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Molecular pharmaceutics of drug particles engineered by application of ultrasonication

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Objectives To evaluate the applicability of ultrasonic energy in designing particles with desired properties and to investigate the effect of mechanistic energy on particles using different tools.

Introduction Application of ultrasonic (US) energy in the particle engineering has been reported in last decade. The main advantage of application of US energy is achievement of crystallization at relatively longer degrees of supersaturation. In the sonocrystallization process, nucleation and crystallization steps are significantly altered. The metastable zone is reduced and nucleation occurs at lower degree of super saturation, hence it has been applied in cases of difficult to nucleate systems.

Methods Molten mass of drug was poured in a vessel containing deionized water maintained at 40 °C using cryostatic bath and sonicated for 1 min using probe ultrasonicator at amplitude of 80% and cycle of 0.8 per second. The product obtained after solidification of dispersed droplets were separated by filtration and dried at room temperature. Melt sonocrystallized celecoxib was characterized by saturation solubility, scanning electron microscopy, differential scanning calorimetry, X-ray powder diffraction, infrared spectroscopy, stability study.

Results Melt sonocrystallization was designed for celecoxib, which undergoes fast recrystallization. The particles obtained by melt sonocrystallization were porous, irregular in shape and amorphous in nature. During initial characterization increase in saturation solubility was observed. These amorphous particles exhibited higher stability as compared with particles obtained by melt quenching or even those containing a stabilizing excipient like PVP.

Conclusions The reported melt sonication technique for celecoxib is a promising technique, which may be exploiting in area of particle design but also in preparation of amorphous particles.

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Formulation and evaluation of medicated microemulsion for topical application

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Objective Microemulsion is a clear thermodynamically stable dispersion of two immiscible liquids with carefully adjusted emulsifier(s). It is an isotropic system of infinite stability, usually consisting of four components, which are surfactant, co-surfactant, oil phase and aqueous phase. Only specific components combination can produce a stable transparent microemulsion system. The aim of present investigation was to formulate a stable microemulsion from cheap components suitable for topical application containing suitable non-volatile carrier for indometacin as a model drug with good physical and chemical stability, and of improved bioavailability.

Method After selecting the components, oil (paraffin oil), co-surfactant (sorbitol 70% or glycerol), surfactant (Brij97) and water, preliminary tests were performed starting with preparation of plain mixtures from the chosen components at different volume ratio. Each sample was checked for the production of microemulsion by visual inspection after 24 h of preparation. Microemulsion formulations were then tested for gel formation. The test was performed by tilting the jar containing the microemulsion to an angle of 90°. Those microemulsions that did not show any change in the upper surface after tilting to this angle within few seconds were considered gels, otherwise it was considered a fluid. Pseudoternary phase diagrams were constructed with the results from the gel test and the existence of microemulsion regions were demonstrated. Indometacin was added to the best concentrations of surfactant, co-surfactant, oil and water, which produced microemulsions in gel form (emulgel) in the previous part. The medicated microemulsions were evaluated for physical characters (phase separation, clarity and gel formation), release rate, physical stability (appearance and clarity test, phase separation, centrifugation test, pH testing and rheological properties), chemical stability (Shelf life stability and accelerated stability at 40, 50, 60 °C) and pharmacodynamic activity (percentage reduction of local edema induced in the rat hind paw by the injection of carrageenan as irritant).

Results Fifty-five formulae produced emulgel and were selected to proceed to the next testing procedures. On incorporation of indometacin only four formulae remained stable, clear emulgels and were used for further studies. Release kinetics of indometacin from the four emulgels were determined. The orders of drug release were found to be first order. Physical stability, degradation rate constants and t_{90} of the studied microemulsions showed no significant difference in any of the parameters studied from the samples maintained at room temperature, or under stress ($P < 0.02$–0.05), except a slight increase in pH values especially those samples maintained at 60 °C, and a slight increase in viscosity range. Shelf life of the studied microemulsions would be a minimum of 492 days (1.349 years), and maximum of 712 days (1.952 years). Indometacin significantly inhibits edema, induced in the rat hind paw by injecting carrageenan as irritant, by different percentage. Effect of emulgels were between the effect of commercial injection form (highest effect), and commercial topical form (lowest effect).

Conclusions From the above results we can conclude that microemulsion emulgel formulations prepared with paraffin oil, brij97, sorbitol 70% or glycerol and water showed acceptable physical properties, drug release, stability and pharmacodynamic activity. The best formula of indometacin emulgel consists of (28.8%V/V) Brij97, (3.2%V/V) Sorbitol 70%, (8.0%V/V) paraffin oil and (60.0%V/V) water. This formula shows the highest stability, release rate and gives comparatively superior anti-inflammatory activity.

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The influence of hypromellose on dipyridamole (a slightly soluble drug) release from aqueous ethylcellulose film-coated pellets

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Objectives To investigate the influence of hypromellose based Opadry pore-former on the release of a slightly soluble in water drug, dipyridamole, from aqueous ethylcellulose (Surelease) film-coated nonpareil beads.

Methods Dipyridamole was layered onto a batch of 550–750 μm sugar spheres (NPTAB 650, NP Pharm) in a Glatt GPCG-1.1 fluid-bed fitted with a Würster column and 1-mm Schlick spraying nozzle. Opadry OY-29020 Clear (Colorcon) was used as a binder. Drug-layered pellets were coated with Surelease E-7–19050 (aqueous ethylcellulose (EC) dispersion with oleic acid as a plasticizer, Colorcon) to 2.5, 3.5, 5, 7.5, 10 and 12% weight gain (wg). Drug-layered beads were also coated with dispersions containing various ratios of Surelease to Opadry OY-29020 to 12% wg to modulate the release rate of dipyridamole. Opadry was used as a pore-former to adjust the permeability of the EC film. Drug release was measured from 1 g of coated beads in a Sotax dissolution bath in accordance with the USP monograph for "Dipyridamole tablets" but using Apparatus I (baskets) at 50 rpm. Dissolution medium was 0.1 N HCl at 37 ± 1°C. A dual beam spectrophotometer (Perkin Elmer) was used for the detection of dipyridamole at a wavelength of 283 nm.

Results Drug layered and ER film coated pellets exhibited good appearance, showing no defects in the film coating. Drug release from the EC coated pellets was highly reproducible with standard deviations of less than 1%. The rate of drug release progressively decreased as the coating level increased from 2.5 to 3.5, 5, 7.5, 10 and 12% wg. At 12% wg only 50% of the drug was released after 12 h. Additionally, a lag time developed as the coating level exceeded 5% wg. The inclusion of Opadry as a pore-former into the EC film increased the dipyridamole release rate. For samples containing 20% w/w or more pore-former in the EC coating, 100% of the drug was dissolved after 12 h, compared with only 50% released from the film with no pore-former. The enhanced dissolution rate is due to an increased permeability of the coating. Various mechanisms have been proposed in the literature to describe the increased permeability of an ethylcellulose film containing HPMC. These include increased porosity, channel formation, leaching out of the HPMC, increased hydrophilicity and water mobility within the film. Results also indicated that dipyridamole release rate increased as the Opadry concentration in the coating formulation was increased.

Conclusions It has been shown that incorporation of Opadry at various concentrations into Surelease E-7-19050 (aqueous ethylcellulose dispersion) film can be used to modulate release of a slightly soluble in water drug, dipyridamole.

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Dose emission and aerodynamic characterization of the terbutaline sulphate dose emitted from a turbuhaler at low inhalation flow

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Objective Deaggregation of the total dose emitted from a dry powder inhaler (DPI) into particles with the greatest potential for lung deposition is dependent on the inhalation flow (IF) (Chrystyn 2003). Previously dose emission below 30 L.min^{-1} through a DPI has not been determined. However during routine use some patients do not achieve an inhalation flow of 30 L.min^{-1}. We have therefore

Table 1 The mean (SD) dose emission characteristics

IF (L min^{-1})	10	20	30	40	50	60
TED*	34.0 (7.4)	48.0 (8.3)	56 (11.1)	64.8 (8)	72.4 (14.5)	76.6 (6.4)
FPD*	1.6 (0.8)	1.9 (0.7)	5.9 (2.5)	12.8 (4.3)	24.2 (1.9)	36.5 (5.1)
MMAD#	2.4	4.3	3.4	3.1	2.7	2.5
GSD	3.1	2.2	1.7	1.8	1.9	1.9

*expressed as % nominal dose, # in μm.

adapted the Pharmacopoeia methods to determine dose emission characteristics for low inhalation flows from a terbutaline sulphate Turbuhaler (Bricanyl, AstraZeneca, UK).

Method The total emitted dose (TED) was determined using inhalation flows of 10–60 L.min^{-1} and an inhaled volume of 4 L. The fine particle dose (FPD) and the mass median aerodynamic diameter (MMAD) were determined over flow rates of 10–60 L.min^{-1} using a mixing chamber attached to the modified Andersen Cascade Impactor (ACI) operated at 60 L.min^{-1} with a 4 L inhalation volume. Stage -1 and -0 replaced 0 and 7. For each determination the characteristics of a single dose were determined (n = 10 for TED and n = 5 in the ACI).

Results The TED % (n = 10 doses) and the aerodynamic particle size characterization (n = 5 doses) of the emitted dose of terbutaline sulphate from the Turbuhaler at different inhalation flows are shown in Table 1. The TED and FPD increase significantly with the increase of the inhalation flow ($P < 0.05$). The flows had a more pronounced effect on the FPD than the TED, thus, a faster inhalation increases the respirable amount more than it increases the emitted dose. The MMAD increases with the decrease of the inhalation flow till a flow of 20 L.min^{-1} then it decreases.

Conclusions The in vitro flow dependent dose emission that has been previously demonstrated for terbutaline sulphate in the Turbuhaler above 30 L.min^{-1} (Ross & Schultz, 1996) is more pronounced below this flow. The minimal FPD below 30 L.min^{-1} suggest that during routine use most of the emitted dose will impact in the mouth. The flow dependent dose emission results highlight the need for the Pharmacopoeias to use a variety of inhalation flows rather than one that is equivalent to pressure drop of 4 KPa. The results are consistent with the most desirable inhalation rate for use with the Turbuhaler which has been reported to be 60 L.min^{-1} (Newman et al 1991).

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Effect of pH of the crystallization medium on the physicomechanical properties of carbamazepine crystals

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Objectives The morphology of crystals has an important role in the physicochemical properties of drugs. Drug properties such as flowability, dissolution, hardness and bioavailability may be affected by crystallinity behaviours of drugs (Martin 1993; Nokhodchi et al 2005). Carbamazepine, a drug used routinely in the treatment of epilepsy, has at least four polymorphic forms and a hydrate (Rustichelli et al 1999; Nokhodchi et al 2005). The objective of this study was to achieve an improved physicomechanical property for carbamazepine powder through recrystallization from aqueous solutions at different pH values.

Methods Carbamazapine was recrystallized from aqueous solutions at different pH values (1, 7 and 11) using two different crystallization temperatures. Saturated solutions of carbamazepine in aqueous media with different pH values were prepared at 80 and 25 °C. The saturated solutions were filtered and the filtrates were kept in a fridge at 8 °C for a period of 48 h. The solutions containing carbamazepine crystals were filtered and dried. The physicomechanical characteristics of the recrystallized carbamazepine were studied as follows: the morphology of crystals was investigated using scanning electron microscopy, X-ray powder diffraction (XRPD) was used to identify polymorphism, the thermodynamic properties were analysed using differential scanning calorimetery (DSC), and dissolution and mechanical behaviours of the crystals were also studied.

Results The SEM studies showed that the crystallization of carbamazepine in different media affected the morphology and size of carbamazepine crystals. According to the SEM, the shape of carbamazepine crystals changed from flaky or thin plate-like to needle shape in all recrystallized samples. The pH of crystallization medium had no significant effect on the crystal shape. XRPD and DSC results showed that the original carbamazepine sample was form III, with no changes occurring under the temperature and pH of crystallization media. The crushing strength of tablets made of different carbamazepine samples indicated that all of the recrystallized carbamazepine samples had better compactiblity than the original carbamazepine powder. *In vitro* dissolution studies of carbamazepine samples, where similar particle sizes were used, showed a higher dissolution rate for carbamazepine crystals obtained from medium with pH 11.

Conclusions Carbamazepine particles recrystallized from aqueous solutions with different pH values appeared to have superior mechanical properties to original carbamazepine sample. This might be due to different morphological structure of carbamazepine samples. The pH of crystallization medium had significant effect on dissolution rate of carbamazepine powders and samples obtained at pH 11 showed a higher dissolution rate in comparison with other recrystallized and original carbamazepine samples.

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Development and in vitro evaluation of osmotically controlled oral drug delivery system of metformin hydrochloride

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Objectives The objective of this research work was to develop and evaluate controlled porosity osmotic pumps for extended delivery of metformin hydrochloride. The aim was to reduce frequency of drug administration and reduce side effects associated with the use of immediate release dosage form, for treatment of type II diabetes. The developed formulation should provide similar release profile as compared with the innovator product, marketed by Andrx Laboratory, USA, which is a laser drilled osmotic pump.

Methods Metformin hydrochloride core tablets of 1000 mg and 500 mg were prepared using standard set of excipients by wet granulation technique. Tablets were coated with different coating formulae to optimize the ratio film former (cellulose acetate) and pore former (sorbitol) using Dichloromethane and Methanol (50:50) mixer as a solvent. Concentration of plasticizer (PEG 400) was optimized. Different formulation variables like weight gain of coat and amount pore former in the coating membrane were studied and optimized to achieve the target release profile. The performance of the optimized formulation was evaluated in media with different pH of 1.2, 4.6 and 6.8. To study the effect of agitational intensity Study-I was conducted under different RPM (50, 100 and 150) and Study-II conducted under stirring and stagnant condition. To establish the mechanism for release of drug, dissolution was conducted in media with different osmotic pressure (0, 15, 30 and 45 atm).

Results The used excipients were found compatible with metformin hydrochloride. Release of metformin from developed formulation was inversely proportional to the membrane weight gain, but directly related to the amount of pore former in the membrane. Drug release was independent of pH and agitational intensity, but dependent on the osmotic pressure of the dissolution medium. Metformin release followed zero order. Results of scanning electron microscopy showed the formation of pores in coating membrane after coming in contact with dissolution media and numbers of pores dependent upon amount of sorbitol in coating membrane. The drug release occurred through these pores and release was controlled by numbers of pores. The f_1 (Difference factor) and f_2 (Similarity factor) values were found to be 7.59 and 63.02, respectively for 1000 mg and 6.89 and 66.53, respectively, for 500 mg formulations, taking release profile of Fortamet 1000 mg and 500 mg as reference, respectively. The manufacturing procedure was found to be reproducible. Formulation was stable after 3 months of accelerated stability study.

Conclusions The developed system was simpler in design, required less number of manufacturing steps as the developed system and did not requires costly and highly sophisticated laser drilling equipment. The manufacturing procedure was economical and easily amenable to mass production. The developed formulation provided similar invitro release profile as compare to Fortamet. Taken together these results demonstrated that controlled porosity osmotic pumps of metfromin hydrochloride were developed successfully and might be a promising approach for extended delivery of drug. Nevertheless, significant work still needs to be carried out to elucidate the in vivo performance of developed formulations.

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Development, characterization and in vitro release of atenolol nanoparticles

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Objectives Nanoparticles of atenolol (antihypertensive agent) were prepared with an aim to improve absorption and to increase bioavailability. The drug nanoparticles were prepared using double emulsion solvent evaporation method (DESE), using ethylcellulose (EC) as a carrier. The drug nanoparticles were evaluated for their suitability.

Methods DESE method involves the dispersion of the aqueous solution of atenolol in a solution of ethylcellulose in dichloromethane. This forms a *w/o* emulsion, which is further dispersed in aqueous poly vinyl alcohol (PVA) solution. Thus, *w/o/w* emulsion was formed, from which dichloromethane was subsequently evaporated. The process variables such as different equipments (Servodyne mixer head stirrer, high speed homogenizer and sonicator), agitation, temperature and evaporation conditions were optimized. The nature of the polymer, copolymer, and volumes of the aqueous and organic phases were evaluated. The average particle size, percent nanoparticles, percent yield, encapsulation efficiency and drug content were studied. For the optimized batch, the surface morphology was studied by transmission electron microscopy (TEM). *In vitro* release studies were carried out.

Results The particle size could be controlled well by varying the mechanical forces required to produce w/o/w emulsion. Sonication method was found to be appropriate with the optimum percent of nanoparticles (81.19 ± 12.6) and mean particle diameter was 201 ± 24 nm. Optimum entrapment efficiency (56.27 ± 4.23) was obtained, when inner aqueous phase volume is high (3 mL). PVA was found to be suitable surfactant with optimum percent yield (89.47 ± 4.9) and with optimum drug content. Higuchi's diffusion model gave the best fit for the release of atenolol. The TEM photographs revealed that the particles have diameter less than 200 nm and the surface was smooth.

Conclusions Atenolol nanoparticles were prepared successfully by DESE technique using EC and PVA. The *in vitro* release of drug was promising to encourage the *in vivo* studies for their possible use of atenolol by oral route.

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Accelerated ageing of gamma-irradiated, lyophilised wafers containing an insoluble API

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Objectives To investigate the particle size stability of an insoluble API when formulated as a lyophilised wafer and exposed to a sterilising dose of gamma-irradiation. Lyophilised wafers have been developed as stable and practicable solid dosage forms for the topical application of both soluble and insoluble APIs directly to the surface of chronic wounds (Matthews et al 2006).

Methods A gel suspension of an insoluble API was prepared and cast to suitably sized and shaped moulds. Following an engineered freeze-drying cycle, the wafers were irradiated with a significant dose of gamma-rays (40 kGy) with a view to producing a sterile dosage form suitable for use as a wound management product. The final product was subjected to an accelerated ageing process (12 weeks at 40 °C) and characterised at intervals of 0, 3, 6 and 12 weeks by laser light scattering (Malvern Mastersizer S). A sample of the mother suspension from which the wafers were produced was kept and subjected to the same ageing conditions as the irradiated and non-irradiated wafers. Particle sizing of the API contained in the wafers was undertaken in a small sample dispersion cell following reconstitution of the pre-lyophilised gel suspension by the addition of volumetric amounts (2 mL) of deionised water to the wafer.

Table 1 Mean particle size (plus standard deviation) of API in aged wafers (40 kGy/40°C/12 weeks) and mother suspension (40°C/12 weeks)

Time (weeks)	Irradiation (kGy)	Mean particle size (μm)	
		Wafer	Suspension
0	0	47.5 (0.7)	47.5 (0.7)
	40	46.5 (0.4)	—
3	0	—	52.5 (1.7)
	40	47.2 (1.2)	—
6	0	48.6 (0.9)	59.2 (4.4)
	40	46.2 (1.3)	—
12	0	48.0 (0.8)	62.0 (0.5)
	40	46.0 (0.7)	—

Results A brief summary of the particle size analyses are presented in Table 1. Accelerated ageing of irradiated wafers containing the API for 12 weeks at 40 °C, produced mean particle sizes, D[4,3], from 46.0 (± 0.7) to 47.2 (± 1.2) μm. These sizes were significantly smaller than those of the API contained in the non-lyophilised mother suspension where changes in distributions between time zero and 12 weeks were accompanied by an increase of 14.5 μm in the mean particle size.

Conclusions Accelerated ageing of gamma-irradiated wafers containing an insoluble API resulted in no significant change in the particle size distributions of the API. De-stabilising processes such as Ostwald ripening and drug particle agglomeration may explain the changes to particle size distributions evident in non-lyophilised, aged suspensions.

Matthews, K. H., et al (2006) *Int. J. Pharm.* **313**: 78–86

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The influence of spray drying on the physical properties of hydroxypropyl cellulose and hypromellose

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Objectives To investigate the influence of a spray drying process on the physical properties of two cellulosic polymers; hydroxypropyl cellulose (HPC) and hypromellose (HPMC). HPMC and HPC are water soluble hydrophilic polymers commonly used as controlled release agents in formulation development. Spray drying is an established process used in the pharmaceutical industry to produce fine powder particles with a controlled particle size. Modified properties of spray dried polymers may offer advantages to their function as controlled release agents.

Methods Aqueous solutions of HPMC (Methocel K100LV, Methocel E50LV, and Methocel E15LV) and HPC (Klucel GF, JF and LF) of various concentrations were prepared. The impact of temperature on the viscosity of each solution was determined. Solutions were spray dried using a Lab Plant spray drier. The influences of polymer concentration, solution viscosity and solution temperature on the physical properties of the spray dried polymers were determined. Polymer particle size and surface appearance were determined using scanning electron microscopy and light microscopy. Thermogravimetric Analysis (TGA) was used to determine moisture content of spray dried samples. Bulk and tapped density of the spray dried and the gelling potential of spray dried material were determined by measuring the viscosity of aqueous solutions of spray dried material and comparing these with aqueous solutions of standard materials. The physical properties determined for spray dried material were compared with those for non spray dried polymer powders.

Results Viscosity measurements of HPMC and HPC aqueous solutions showed that heating reduced viscosity. The viscosity of the polymer solution impacts the spray drying process by reducing flow rate and affecting atomisation. Polymer concentration improves process yield but increases solution viscosity. For this reason low concentrations (5%w/w) of K100LV HPMC may be used for spray drying. However, solution viscosity may be reduced by holding the solution at higher temperature during spray drying. This enables higher polymer concentrations to be used without compromising solution flow rate and atomisation. Spray dried HPMC has a higher porous surface compared with non-spray dried HPMC powder. Higher viscosity solutions produce materials with a larger particle size than lower viscosity solutions. Particle size of spray dried polymer material may be influenced by solution viscosity.

Conclusions Spray dried HPC and HPMC have different physical characteristics compared with non spray dried polymers. The modification in particle size and surface appearance could be used to improve the effectiveness of these materials as modified release pharmaceutical agents.

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Confocal laser scanning microscopy as a methodology to explore the effects of a model drug series on HPMC hydrophilic matrices

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Objectives Hydroxypropyl methycellulose (HPMC) is a widely used hydrophilic carrier material for matrix tablets with the aim of providing sustained release.

Incompatibilities between HPMC and drugs are known within the literature (Mitchell et al 1993), yet the mechanisms by which drugs disrupt the HPMC extended release capability have yet to be elucidated. Using a recently developed confocal laser scanning microscopy technique (Bajwa et al 2006), we have investigated the effect of a model drug series on initial HPMC gel microstructure, which is hoped will provide an insight into the nature by which these drugs interact with HPMC.

Methods 8 mm tablets (200 mg) containing various percentages of HPMC (E4M), a model drug series (diclofenac sodium and meclofenamate sodium) or a control substance (silicon dioxide) were manufactured to a constant compression force using an F3 Manesty Instrumented tablet press. The tablets were held between two clear Perspex discs, allowing imaging from above using a Bio-Rad MRC 600 confocal microscope. Tablets were hydrated in aqueous 0.008% Congo red, maintained at 37 °C. Congo red is known to fluoresce when bound to hydrated cellulose, the backbone of HPMC and thus allows a fluorescent image of the tablet to be obtained as hydration proceeds.

Results The results suggest the differing effects that members of this group have on the early HPMC microstructure, with a more rapid swelling being observed for meclofenamate sodium compared to diclofenac sodium and silicon dioxide. The clearest differences are shown in tablets containing 80% drug. Lower drug loadings showed little effect on either swelling or morphological features of the nascent gel layer. Diclofenac sodium appeared to suppress HPMC swelling compared to silicon dioxide. This may be suggestive of a mechanism by which diclofenac progressively "salts-out" the polymer, restricting hydration and subsequent gelling of the polymer. In contrast, meclofenamate appears to encourage polymer hydration and swelling, which manifests as a rapidly growing, yet more diffuse gel layer. Results with silicon dioxide suggest that dilution of the HPMC alone has an effect on the gel layer, although the microstructure appears to be more coherent than that of meclofenamate.

Conclusions The value of this technique in exploiting the capabilities of confocal microscopy to image the emerging gel layer in a model tablet system has been demonstrated. It has allowed repeatable measurements of the emerging gel layer to be made, and investigation of the effects of a model drug series on the rate of swelling and morphological development to a high temporal and spatial resolution. The effects on early gel layer formation may manifest in changes in drug release from hydrophilic matrices, particularly where the drug loading is high. The information obtained from the imaging techniques provides no insight into the physical composition and nature of the gel layer formed, thereby limiting the study.

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Mechanisms of dielectric relaxation in freeze-dried disaccharides and the potential significance to the stability of freeze-dried products

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Objectives Measurements of dynamics below the glass transition are thought to provide some indication of the physical stability of a product (Alie et al 2004). Excipients, such as dissacarides, are used routinely in lyophilised product formulation and there is some understanding of the mechanisms of sub-Tg relaxation in these materials (Kaminski et al 2006). This paper aims to examine the mechanisms of relaxation in amorphous dissacharides (through structure-activity relationships), to establish the sensitivity of sub-Tg relaxations to moisture, and to speculate as to the significance of these findings in the context of product stability.

Methods Disaccharide lyophiles (lactose, trehalose, sucrose and maltose) of different moisture content were measured using a Solartron-1296 dielectric interface connected to a Solartron-1255 frequency response analyser. The frequency and temperature ranges investigated were 0.1 Hz–1 MHz and −120 °C to 60 °C, respectively.

Results All four types of disaccharides revealed two sub-Tg processes at low moisture content (<3%) which merge at higher moisture content (>5%). Each relaxation was fitted to the Havriliak-Negami function, and the temperature dependency of the fit parameters (including the activation energy, δH, and the Fröhlich parameter, B) was examined. The wing of a 3rd process was also observed for each material towards high temperature (>0 °C) and low frequency. The mechanism of the *first relaxation process* (at low temperatures) was ascribed to the rotation of the pendant hydroxymethyl group on each sugar ring, as evidenced by the greater volume density of hydroxymethyl groups on sucrose and an associated increase in dielectric strength observed for sucrose (as compared to the other dissacharides). *The second process* (at intermediate temperatures) is thought to be a Johari-Goldstein process associated with segmental rotations of the ring (Kaminski et al 2006). An increase in water content has a dramatic effect on process 2, whereas process 1 is much less affected. This is consistent with the sensitivity that the dynamic glass transition has to moisture and the emerging role that Johari-Goldstein processes have in the dynamic glass transition. Further evidence for and against the mechanisms for the first and second processes (in particular changes in δH and B(T)) will be discussed. In some materials (lactose especially) *the third process* splits into two separate processes. One of these processes is due to the self-diffusion of charge carriers over the surfaces of crystallites within an otherwise amorphous matrix (discussed in a related abstract) and the other process is the dynamic glass transition (or α-process). The 'peak' frequency of the latter shows a strong dependence on moisture, which is consistent with the influence of moisture on the calorimetric glass transition temperature determined by DSC.

Conclusions It is proposed that the particular sensitivity of the second β-process (assumed to be a Johari-Goldstein process) to the moisture content of the material is significant in the context of which molecular degrees of freedom underpin the physical instability of amorphous materials (such as devitrification).

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Dielectric properties of lactose monohydrate: mechanisms of relaxation and the influence of particle size and hydration water

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Objectives Dielectric spectroscopy is particularly sensitive to dynamics and structure at the level of the mesoscale and so finds many applications in the characterization of various types of porous and/or granular materials (Feldman et al 2006). This study investigates the dielectric properties of lactose monohydrate as a function of particle size and hydration, and aims to elucidate mechanisms underlying the observed dielectric response.

Methods A batch of lactose monohydrate BP (EuroPharma) was sieved through a cascade of 45, 80, 120 and 200 mesh sizes to produce fractions with nominal particle sizes of 350, 180, 125 and 75 μm, respectively. The samples were equilibrated for 24 h at various %RH, to adjust the surface moisture content, prior to dielectric measurement between 0.1 Hz–1 MHz and temperatures of −50 and +100 °C (+/−1 °C). Dielectric data is presented in both frequency domain and by time domain correlation functions (derived from each spectrum by inverse Fourier transform). The correlation function was fitted with a stretch exponential function to give the relaxation time (τ) and stretched exponent (υ), from which the fractal dimension was calculated ($D = 3\upsilon$).

Results A sharp percolation peak (process 1) was observed for all size fractions and centred within the temperature range: 5–30 °C. At higher temperatures, the wing of a second process is observed (process 2), again for all size fractions. The amplitude of process 1 was independent of particle size but strongly dependent on surface moisture content (with the peak disappearing on drying), whereas the amplitude of process 2 remains almost unaffected both by the loss of both the surface moisture and the crystal hydrate water. The percolation temperature of process 1 is linear with the square of the nominal particle size of the sieve fraction, but independent of surface moisture concentration. The fractal dimension associated with process 1 correlates with the amplitude of the process, with values for amplitude increasing gradually as the value of D increases from 1.5 to 1.95 (corresponding to the percolation fractal developing from one dimension to a two dimension). Thereafter (i.e. when the surface coverage is monolayer, or greater, and $1.95 < D > 2.25$) the amplitude of the process increases dramatically as percolation is assisted between particles and hence charge transport propagates throughout the whole sample.

Conclusions Together these observations confirm that the underlying charge transport mechanism of process 1 is associated with surface percolation within the external surface hydration layer of the particles, whereas process 2 probably originates within the volume of the particles. Further higher temperature studies are required to confirm the exact characteristics and underlying mechanism of process 2. Through the careful control of moisture content, various applications for monitoring particle size, surface topography and structure (e.g. crystal defects) are envisaged. For example, in a separate abstract we present data showing the sensitivity of the technique to the presence of adsorbed amorphous material.

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Dielectric properties of mixtures of amorphous lactose and crystalline lactose monohydrate

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Objectives Dielectric spectroscopy is able to measure mesoscale phenomena such as the percolation of delocalised charge carriers (e.g. protons from surface water) in

porous and/or granular systems, and can therefore be used to map out certain structural and topographical features of the material (such as porosity, grain size and surface properties) (Feldman et al 2006). This study investigates the dielectric properties of lactose monohydrate with addition amorphous material in order to demonstrate the possibility for detecting amorphous material at the interfaces of an otherwise crystalline material.

Methods Lactose monohydrate was mixed with amorphous lactose (prepared by freeze-drying) in ratios between 9:1 and 1:9 and the samples agitated to distribute the amorphous phase within the crystalline phase. Other samples with some amorphous content were prepared by milling lactose monohydrate crystals and recovering the sieve fraction ~75 μm. Dielectric measurements between 0.1 Hz–1 MHz and temperatures of −50 and +100 °C (+/−1 °C) were taken immediately after preparation. Additional measurements were taken on the pure crystalline material.

Results Two processes are observed for the crystalline material: a sharp percolation peak (process 1) centred on 20 °C and the wing of a second process located at higher temperatures (process 2). On addition of amorphous material, the percolation temperature of process 1 (T_p) shifts to higher temperature and is reduced significantly in magnitude (For example, $T_p > 45$ °C, and ε' at 0.1 Hz reduces from ~1600 to 35 on addition of 10% amorphous material). The micronised material also displays a characteristic percolation peak but in addition a separate dielectric relaxation process was observed which has the characteristics of pure amorphous lactose. This additional process was also observed in the mixtures. From separate measurements on pure amorphous lactose, and from the mixtures of amorphous and crystalline lactose measured here, it was demonstrated that the height of the relaxation peak in the micronised material was consistent with an amorphous loading of 8%. It is suggested that the increase in the percolation temperature and reduction in the magnitude of the peak is a result of the impact of the amorphous phase located at the interfaces between particles, which increases the energy requirements for charge hopping between particles (hence shifting the temperature) while reducing the frequency and hence number of charge transport events and thereby reducing the size of the induced macroscopic dipole moment (hence the significant reduction in magnitude of process 1).

Conclusions These observations and those reported elsewhere support the suggestion that the two processes are associated with the percolation of charge carriers (e.g. protons) across the external and internal surfaces of the particles, respectively. Process 1 is shown to be very sensitive to low levels of a surface amorphous phase. Further work will be presented on the detection limit of the amorphous phase.

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Formation of cefuroxime axetil nanoparticles through rapid expansion of supercritical solutions (RESS)

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Objectives Many pharmacuetical substances are often insoluble or only slightly soluble in aqueous media and the application of oral or injectable drug is often limited by this solubility and so, bioavalibility of the drug is low compared with initial dose. Cefuroxime axetil (1-acetoxy ethyl ester) is a cephalosporin antibiotic, possessing a high activity against a wide spectrum of gram positive and gram negative micro-organisms, which has this problem. According to the Osward-Freundlich and Noyes-Whitney equation, solubility and dissolution rate of a drug can be increased by reducing the particle size to increase the interfacial surface area (Zhang et al 2006). As the rapid expansion of supercritical solutions (RESS) has provided a promising alternative to produce contaminant-free submicron particles of heat sensitive materials (Huang et al 2005; Thakur & Gupta 2006), it was decided to produce cefuroxime axetil nanoparticles through this method.

Methods High purity carbon dioxide was supplied from a gas cylinder.then the gas was liquefied through a cooler and pressurized to the 3000 psi pressure, by means of an HPLC pump. Then the CO_2 entered the extraction vessel which contained cefuroxime axetil powder (the temperature of the extraction vessel was accurately controlled). Then the supercritical solution passed the pre-expansion part (with constant temperature of 105 °C), and expanded through a nozzle with constant diameter, and the particles were collected on a filter. In this study we examined the temperature of extraction vessel and the nozzle temperature on the obtained particles.

Results As it summarized in Table 1, the different experimental condition had significant effect on particle size. X-ray diffraction showed that particles obtained were amorphous. The dissolution test showed a significant increase in dissolution rate compared with unprocessed powder. SEM showed the morphology of the particles.

Conclusions This study showed that rapid expansion of supercritical solutions (RESS) can significantly improve physical characteristics of the particles of cefuroxime axetil and hence increase the bioavailability of drug.

Table 1 Different experimental conditions and results for the cefuroxime axetil RESS processes

Sample	Tnozzle (°C)	Textraction (°C)	Average particle size (nm)
Original	—	—	15873
D	50	60	216.81
E	50	75	440.34
F	50	90	437.76
G	60	60	277.26
H	60	75	326.37
I	60	90	158.57
K	70	60	264.75
L	70	75	513.18
M	70	90	333.11

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Enhanced drug release of ciprofloxacin dental implants: an impact by surfactant

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Objectives The objective of the study was to formulate and improve drug release of ciprofloxacin-carbopol dental implants using surfactant pluronic F 127.

Methods The dental implants were prepared by using 3^2 factorial design employing carbopol polymer with pluronic F 127 surfactant along with plasticizer glycerol by solvent casting technique with the aid of aluminium foil. The amount of drug and polymer used were 10%, 15% and 20%, respectively, while keeping the amount of surfactant constant. The parameters studied were folding endurance, content uniformity, bioadhesive force, patch thickness, *invitro* drug release, FT-IR interaction and stability studies.

Results It was observed that folding endurance of all formulation was greater than 400. The dental implants showed drug uniformity equally at various points. Bioadhesive force of 657 ($\times 10^2$ kg $m^{-1}s^{-2}$) was recorded for formulation containing 20% of polymer and 10% of ciprofloxacin. The implant thickness significantly increased with an increase in the amount of polymer used. Formulation containing 10% of carbopol and 10% ciprofloxacin showed low thickness of 0.951 mm while high thickness of 2.131 mm was observed for formulation containing 20% carbopol and 20% ciprofloxacin. In time, a marked rise in the release rate from carbopol implants was observed. The extent of ciprofloxacin *invitro* release within 1 h from 10% and 20% formulae was 47.3 and 39.6%, respectively. FT-IR studies suggest no chemical interaction between carbopol, ciprofloxacin and the surfactant. Dental implants were stable when kept for short-term studies in accordance to the ICH guidelines.

Conclusion The present study reveals the applicability of ciprofloxacin implants to treat dental disorders. Carbopol was found to increase the bioadhesive force of dental implants. The *invitro* drug release can be significantly improved with the amount of surfactant irrespective of high concentration of the carbopol.

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Sustained release sodium alginate microspheres formulation of aceclofenac and paracetamol as potential combination therapy in arthritis

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Objective Development and evaluation of alginate microspheres as drug carrier to reduce dose and dosing frequency of aceclofenac and paracetamol in the management of arthritis, which otherwise demands prolonged treatment.

Methods Alginate microspheres loaded with aceclofenac and paracetamol were prepared by emulsification method. Both agents were either co-entrapped in a single microspheres formulation or individually entrapped in two separate microsphere formulations. Microspheres were formulated using drug to polymer ratio with in the range of 1:1 to 1: 10. This method consists of aqueous phase and oil phase having sodium alginate and drug, liquid paraffin and span 80, respectively. Aqueous phase

was dispersed into oil phase by continuous stirring at 800–1200 rpm for 2 h followed by the addition of 7.5% calcium chloride solution as a cross linking agent. Microspheres were collected by filtration and finally washed with n-hexane and dried. The entrapment efficiency of the microspheres was determined using simple liquid extraction method. A known amount of microspheres were dissolved in suitable medium (phosphate buffer pH 6.8 or ethanol) by using ultrasonic water bath for three consecutive periods of 20 min with 60 min of rest in between. Sample was left to stand overnight at 28–30 °C, filtered using 0.45 mm filter and drug content was analysed spectrophotometrically at 273 nm, 276 nm (accelcofenac) and 243 nm, 249 nm (paracetamol), respectively, for each medium. The microspheres were further coated with Eudragit RS 100, RL 100 and S 100 to sustain the drug release. The in vitro release studies were performed at 50 rpm in different dissolution medium (pH 1.2, phosphate buffer pH 6.8 and 7.2) at 37 ± 0.5 °C using USP dissolution apparatus II. The optimized microsphere formulation was characterized by infrared spectroscopy, differential scanning calorimetry and scanning electron microscopy.

Results Entrapment efficiency of microspheres loaded with aceclofenac and paracetamol individually in separate formulation and aceclofenac and paracetamol in one formulation was found to be 80–95%, 70–60% and 60–75%, respectively. The prepared microspheres were spherical in shape. Uncoated microspheres had a size range of 20–80 mm but coated microspheres had a larger size than the uncoated microspheres. The drug release from uncoated alginate microspheres was rapid. Coating these microspheres with Eudragit polymer retarded the drug release in all the mediums used. The drug release from the optimized formulation was sustained for 8–12 h. The infrared spectrum and thermogram showed stable character of drugs in the microspheres and revealed an absence of drug polymer interaction.

Conclusions Emulsification technique was successful in producing aceclofenac and paracetamol microspheres. The formulation variables (i.e. drug percentage, polymer content, volume of oil phase used and speed) influenced the microencapsulation efficiency, micrometrics and in vitro drug release characteristics of the prepared microspheres. The developed formulation could be a promising combination drug delivery system in the management of arthritis.

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Nanoparticle preparation of indometacin using high pressure carbon dioxide

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Objectives The objective of this study is to demonstrate a new method for preparing nanocrystals of an active pharmaceutical ingredient using a continuous system with high pressure carbon dioxide (CO_2).

Methods An improved system using both supercritical antisolvent precipitation and rapid expansion from supercritical to aqueous solution (RESAS) was used in order to overcome the problem of low solubility of medicinal substances in supercritical CO_2. Indometacin (IMC) was used as a model compound. A solution of IMC in ethanol at specific concentrations was purged into supercritical CO_2 and then expanded into water. The suspension was freeze dried, thereafter the properties of the resulting powder were evaluated by particle size distribution analysis, X-ray diffractometry, differential scanning calorimetry and scanning electron microscopy.

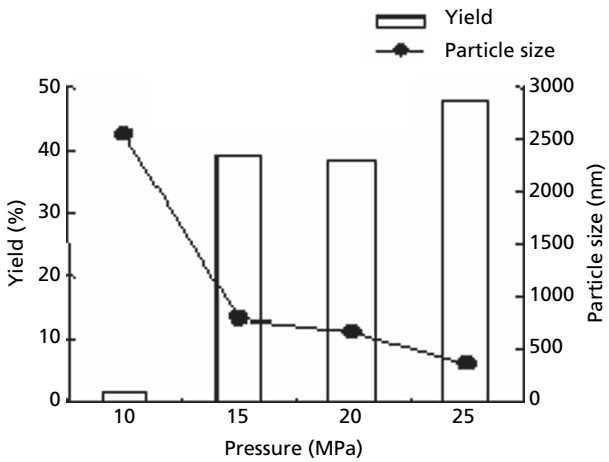

Figure 1 Changes in the particle size and yield of indometacin under various CO_2 pressures and temperatures in the vessel.

Results When the ethanol solution with IMC was sprayed into the vessel purged with supercritical CO_2, IMC was precipitated at a relatively low CO_2 pressure (less than 10 MPa at 40 °C). On the other hand, no precipitation of IMC was observed if the CO_2 pressure was more than 15 MPa at 40 °C. This indicates that the ethanol solution with IMC dissolves in the high pressure CO_2. After expansion into distilled water using an RESAS device, this same solution, in CO_2 at high pressure, produced nanocrystals of IMC. The average particle size of IMC depended significantly on the pressure and temperature in the vessel (Figure 1). It was found that 25 MPa at 40 °C was an optimal condition for this apparatus to create nanoparticles of IMC (ca. 350 nm). SEM images showed that the freeze-dried samples of the suspension were composed of submicron particles. Using X-ray diffractometry and differential scanning calorimetry, these crystals were found to be a metastable form of IMC. Interestingly, the freeze dried sample disperses well into an aqueous solution as nanocrystals.

Conclusions This apparatus produces fine crystals of indomethacin with a high yield. The freeze dried sample of the indometacin suspension showed good redispersibility as a nanosuspension.