscible drug/polymer system after being processed using hot-melt extrusion. The presence of phase separation which varied with the drug/polymer ratio in the formulations was identified using PFM-AFM in conjunction with LTA analysis. The drug distribution across the HME solid-dispersion strands was characterized using PT-MS combined with conventional ATR-FTIR and PAS. The detailed depth profiles of the drug concentration at different layers of the HME formulations were obtained on a micrometre scale. These approaches are considered to represent a promising new approach to studying phase separation, particularly as the drug distribution within the HME strands may potentially affect the drug-release behaviour.

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Preparation and characterization of glibenclamide microcrystals

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Objectives Dissolution rate of hydrophobic drugs is the rate-limiting step for drug absorption. Increasing the specific surface area of the drug (by micronization) will lead to increasing the drug dissolution rate (Noyes–Whitney equation). Accordingly, glibenclamide, a model hydrophobic drug, was microcrystallized by *in situ* micronization method. The aim was to prepare glibenclamide microcrystals for oral delivery.

Methods A solvent change method was utilized to prepare drug microcrystals. In this method, Solutol-HS15 and Cremophor-RH40 (non-ionic surfactants) were used as stabilizers to control the size of precipitating crystals. Glibenclamide was dissolved in dichloromethane (0.2% w/v). Surfactants were dissolved in water in concentrations of 1, 2 and 5% w/v. Drug solution (10 mL) was mixed with surfactant solution (40 mL) by magnetic stirrer. Accordingly, microcrystals were formed spontaneously. The mixtures were centrifuged at 10000 rpm for 5 minutes and the precipitated crystals were freeze-dried via VirTis freeze drier. The dried glibenclamide microcrystals were characterized for particle size analysis (via Zeta Sizer), microcrystal morphology using scanning electron microscopy (SEM), drug solubility, drug dissolution using capsules containing 5 mg drug and structural analysis via Fourier-transform infrared (FTIR) spectroscopy.

Results Glibenclamide microcrystals produced a higher solubility ($P < 0.05$, analysis of variance) compared with that of commercial glibenclamide. This may be explained by large surface area and good wetting properties of drug microcrystals. The release of the drug from microcrystals was significantly higher ($P < 0.05$, analysis of variance) than that of commercial drug. After 5 minutes, the average percentages of drug release were 80% from microcrystals prepared with

Solutol-HS15 as a stabilizing agent, 100% from microcrystals prepared with Cremophor-RH40 as a stabilizing agent and only 21% from commercial drug. The higher drug release from Cremophor-RH40 can be attributed to the nature of the surfactant, which led to formation of homogenous microcrystal size and shape compared with Solutol-HS15 as explained by particle size and SEM analyses. The particle size of microcrystals ranged from 1 to 3.7 μm depending on the type and concentration of the surfactant. FTIR spectra of drug microcrystals showed shifts in peaks at 1731 and 1763 cm^{-1} corresponding to carbonyl stretching. This explains formation of hydrogen bonding between the drug and surfactants, and as a result high drug solubility and drug dissolution were achieved from glibenclamide microcrystals.

Conclusions Glibenclamide microcrystals produced by *in situ* micronization in the presence of stabilizing agents enhanced the drug dissolution rate due to uniform drug particle-size distribution and shape.

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Microbiological (methicillin-resistant *Staphylococcus aureus*) and rheological testing of novel anti-microbial karaya wafers

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Objectives To formulate lyophilized wafers containing a selection of broad-spectrum anti-microbial compounds and test their efficacy against *Staphylococcus aureus* (SA) and methicillin-resistant *Staphylococcus aureus* (MRSA) using an *in vitro* wound model based on a disc diffusion method. Impaired healing of chronic wounds can result from polymicrobial infection of the wound bed and indiscriminate use of anti-microbials can lead to anti-microbial resistance. Anti-microbial wafers may offer the possibility of delivering precise amounts of therapeutic agent, selectively and at a controlled rate, directly to the suppurating wound bed, hence improving management of the wound-healing process.

Methods Karaya gum was prepared as a 3% w/v gel in distilled water and the anti-microbials neomycin sulphate (NS), povidone iodine (PVP-I), chlorhexidine digluconate (ChD) and silver sulphadiazine (SS) were incorporated as solutions or suspensions. Aliquots (1.5 ± 0.02 g) of each gel formulation were cast to the individual compartments of 12-well polystyrene culture plates and freeze-dried. Lyophilized wafers were removed from the culture plates (used as moulds) and tested *in vitro* against known concentrations of SA and MRSA. The freeze-dried discs (diameter 21 ± 0.5 mm) were placed in the centre of a Petri dish containing 1.5% w/v nutrient agar seeded with the bacterial colony (5×10^5 cfu/mL). Wafer diameters before and after 21 hours' incubation, unswollen (D_o) and swollen (D_t), were measured and expansion ratios (D_t/D_o) calculated (Matthews et al 2005). Anti-microbial activity was determined by measuring the diameter of inhibition (D_i) – or inhibition zone – on the Petri dishes and calculating the inhibition ratio (IR = D_i/D_o). Rheological properties of pre-lyophilized gels were also characterized by continuous shear measurements using a cone and plate geometry.

Table 1 Viscosity coefficients (η') and results of *in vitro* tests

Karaya/ anti-microbial	η' (± 0.005) (Pa·s)	Expansion ratio (±0.05)		Inhibition ratio (±0.05)	
		SA	MRSA	SA	MRSA
Placebo	12.89	1.11	1.14	0.00	0.00
NS 0.10% w/v	8.36	1.13	1.19	0.95	0.61
PVP-I 1.00% w/v	6.05	1.07	1.07	1.43	1.57
ChD 0.05% w/v	11.95	1.06	1.07	1.61	1.61
SS 0.02% w/v	16.08	1.08	1.12	1.38	1.41

Results All results are detailed in Table 1.

Conclusions Clear changes to gel consistency (η') were attributed to the interaction of individual anti-microbial compounds with karaya. The efficacy of all anti-microbial wafers against both SA and MRSA, as indicated by the inhibition ratio, was apparent, with 0.05% w/v ChD being of particular note.

Matthews, K. H. et al (2005) *Int. J. Pharm.* **289**: 51–62