withdrawal of the MN. Therefore, lower microorganism penetration resulted. In addition, when MNs were left in place, blockage of the holes by the MN allowed lower penetration of microorganisms than the hypodermic needle-punctured membranes.

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Anti-microbial activity of liposomal tea tree oil and its constituents

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Objectives The aim of these studies was to assess the anti-microbial activity of tea tree oil (TTO), liposome-encapsulated TTO emulsions and the constituents of TTO against *Staphylococcus aureus, Pseudomonas aeruginosa* and *Candida albicans* using the standard disc diffusion assay. Natural products are increasingly seen as a main source of novel therapeutic agents for infectious diseases; the monoterpene alcohols are particularly anti-microbially active because of their relatively high water solubility and the presence of the alcohol moiety (Hammer et al 2003).

Methods Emulsions of TTO with different molecular weights of poly(vinyl alcohol) (PVA) (13–23, 30–70, 70–100 kDa) at 0.1 and 1.0% w/v and subsequent liposome encapsulation were performed as previously reported (Martin et al 2007). Anti-microbial activity was assessed with a 100 μL sample of each culture suspension spread uniformly over 20 mL tryptic soy agar for *P. aeruginosa* and *S. aureus*; malt extract agar plates were used for *C. albicans*. After inoculation a 5 mm sterile filter disc was centrally placed and 50 μL of sample added: TTO, TTO emulsion, liposomal TTO emulsion and TTO components (α-terpineol, *p*-cymol, γ-terpinene, α-pinene, 1,8-cineole, α-terpinene, terpinene-4-ol, limonene and terpinolene). After disc saturation, plates were inverted and incubated at 37 ± 2°C for 24 hours and the zone of no growth (zone of growth inhibition, ZOI) around each disc was assessed (Figure 1). The ZOI radius was measured from disc centre to ZOI edge.

Results Anti-microbial activity studies reveal the efficacy of various TTO formulations and TTO components against three common microorganisms. ZOI development with free TTO, TTO-PVA emulsion and TTO-PVA liposomes was studied for 24, 48 and 78 hours; times were selected to investigate the duration of action of individual constituents. The activity of free TTO compared with TTO-PVA emulsion and TTO-PVA liposomes was much higher against *S. aureus* ($P < 0.02$) and *C. albicans* ($P < 0.025$), while *P. aeruginosa* showed less sensitivity against free TTO and after an interval of 78 hours no ZOI was shown. No activity against *P. aeruginosa* was found for TTO-PVA emulsion formulations, which may indicate resistance against PVA-formulated TTO. *C. albicans* showed the highest sensitivity to TTO for all emulsion formulations, with greatest sensitivity to $PVA_{70–100kDa}$-TTO emulsion. Results for encapsulated formulations (liposomal $PVA_{30–70kDa}$-TTO and liposomal $PVA_{13–23kDa}$-TTO) revealed anti-microbial activity against *P. aeruginosa* at less than 24 hours. The anti-microbial activity of major components present in TTO was also examined. There was little or no activity shown by the majority of TTO components against *P. aeruginosa* except terpinene-4-ol (the major TTO constituent); a 7 mm ZOI (which was the same for free TTO) was observed. Efficacy of TTO components (1,8-cineole, $P < 0.1$; terpinene-4-ol, $P < 0.005$; terpinolene, $P < 0.1$) was greatest against *C. albicans*.

Conclusions In conclusion, TTO-PVA emulsions were found most effective against *S. aureus* and *C. albicans*, with *P. aeruginosa* demonstrating resistance to most formulations. The major TTO constituent (terpinene-4-ol) displayed the greatest efficacy against all microorganisms, including *P. aeruginosa*; the other components, however, showed only limited anti-microbial efficacy with the greatest activity against *C. albicans*. Future work aims to identify potential synergistic activity of TTO and its constituents in combination with traditional anti-microbial therapies, to combat the development of antibiotic resistance.

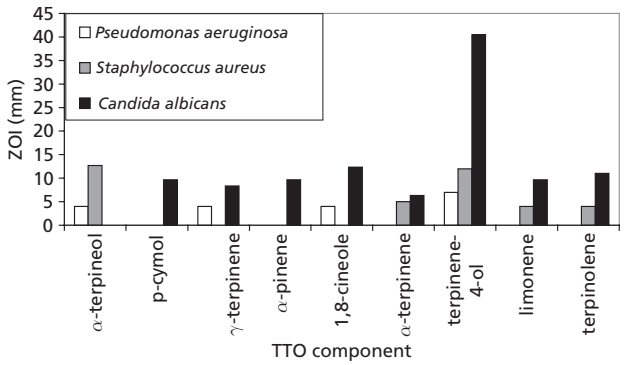

Figure 1 Zone of growth inhibition (ZOI) obtained for various tea tree oil (TTO) components against three common microorganisms.

Hammer, K. et al (2003) *J. Appl. Microbiol.* **95**: 853–860
Martin, C. et al (2007) *J. Pharm. Pharmacol.* **59** (Suppl.): A19

Pharmaceutical Technology

113
Study of *in vitro* release characteristics of etoricoxib semisolid dispersion in Gelucire-based capsules

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Objectives The aim of the present work was to prepare and characterize different dispersions of etoricoxib with Gelucire 44/14 and Gelucire 50/13 so as to improve its dissolution and stability properties.

Methods Solubility measurements were performed according to the method of Higuchi and Connors (1965) with various concentrations of aqueous solutions of Gelucire 44/14 and Gelucire 50/13 prepared in distilled water with drug. The carrier fusion method was used to prepare different dispersions of etoricoxib using Gelucire 44/14 and Gelucire 50/13. Differential scanning calorimetry (DSC) of drug dispersion into carriers was studied using a DSC-60 calorimeter (Shimadzu). The *in vitro* release of etoricoxib capsules was performed by using DisSolution test apparatus (Veego UDA-8D) to the US Pharmacopoeia (USP) standard method at a paddle rotation speed of 100 rpm, with 900 mL 0.1 M HCl or phosphate buffer, pH 6.8, as a dissolution medium at 37 ± 0.5°C. At the specified time, 10 mL samples were withdrawn and filtered through 0.45 μm Whatman filter paper and then assayed for etoricoxib content by measuring the absorbance at 233 nm using a UV-1700 Shimadzu UV-visible spectrophotometer. The optimized formulation capsules were stored in glass bottles (unpacked capsules) and subjected to accelerated stability studies as per International Conference on Harmonisation (ICH) guidelines; that is, at 40°C and 75% relative humidity, and at room temperature and normal humidity conditions.

Results The phase solubility study was carried out using different Gelucire 44/14 solutions in distilled water (1, 2, 5, 10 and 15% w/v). The 15% w/v solution showed maximum solubility. The same study was carried out using Gelucire 50/13 solutions in distilled water (1, 2, 3, 4 and 5% w/v), and the 5% w/v solution showed maximum solubility. DSC showed there was no well-defined interaction between etoricoxib and the carriers. An *in vitro* release study was carried out for prepared capsules using Gelucire 44/14 as a carrier in 0.1 M HCl or phosphate buffer, pH 6.8. 80.6% drug release was obtained within 10 minutes. The same test was done on prepared capsules with Gelucire 50/13 as a carrier in 0.1 M HCl or phosphate buffer, pH 6.8. 81.4% drug release was obtained within 60 minutes. The stability study indicated that etoricoxib was stable at room temperature and normal humidity conditions while high temperature and humidity led to crystallization of the drug.

Conclusions Etoricoxib polymer dispersions were formed at different ratios using the melting method and put into hard gelatin capsules. Solubility studies showed a solubilizing effect of this polymer on etoricoxib at different temperatures. The negative values of the Gibbs free energy and enthalpy of transfer from water to an aqueous solution of this polymer indicated the spontaneity of the transfer. DSC studies indicated a lack of interaction between carrier and etoricoxib. The dissolution rates of etoricoxib dispersions were higher than those of the pure drug; this was possibly caused by increased wettability and dispersibility of etoricoxib, the surface tension-lowering effect of polymer to the medium and the solubilizing effect of the carrier.

Higuchi, T., Connors, K. A. (1965) *Adv. Anal. Chem. Instr.* **4**: 117–212

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Dilute solution viscometry and flow properties of a new natural polymer

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Objectives A natural polysaccharide polymer was obtained by extraction from the inner-stem bark of the tropical shrub *Grewia mollis* (Family Tiliaceae) and its potential as a pharmaceutical excipient was investigated. The dried and pulverized

inner-stem bark is used as a thickening agent in its native country. The apparent/intrinsic viscosity and flow properties of the polymer are reported. Viscosity is essential to understanding the molecular structure of these natural polymers and also in their utilization. Valuable information regarding length and shape of polymer can be obtained from determinations of intrinsic viscosity. The suitability of the polymer as a stabilizer was investigated.

Methods The dried and pulverized inner-stem bark of *G. mollis* shrub was dispersed in 0.1% w/v sodium metabisulphite solution and hydrated for 48 hours. The mucilage obtained was passed through a muslin bag and the filtrate was treated with 20 mL 1.0 M NaOH and centrifugated at 4000 rpm for 10 minutes. Absolute ethanol containing 750 mL of 0.1 M HCl was used to precipitate the supernatant and precipitate was washed with absolute ethanol and wet-milled. At this stage further processing was determined by the drying method. The wet-milled precipitate was squeezed through a muslin bag and then air-dried to obtain the air-dried polymer. This was dry-milled and passed through a 1.0 mm sieve and further dried in an oven at 50°C for 24 hours. Finally, the dried product was weighed and stored in air-tight containers. Freeze-dried sample was obtained by freeze-drying the wet-milled polymer precipitate at –40°C for 72 hours. The viscosity and flow behaviour of a 1% w/v aqueous dispersion of the polymer were studied using a Brookfield viscometer. Viscosity was read over 3 minutes for a range of shear rates between 5 and 100 rpm at 23°C using spindle number 2. Sample volume was 200 mL in a 250 mL beaker. Dilute solution viscometry was determined using an Anton Paar Automated micro viscometer (Graz, Austria). A 0.1% w/v aqueous dispersion of polymer was hydrated at room temperature for 24 hours. The hydrated polymer dispersion was filtered and serially diluted before determination of apparent viscosity.

Results The 1.0 % w/v aqueous dispersion of the freeze-dried polymer gave a viscosity of 380.1 ± 0.2 cP compared with 227.3 ± 0.2 cP for the air-dried polymer at 5 rpm. The apparent viscosity of the polymer decreased with an increase in shear rate. Both the air-dried and freeze-dried samples exhibited shear thinning or pseudoplastic flow behaviour. Dilute solution viscometry studies showed that the air-dried *G. mollis* polymer has an intrinsic viscosity of 1.0913 ± 0.0097 MPa·s compared with 1.1516 ± 0.0332 MPa·s for the freeze-dried sample.

Conclusions Most natural polymers form very viscous solutions at low or high concentrations. High viscosity is important in the production and stabilization of emulsions and suspensions. Shear thinning is desirable for suspension stabilizers as this favours redispersion of suspended drug substances. *G. mollis* polymer may have potential as a stabilizer in emulsions and suspensions.

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The influence of tablet diluent choice on the performance of hydroxypropyl methylcellulose matrices in sugar-rich dissolution environments

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Objectives The extended release (ER) properties of hydroxypropyl methylcellulose (HPMC) matrices can be diminished in ionic (Mitchell et al 1990) and sugar-rich (Williams et al 2008) environments, which arises from their effects on polymer swelling and coalescence during gel-layer formation (Bajwa et al 2006). This work aims to establish whether the choice of tablet diluent influences the ER profile of HPMC matrices in an environment rich in dietary sugar.

Methods 8 mm round, flat faced tablets (250 mg) containing 10% w/w caffeine anhydrous, 30% w/w HPMC (Methocel™ K4M-CR) and 60% w/w diluent were manufactured using a F3 Manesty tablet press (Liverpool, UK) at 230 MPa. Diluents chosen were soluble (lactose, glucose, mannitol, fructose) or insoluble (microcrystalline cellulose, MCC). Dissolution tests were performed in de-aerated media using US Pharmacopoeia (USP) apparatus I at 100 rpm, 37 ± 0.5°C. Studies of early gel-layer formation were undertaken using a Bio-Rad MRC-600 confocal microscope (Hemel Hempstead, UK) using a method described previously (Bajwa et al 2006).

Results In water, all matrices exhibited ER profiles, with those containing MCC being significantly slower ($T_{80\%}$ ≈8 hours) than matrices containing sugar diluents ($T_{80\%}$ ≈4.5 hours). $T_{80\%}$ values for matrices containing different sugars ranged from 4.00 to 4.76 hours and were statistically indistinguishable. Images of early gel-layer formation revealed that within 10 minutes all matrices had formed compact and coherent gel layers, which restricted the further ingress of the hydration medium into the matrix core. MCC matrices showed the least water penetration. In dissolution media containing less than 0.65 M sucrose, all matrices showed the characteristic ER root time profiles ($r > 0.999$) observed in water. In 0.65 M sucrose, however, a sigmoidal ER dissolution profile emerged from matrices containing certain sugars (lactose, mannitol or glucose). In 0.7 M sucrose all matrices containing sugar diluents exhibited sigmoidal immediate-release profiles in which 80% of drug was released within 2–3 hours. Matrices containing fructose or glucose were only marginally more resistant to the sucrose-rich environments than matrices containing lactose or mannitol. Studies of early gel-layer formation in 0.7 M sucrose showed diffuse gels and enhanced matrix penetration, whereas MCC matrices showed extended drug release and compact gel morphologies in all dissolution media.

Conclusions Matrices containing soluble sugar diluents showed a marked change from extended to immediate drug release in media with high sugar contents. This change occurred over a very narrow concentration range (0.65–0.7 M), and there was little discrimination between the effects of different sugar diluents. Imaging studies showed clear changes in gel-layer morphology and enhanced matrix penetration, suggesting a profound effect on polymer hydration and interference with gel-layer barrier properties. In contrast, matrices containing an insoluble diluent MCC did not show these effects and were robust to changes in sugar concentration in the dissolution medium. This work highlights the potential for diluent choice to influence the ER properties of HPMC matrices in a highly sugar-rich medium.

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Mitchell, K. et al (1990) *Int. J. Pharm.* **66** (1–3): 233–242
Williams, H. D. et al (2008) abstract 5, this issue

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Physical stability of amorphous drugs: evaluation of thermodynamic and kinetic parameters

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Objectives Until now, the stability of amorphous compounds has been predicted mainly by conducting time-consuming experiments such as physical stability studies under various stress conditions. The theoretical considerations behind these approaches have been shown to have limitations. Recently, attempts have been made to predict stability on the basis of thermodynamic and kinetic factors. These factors have been successfully applied for a limited number of compounds. However, a systematic approach for a greater sample size is currently lacking, and thus general conclusions are currently difficult to draw. This study was intended to evaluate the thermodynamic and kinetic parameters for a larger group of drugs and compare the theoretical results with actual stability data.

Methods A sample of 14 drugs with different physical (high and low T_g) and chemical properties (acidic, basic and neutral) was used. Amorphous samples were prepared in a differential scanning calorimetry (DSC) instrument (Q1000, TA Instruments). Thermodynamic parameters (configurational entropy and enthalpy) were calculated from measurements of configurational heat capacities. These were obtained from modulated DSC scans. Kinetic factors (T_g, relaxation times, fragility) were derived from the heating rate (1, 2, 5, 10 and 20 K/minute) dependence of T_g. Amorphous drugs were stored at temperatures 20 K below the T_g of the respective drugs for a duration of 100 days and the stability was monitored by DSC. From a thermodynamic perspective physically stable drugs should have high values of configurational entropy and/or low values of configurational enthalpy. From a kinetic perspective it can be concluded that compounds that show high values of the initial relaxation time, τ°, and high values of the relaxation time, τ, should be stable.

Results Calculations of the fragility parameter (m) classified the drugs as 'fragile' glass-formers but variation in the degree of fragility could be measured. Stronger glass-forming liquids show less temperature dependence of their mobility. Tolbutamide and cefuroxime axetil exhibited the largest proportion of 'strong' glass-former characteristics, with m values of 49.7 and 57.5 respectively compared with 82.6 for troglitazone. Due to the restricted applicability of the configurational calculations below T_g, no direct correlation could be found. The kinetic factor τ° correlated well with stability after 1 day if the exceptional 'strong' glass-formers were excluded (r^2 values of 0.723). Continuing storage led to r^2 values of 0.333 for values after 36 days.

Conclusions The results from this study showed that the methods of predicting stability on the basis of the configurational entropy or enthalpy and kinetic parameters such as the initial relaxation time cannot generally be applied. Recrystallization from the amorphous state is a complex process. Other characteristics of the amorphous state such as fragility, local mobility or hydrogen bonding are hypothesized to play an important role in the stability as well and it may be that for different drugs these factors contribute to different degrees. We therefore conclude that no single method is currently able to predict the stability and that recrystallization is governed by a variety of factors that all need to be taken into consideration in order to make reliable predictions. A multivariate approach, including modified thermodynamic and kinetic parameters as well as factors such as hydrogen bonding and local mobility, appears to be necessary to predict the stability of amorphous compounds.

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Physico-chemical, rheological and drug-release characteristics of quinine and Eudragit E100 prepared by hot-melt extrusion

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Objectives To prepare solid dispersions of quinine base and quinine hydrochloride in Eudragit E100 polymer to study the effect of drug loading on solid-state characteristics, polymer plasticization and *in vitro* drug-release properties. Hot-melt extrusion (HME) technology was used to prepare drug–polymer solid dispersions using twin-screw extrusion equipment. The use of HME to prepare solid dispersions is an expanding area of pharmaceutical research; the technique has been demonstrated to produce bioenhanced formulations for poorly soluble active pharmaceutical ingredients, and offers the possibility of an efficient 'continuous' manufacturing process for solid oral dosage forms. The interaction of quinine base and quinine hydrochloride with Eudragit E100 was studied by analysing changes in glass transition temperature and the rheological (flow) properties of the systems.

Methods A prism 16 mm twin-screw extruder (Thermo Scientific, UK) was used to prepare quinine-loaded matrices utilizing HME technology. The quinine-loaded matrices were characterized using thermal and chemical analysis techniques including differential scanning calorimetry (DSC), dynamic-mechanical thermal analysis (DMTA), X-ray diffraction (XRD) and dynamic vapour sorption to determine solid-state characteristics. Quinine base and quinine hydrochloride were incorporated in Eudragit E100 at 5, 10 and 20% (w/w) to study the effect of drug loading on polymer processability and drug–polymer solubility. Capillary rheology was used to determine the effect of incorporating quinine on Eudragit E100 polymer flow. The *in vitro* drug-release properties were assessed in simulated intestinal fluid (pH 6.8) using US Pharmacopoeia (USP) 2 dissolution apparatus.

Results This investigation highlighted the differences in solubility and interaction between quinine base and quinine hydrochloride with Eudragit E100 polymer. The results show that quinine (base) has greater solubility in Eudragit E100 than quinine hydrochloride, and acts as a plasticizer for Eudragit E100. At concentrations above 10% (w/w) quinine hydrochloride saturated solubility is reached in Eudragit E100, and a solid (crystalline) dispersion is formed. DMTA results show the glass transition temperatures of the extrudates are influenced by drug loading and salt form, with 20% (w/w) quinine base lowering the glass transition temperature by 17°C. These findings demonstrate that drug–polymer solubility and loading can strongly influence solid-state characteristics (crystalline/amorphous state) and polymer flow, and hence affect polymer-processing attributes.

Conclusions HME technology allows solid dispersions of quinine to be produced in Eudragit E100 in a single manufacturing process. The results show that drugs can act as plasticizers for polymers or as anti-plasticizers when there is little miscibility, solubility or chemical interaction between the drug and polymer. The plasticization of Eudragit E100 is dependent on quinine concentration and draws attention to the impact that drugs can exert on the physico-chemical properties of polymers. The understanding of solid-state characteristics and how these affect the processing characteristics of polymers shows that consideration must be given to the physical properties of solid dispersion formulations. This study helps to link thermal and chemical characteristics of drug–polymer blends to develop our understanding of their relationship to polymer flow and process parameters.

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The influence of ethanol on diltiazem hydrochloride release from matrix and multiparticulate modified-release systems

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Objectives Unintended, rapid drug release from modified-release (MR) oral dosage forms (dose dumping) is usually caused by a compromise of the release-rate-controlling mechanism. Roberts et al (2007) showed that ethanol affected aspirin release from hypromellose matrices. The aim was to assess the release of diltiazem hydrochloride from hypromellose matrices or ethylcellulose-coated multiparticulates in hydro-ethanolic media.

Methods MR matrices were compressed to a target weight of 180 ± 10 mg at 7 ± 1 kN using a Manesty F3 press fitted with 7 mm flat tooling. Matrices comprised 59.6 mg diltiazem hydrochloride, lactose (Tablettose® 80, Meggle, Germany), hypromellose (K4M, Dow Co., USA) and 0.6 % w/w magnesium stearate (BDH, UK). MR pellets were prepared using a Ventilus 1 (Innojet, Germany) fluidized bed system by coating 400 g of sugar spheres (0.55–0.75 mm, NP Pharm, France) with diltiazem hydrochloride and subsequently with an aqueous ethylcellulose dispersion (Surelease® E-7-19040, Colorcon, UK). 500 mg pellets (30.75 mg drug) were filled into size 0 hard gelatin capsules. Drug release was monitored using US Pharmacopoeia (USP) apparatus 2 at 100 rpm and 37°C. Media comprised 900 mL (i) distilled water with (ii) 20 or (iii) 40 % v/v ethanol. For each medium, six units were tested and drug release monitored spectrophotometrically at 237 nm. Additionally, pellets were placed in each dissolution medium for 90 minutes and dried for 12 hours at 30°C, and scanning electron microscope (SEM) images obtained (JSM-840, Jeol, Japan).

Table 1 Diltiazem hydrochloride release from hypromellose matrices and ethylcellulose-coated pellets in water and hydro-ethanolic media (n = 6 for each dataset)

Time (min)	Diltiazem hydrochloride release (% ± SD)					
	HPMC matrices			EC pellets		
	(i)	(ii)	(iii)	(i)	(ii)	(iii)
5	3 ± 0.5	4 ± 0.5	8 ± 0.3	3 ± 0.5	2 ± 0.5	2 ± 1
15	8 ± 1	9 ± 1	12 ± 1	6 ± 0.4	7 ± 0.4	28 ± 2
30	14 ± 1	14 ± 2	17 ± 1	12 ± 1	20 ± 1	68 ± 1
60	23 ± 2	22 ± 2	22 ± 1	24 ± 1	45 ± 2	87 ± 1
90	30 ± 7	31 ± 3	30 ± 4	36 ± 1	60 ± 2	92 ± 2
120	37 ± 2	37 ± 4	35 ± 3	47 ± 2	68 ± 2	95 ± 2
240	57 ± 5	54 ± 4	52 ± 3	68 ± 3	83 ± 2	99 ± 2
360	68 ± 6	68 ± 4	70 ± 4	77 ± 2	90 ± 2	100 ± 2

EC, ethylcellulose; HPMC, hydroxypropyl methylcellulose.

Results Results are shown in Table 1.

Conclusions Diltiazem hydrochloride release from hypromellose matrices was consistent in all media. Release from ethylcellulose-coated pellets was dependent on ethanol levels with a dose-dumping effect evident in the 40% v/v medium. SEM images indicated that the integrity of the plasticized ethylcellulose coat, while intact in water, was compromised in the hydro-ethanolic media, suggesting an interaction between ethanol and the polymer or plasticizer present in the rate-controlling membrane.

Roberts, M. et al (2007) *Int. J. Pharm.* **332**: 31–37

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Comparison of fluidized hot-melt granulation and conventional wet granulation on processing water-soluble or poorly water-soluble active pharmaceutical ingredient

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Objectives The purpose of this work is to determine the feasibility of fluidized hot-melt granulation (FHMG) as a novel process for the granulation of commonly used pharmaceutical powders, and also to compare the advantages and disadvantages of the FHMG technique with conventional wet granulation in processing water-soluble or poorly water-soluble active pharmaceutical ingredient (API).

Methods Three granulation methods (one of wet granulation, two of FHMG) for processing two model drugs (metronidazole and mefenamic acid used as model drugs for a water-soluble API and a poorly water-soluble API, separately) and two drug loadings (2 and 20%) were compared in this study. For FHMG, a low-melting point copolymer of polyoxyethylene-polyoxypropylene (Lutrol F68 Poloxamer 188) was used as a meltable binder for granulating, whereas for wet granulation 5% poly(vinyl pyrrolidone)/water solution was used as the liquid binder. In the FHMG process, two granulation methods were used. Method a used polymer alone as the meltable binder, granulated with the physical mixture of fillers and drug, named FHMG PM. In method b we pre-dissolved the drug powder into meltable binder by hot-melt method and used the solidified drug–polymer solid dispersion as the meltable binder, granulated with the mixture of fillers, named FHMG SD. Similar formulations were used in all granulation techniques. The particle-size distribution of the granules was investigated by standard sieve method. The bulk/tap densities, flowability of granules and the drug content in each granule size range were also evaluated. The granules were then pressed into tablets. Tablet properties, such as friability, hardness, uniformity of content and drug-release profile, were investigated and compared.

Results The granules produced by FHMG showed lower bulk/tap densities and better flowability than the granules produced by wet granulation. The drug content

in different size ranges of granules produced by FHMG SD illustrated good uniformity in both water-soluble and poorly water-soluble formulations, while for the wet granulation process the smaller particles contained more drug than the bigger particles, which indicated that the drug may be transferred from granule to granule during the drying process. The content uniformity of tablets showed similar results. The hardness of tablets produced by the granules from FHMG technique was lower than the tablets made by wet granulation process. The drug-release rates of both water-soluble and poorly water-soluble APIs were increased by using the solid dispersion as a binder for the FHMG process. Furthermore, the lack of drying process in FHMG compared with wet granulation decreased the total processing time considerably.

Conclusions FHMG is a simple and novel granulation process that could be developed to process both water-soluble and poorly water-soluble APIs. The application of solid dispersions in the FHMG process is an effective procedure in pharmaceutical manufacture to improve drug-content uniformity, dissolution rate and hence the bioavailability of drugs. Compared with conventional wet granulation process, FHMG has no drying step, which may be a good way to save process time and energy.

SESSION 3
Analytical Chemistry

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The effect of milling-process parameters on granule and tablet properties

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Objectives The wet granulation process is often used to produce large agglomerates from primary particles. Control of granulation allows optimization of the granule-size distribution, affecting powder flow and the key tablet properties of hardness and dissolution. To produce an optimal uni-modal size distribution and to remove any lumps from the granulation, the milling process is used as a control step. Very little work has been reported in the scientific literature on the importance of the milling process. In this study an experimental investigation was carried out to understand the impact of milling-process conditions on the granule and tablet properties using both laboratory- and pilot-scale equipment. An attempt was made to develop a scale-up relationship between laboratory-scale and pilot-scale cone mills using the geometry of the cone and rotor-tip speeds.

Methods A design of experiment (DoE) approach was used to relate the milling process parameters with the granule and tablet properties. Granule-size distribution was measured using a Malvern Mastersizer (dry powder dispersion) and flow properties were measured using a Ring Shear Tester. Coarse, intermediate and fine granules were used in tablet production to assess their impact on the tablet properties.

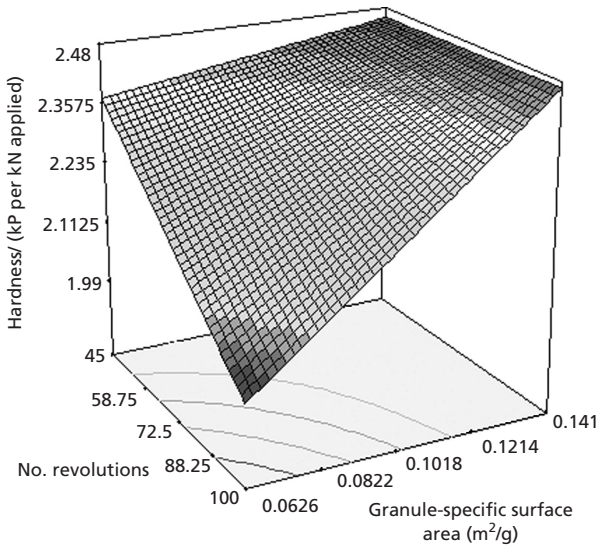

Figure 1 Effect of granule-specific surface area on tablet hardness.

Results The mill speed and screen size were found to have a significant effect on granule properties. Low mill speed and smaller screen size produced granules with minimum fines and good flow properties. A grater-type screen surface (something like a cheese grater, with a bit-shaped surface) generated less fines than a smooth screen surface. Using a mill beater tip-speed calculation, it was possible to produce granules with similar properties at both scales. Three batches of milled granules with various granule-specific surface areas (GSSAs) were compressed to understand the impact of GSSA on tablet hardness. Figure 1 shows tablet hardness as a function of GSSA and blender speed. Coarser granules were sensitive to lubrication and produced softer tablets. However, finer granules had a greater tendency to sticking. This work highlighted the importance of the milling process in producing optimum granules.

Conclusions Optimization of the milling process is important to produce good and consistent granules and tablet properties. The mill speed, screen size and type were found to have significant effect on granule properties. A tip-speed approach was found to be suitable for scaling up the milling process.

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High-performance liquid chromatography method validation for the quantification of tobramycin in urine samples after inhalation using pre-column derivatization with fluorescent 9-fluorenylmethylchloroformate

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Objective A reversed-phase high-performance liquid chromatography (HPLC) method has been developed for determination of tobramycin in urine samples after inhalation of tobramycin. Several previous studies (Essers 1984, Lai and Sheehan 1992, Marples and Oates 1982) used pre-column derivatization with *o*-phthalaldehyde (OPA) but OPA has a poor-stability derivative that results. In this study fluorenylmethylchloroformate (FMOC-CL) was used. Tobramycin was determined following pre-column derivatization with FMOC-CL, which reacts very rapidly with the primary amino groups of tobramycin and other aminoglycosides under mild conditions to form stable derivatives.

Methods Chromatographic separation was carried out on a Phenomenex Luna C_{18} column at ambient temperature using a constant flow rate of 1 mL/minute. The mobile phase was acetonitrile/glacial acetic acid/water (900:2:98, by vol.), and fluorescent detection was at an excitation wavelength of 265 nm and emission wavelength of 320 nm.

Results The assay was linear at seven different concentrations of tobramycin extracted from spiked urine ranging from 0.25 to 3 μg/mL. Tobramycin and neomycin (used as internal standard) were extracted from spiked urine by solid-phase extraction using a carboxypropyl-bonded phase (CBA) weak cation-exchange cartridge and the relative recovery was more than 98% (n = 5). The limits of detection and quantitation in urine were 38 and 115.2 ng/mL, respectively. The intra-day and inter-day precision (in terms of the percentage coefficient of variation) were less than 5.53 and 4.15%, respectively.

Conclusions This assay is simple, precise and accurate and was applied to pharmacokinetic studies to identify the relative lung deposition of tobramycin following inhalation of tobramycin inhaled solution 300 mg per 5 mL (TOBI®) by Pari LC Plus® jet nebulizer.

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Evaluation of nuclear quadrupole resonance for use in pharmaceutical analysis

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Objectives Pharmaceutical analysis increasingly emphasizes the use of spectroscopic methods (e.g. Raman and near-infrared) for the direct analysis of solid dosage forms. In this work we report on the use of nuclear quadrupole resonance (NQR) in this field. NQR is a solid-state analysis technique that shows promise in selective and quantitative pharmaceutical analysis (Balchin et al 2005, Perez et al 2005, Latosinska 2007). We have studied NQR signals due to the ^{14}N and ^{35}Cl nuclei in a range of drug substances and drug products including atenolol, sulfapyridine, furosemide and chlorpropamide, without interference from the excipients.

Methods NQR is a radio frequency technique that is related to the more widely known nuclear magnetic resonance (NMR), but is only applicable to nuclei with a