monohydrate (94.4%) (Borculo Whey Products, Cheshire, UK) and β-lactose (86%) (Sigma-Aldrich, UK) (Chidavaenzi et al 1997). The anomeric composition of crystalline and amorphous lactose was determined by Gas Chromatography (Dwiwedi & Mitchell 1989). Solution calorimetry data were collected as described by (Hogan & Buckton 2000). Partially amorphous samples were prepared by directly weighing proportional masses of crystalline and amorphous lactose (prepared from that crystalline batch) into glass-crushing ampoules. The mass of the crystalline component was kept constant in all the mixtures (200 ± 0.01 mg) and an appropriate amount of spray-dried material was added to make 1, 3 and 5% amorphous samples. In the same way, in the perfusion experiments the 1, 3 and 5% amorphous samples were directly prepared into the calorimetric ampoule, using 50 ± 0.01 mg of the crystalline component. Calorimetric data were recorded using a 2277 Thermal Activity Monitor (TAM; Thermometric AB, Sweden) at 25°C equipped with a gas perfusion unit. The following RH programme was used: 0% for 5 h, 95% for 15 h and 0% for 5 h. The determined enthalpies of solution and crystallisation for each of the analysed samples are shown in Table 1. For the perfusion data, the samples prepared from β-lactose returned a higher heat output, which could have been due to mutarotation of β-lactose to α-lactose. On the solution calorimetry experiments samples prepared from α-lactose monohydrate returned a higher enthalpy of solution, as α-lactose monohydrate exhibits a higher enthalpy of solution than β-lactose. Calibration curves were constructed by plotting the heat of crystallisation and solution versus the known amorphous content. Due to the differences in the measured enthalpies for the different samples, the calibration curves were shown to be significantly different for the two batches, for each of the techniques. Thus it is shown that quantification of the amorphous content of a processed sample of unknown anomeric composition would be problematic, unless the calibration curve is prepared from the same batch of material as the processed sample.

Table 1 Enthalpies of solution and crystallisation of partially amorphous samples, as determined by solution calorimetry and isothermal calorimetry

Amorphous % (w/w)	Solution calorimetry H_{sol} (J g^{-1}) ± s.d. (n = 3)		Isothermal calorimetry H_{cryst} (J g^{-1}) ± s.d. (n = 3)	
	Prepared from α-lactose monohydrate	Prepared from β-lactose	Prepared from α-lactose monohydrate	Prepared from β-lactose
1	55.17 ± 0.06	5.75 ± 0.12	2.0 ± 0.1	10.0 ± 0.3
3	53.28 ± 0.04	4.21 ± 0.04	5.5 ± 0.3	12.5 ± 0.7
5	50.71 ± 0.02	2.76 ± 0.25	9.8 ± 0.2	16.3 ± 0.7

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Poster Session 2 – Pharmaceutical Technology

127
Effect of drying process on the stability of four Thai herbal capsules

W. Saohin, P. Boonchoong and B. Sethabouppha

Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Warin Chamrap, Ubon Ratchathani 34190, Thailand. E-mail: saohin@hotmail.com

Capsules are one of the most popular dosage forms of herbal products. The main manufacturing process is drying the fresh ground plant until it reaches appropriate moisture content. Dried powder is then filled into the capsules. As most herbal capsules do not contain any other excipients, such as filler and glidant, drying condition is crucial for the quality of capsules, which depends upon the flow ability of dried powder. The drying process also provide a suitable moisture content that limits the growth of contaminating microorganisms. This work aimed to study the effect of the manufacturing process, in particular the drying temperature and moisture content, on the physical, chemical and microbiological stability of four Thai herbal capsules, including ginger (*Zingiber officinale*), turmeric (*Curcuma longa*), Chum-het-thet (*Cassia alata*) and Fa-tha-li (*Andrographis paniculata*). In the first experiment, fresh herbs were collected from the Ubon Ratchathani region. The herbs were ground and dried at three different temperatures until their moisture content was below 10%. The content of the active ingredient in each plant after drying was analysed and the drying temperature that gave the highest amount was chosen. The second experiment involved selecting the appropriate moisture content for manufacturing herbal capsules. The procedures were similar to those of the first experiment except that only one suitable drying temperature was used. The drying process was carried out until the moisture content of the powder fell to one of three levels (4.0, 4.1–7.9 and 8.0–10.0%). The dried powders with different moisture contents were tested for flowability (angle of repose and compressibility), the amount of active ingredient and the contamination of microorganisms. Capsules were also tested for their quality, including weight variation and disintegration time. It was found that the optimum drying temperature and moisture content (MC) for the highest remaining active compounds of each herbal capsule were: 60°C, 6–7% MC (*Zingiber officinale*); 55°C, 8–10% MC (*Curcuma longa*); 50°C, 8–10% MC (*Cassia alata*); 60°C, 8–10% MC (*Andrographis paniculata*). All samples were found to be contaminated with microorganisms, suggesting that a final product sterilisation process would be required. Further investigations on the accelerated and long-term stability studies of these herbal capsules and also the methods to improve their stability in these three aspects are in progress.

128
Measurement and modelling of granule friability

N. MacPhail, S. Fitzpatrick, I. C. Sinka and P. Rajniak[1]

Merck Sharp and Dohme, Hertford Road, Hoddesdon, Herts EN11 9BU, UK and [1]Merck and Co Inc., Sumneytown Pike, West Point, PA 19446, USA. E-mail: neil_macphail@merck.com

Pneumatic Conveyance systems are used within pharmaceutical manufacturing sites to transport granular materials. Granule attrition can occur during the dilute phase transfer of materials, which can reduce the particulate d_{50} by as much as 50% (Chapelle et al 2004). Under-lubrication can occur post pneumatic conveying due to a large increase in the granule surface area, which can produce tablet elegance issues. Using an early phase friability model to understand the mechanical effects of conveying upon granules will reduce granule robustness issues upon scale-up. The particle size distribution (PSD) of a powder system is routinely measured by laser diffraction using benchtop equipment, such as the Malvern Mastersizer (Malvern Instruments, Malvern, UK). The apparatus is provided with a dry powder feeder. The powder under test is fed using a vibrating feeder then suspended by a jet of compressed air. Increasing the air jet pressure has been shown to produce a proportional increase in volumetric surface area. It is hypothesized that more friable granules would have a larger change in surface area with jet pressure, and from this a quantitative measure of the granule friability has been developed. Granule samples have been sized using the Malvern Mastersizer, producing a linear increase in volumetric surface area between feed air jet pressures of 0.5–2 bar. The particle size data has been evaluated using a breakage model to evaluate the breakage rate constant S_i. The breakage rate constant can be correlated with the volumetric surface area, with both showing a linear increase in relation to change in air jet pressure. Table 1 shows an example correlation of volumetric surface area with breakage rate constant. Fluent 6.1 computational fluid dynamics software has been used to develop a 2-D model for solid and gas movement within the Malvern Mastersizer. This has been used to determine the shear rate within the dry powder feeder. By running the model using the equivalent air jet pressures, a linear correlation between increasing shear rate and air jet pressures has been found. It is now possible to correlate the observed changes in particle size with the shear forces within the system. Consequently, the friability metric can be scaled to a production scale powder transfer system, and can be used to assess the suitability of a granule for larger scale processing.

Table 1 Volumetric surface area and Breakage rate constant for a sample material between 0.5 and 2 bar feed air jet pressure using the Malvern Mastersizer

Feed air jet pressure (bar)	Volumetric surface area ($m^2\,cm^{-3}$)	Breakage rate constant (100 size classes)	Breakage rate constant (25 size classes)	Breakage rate constant (10 size classes)
0.5	0.0606	—	—	—
1.0	0.0794	0.220	0.200	0.150
1.3	0.1094	0.345	0.305	0.245
1.7	0.1313	0.420	0.375	0.300
2.0	0.1480	0.465	0.425	0.330

Chappelle, P. et al (2004) *Powder Technol.* **143–144**: 321–330

129

Predicting the density of powder blends: application for accelerating formulation development

S. Fitzpatrick, C. Smith[1] and K. Pitt

Merck Sharp and Dohme, Hertford Road, Hoddesdon, Herts EN11 9BU and Dept of Pharmaceutical Sciences, University of Nottingham, Nottingham NG7 2RE, UK. E-mail: shaun_fitzpatrick@merck.com

In the current environment of high throughput screening to support drug discovery, the aim of this work was to assess a methodology to accelerate the development of dry filled capsule formulations for early phase clinical studies. A common approach for a rapid, first into man formulation is to fill a blend of the API (active pharmaceutical ingredient) and excipients into a hard gelatin capsule. The Bonapace capsule filling equipment relies upon a constant volumetric fill to ensure uniformity of the individual capsules. To ensure that each capsule contains the appropriate potency of API, the density of each powder blend must be known in advance. This can be achieved through a trial-and-error approach of preparing various powder blends, filling capsules and weighing the contents to determine the fill and subsequent potency. This is then repeated until the composition of the blend has the appropriate density. This can require several iterations and is clearly an inefficient use of resources. An alternative approach has been assessed, which is based on a predictive model of blend density (Newton & Bader 1981). In this work a range of common pharmaceutical excipients and APIs has been assessed. The materials have been characterised in terms of particle size distribution, flow properties and density. The predictive model has been used to determine the theoretical blend density, which has then been compared with the actual blend density. The results show that the model was able to successfully predict the blend density for a wide range of materials. The applicability of the model has been demonstrated through an ability to successfully predict the blend density for a range of particle sizes and shapes. This will streamline the development of early phase formulations by reducing the overall development time and API needs. This will have significant benefits for the pharmaceutical development of early phase programmes.

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130

Correlation of granule hardness with large scale high shear wet granulation processing parameters

S. E. Dilworth, P. Doyle, S. Holland, C. Mackay and L.A. Mackin

Pharmaceutical and Analytical R&D, AstraZeneca, Charter Way, Macclesfield SK10 2NA, UK. E-mail: Sarah.Dilworth@AstraZeneca.com

High shear wet granulation is a size enlargement process during which granules are produced from fine particles to improve flow properties, content uniformity and reduce dust. Agglomeration is achieved through liquid addition onto a shearing mass of fine powders. Changes to wet granulation processing parameters affect resultant granules properties, thus altering tablet compression. This work forms part of a preliminary investigation into the characterisation of dry granules in an attempt to correlate granulation processing parameters with granule properties and subsequent compression behaviour. A design matrix of nine experiments was compiled, varying three wet granulation processing parameters (water added, impeller speed, granulation duration) at three levels (low, medium and high). All granulations were performed at 50 kg scale in a high shear bottom-driven granulator (PMA200, GEA) and subsequently dried in a fluid bed dryer (T3, GEA). From the 250–500 μm sieve fraction of each batch, twenty granules were randomly selected and tested individually on a Texture Analyser (Stable Micro Systems) to generate a set of force-displacement profiles for each batch. Each granule was placed on a base plate and a 4 mm diameter stainless steel probe was lowered onto it at a speed of 1 mm per second. The load required to compress each granule by 10% of its diameter was measured. All granules underwent an initial period of increasing load required to maintain the increasing linear displacement caused by the probe. At this point, some granules reached a plateau, whereby no further load increase was measured; others showed a sudden drop in the load measured. The type of profile obtained relates to the different mechanisms of granule compression, and a considerable variation within each batch was observed, reflecting differences in porosity, size and strength between granules. It was found that granules manufactured with all processing parameters at the lowest level had the lowest average maximum recorded load (19.7 g), and that the average maximum load increased when granulation parameters were at the medium level (42.7 g) and again at the highest level (114.7 g). Multivariate analysis was used in an attempt to correlate the granule profiles obtained with processing parameters, in an effort to overcome the numerous mechanisms of granule compression observed. Each entire force-displacement curve from all nine experiments was reduced to principal components and a scores plot was built, assigning the data from each granule to a distinct point on the graph. A clear correlation between granule hardness and granulating water was found, which was markedly stronger than the relationship between granule hardness and either impeller speed or granulation duration. This finding gives an initial insight into the relative importance of granulation processing parameters in determining product properties. As part of a preliminary investigation, these data emphasise the potential of granule hardness testing as a granule characterisation technique. Through further method development and the investigation of other key dry granule characteristics (e.g. granule porosity,) it is hoped that a link between wet granulation processing parameters and downstream product attributes can be established, thus enhancing process understanding.

131

Compaction of commercial lactose α-monohydrate and lactose crystallized from Carbopol gel

M. Aref, R. Overend, L. Seton, J. L.Ford and H. Larhrib

School of Pharmacy & Chemistry, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, UK. E-mail: L.elhassane@livjm.ac.uk

Lactose is the sugar present in milk and is manufactured from whey. It is used extensively in the pharmaceutical industry as an excipient in tablets, capsules and inhalation products. Lactose is physicochemically stable; inert to most therapeutic substances and well recognised as a safe pharmaceutical excipient for both oral dosage and inhalation. Its additional roles include acting as a diluent, which helps in the handlability and flowability of powdered batches. Although different grades of lactose are commercially available to the pharmaceutical industry, understanding of the effects of crystallization conditions on the particle characteristics of lactose, such as size, shape and surface texture, is incomplete (Zeng et al 2000). These factors are of great importance in determining physical properties, such as crystallinity, solubility, flow properties and interaction with other adhered particles such as drug powder. This study will investigate the effects of preparative conditions on the morphological features of lactose particles and study the effect of these on compaction properties. Lactose was crystallized from Carbopol gel using the procedure described by Larhrib et al (2003). Commercial lactose and lactose crystallized from Carbopol were sieved manually and the fraction of 90–125 μm was collected. Compaction was carried out using compression forces of 5, 10, 15 and 20 kN and two compression speeds, 10 and 200 mm s^{-1}, using a high speed compaction simulator. Commercial lactose and crystallized lactose were analysed using scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and X-ray powder diffraction (X-RPD). The crystallized lactose was shiny, smooth and regularly shaped compared with commercial lactose. The Carbopol gel may have provided a protective barrier for the growing crystals and permitted a steady diffusion of crystallizing molecules. The polymorphic form for both lactose samples was similar (α-form) as shown from both DSC and X-RPD. The tablet crushing strength increased with compression force for both samples as did the plastic energy, suggesting that most of the compaction energy was used for bond formation. Tablets produced from Carbopol gel were generally softer and their plastic energy lower compared with the commercial lactose, suggesting a good correlation between plastic energy and the crushing strength. Commercial lactose showed less dependence on the compression speed. The mean yield pressure derived from a Heckel plot remained nearly the same when compression speed was increased from 10 to 200 mm s^{-1} as did the crushing strength, suggesting brittle behaviour of commercial lactose. However, crystallized lactose showed some stain rate sensitivity as suggested by the increase in the mean yield pressure from 99.14 ± 0.93 MPa to 120 ± 1.7 MPa when the compression speed was increased from 10 to 200 mm s^{-1}. Probably, the presence of Carbopol within the particles may have imparted to them some plastic deformation making their compression behaviour time dependent. In conclusion: crystallization from Carbopol gel improved lactose surface texture, such as surface smoothness. Carbopol imparted to lactose particles some plastic deformation. However, it did not improve tablet crushing strength.

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132

The influence of dissolution media on drug release profiles from gliclazide extended release formulations

F. Palmer, M. Levina and A. R. Rajabi-Siahboomi

Colorcon Limited, Flagship House, Victory Way, Crossways, Dartford, Kent DA2 6QD, UK. E-mail: modified_release@colorcon.com

Gliclazide is used in the treatment of non-insulin dependent diabetes mellitus. There are reports that an extended release (ER) formulation of gliclazide exhibits superior therapeutic effect compared with instant release dosage

forms. Consequently, similar glycaemic control may be achieved even when the ER formulation contains a lower drug dose, which will lead to reduced manufacturing costs as well as increased patient compliance. The application of hypromellose (HPMC) in ER formulations is widely studied. Gliclazide is a weak acid with a good lipophilicity and a pH-dependent solubility. It belongs to Class II of the biopharmaceutical classification (Delrat et al 2002) in which dissolution rate is the controlling step in drug absorption. In this study, the influence of filler type and dissolution media on drug release from a gliclazide ER matrix formulation using HPMC was investigated. All the studied formulations contained 13.6% w/w gliclazide (Synergy Enterprises), 35.0% w/w HPMC (Methocel K100LVCR, Colorcon), 10.0% w/w of partially pregelatinized maize starch (Starch 1500, Colorcon), 0.5% w/w fumed silica (Aerosil 200, Degussa) and 0.5% w/w magnesium stearate (Peter Greven). Three different fillers were used at 40.4% w/w: spray dried lactose (SDL, FastFlo, Foremost); microcrystalline cellulose (MCC, Avicel PH102, FMC) and dibasic calcium phosphate dihydrate (DCP, Emcompress, Penwest). Tablets of 220 mg containing 30 mg gliclazide were manufactured using an instrumented 10-station rotary press (Piccola, Riva) fitted with 7 mm standard concave tooling; at 4–14 kN. Tablets manufactured at 10 kN were tested for drug release using an automated dissolution bath (Sotax) Apparatus II (paddles) at 100 rev min^{-1} with sinkers. Dissolution media were 900 mL of purified water, pH 6.8 or pH 7.4 phosphate buffers BP. All formulations produced relatively low ejection forces. Tablet mechanical strength was the highest for MCC and the lowest for DCP tablets. All formulations resulted in extended drug release over 12 h. To investigate drug release mechanism from manufactured matrices, the percent drug dissolved versus time profiles were further analysed. Data corresponding to 5–60% release showed a good fit to the Power Law Model (Spiepmann & Peppas 2001). The results indicated predominantly erosion-controlled dissolution. This was expected due to low solubility of the drug as well as low molecular weight of the polymer (HPMC) used in the study. Dissolution profiles from the same formulation tablets, in different media, were compared using f2 similarity factor (Moore & Flanner 1996) between drug release in water and each of the used buffers. Tablets containing SDL or MCC as fillers, showed only small differences in release profiles in various dissolution media (f2 of 73, 81 for SDL and 70, 74 for MCC). However, in the case of matrices containing DCP, f2 value of 51 was obtained for both buffers. This indicated a greater effect of dissolution media on release profiles. It was found that choice of fillers used in HPMC ER matrix formulation of gliclazide significantly affected tablet mechanical properties and drug release in various dissolution media. While MCC and lactose containing formulations released gliclazide in water and phosphate buffers in similar manner, drug dissolution from DCP containing formulations was significantly faster in water as compared with phosphate buffers.

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133
Mapping powder flow behaviour at different pharmaceutical processing stage

B. Gururajan[1,2], A. C. Bentham[1], J. C. Mitchell[2] and M. J. Snowden[2]

[1]Pharmaceutical R&D, Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ and [2]Medway Sciences, University of Greenwich, Medway Campus, Chatham, Kent ME4 4TB, UK. E-mail: Bindhu.Gururajan@Pfizer.com

Understanding the flow properties of particulate materials is important for the design and control of particulate processes, especially for powder storage and handling. Bins, silos and hoppers used to store and transport the bulk materials to various processing equipment can vary in capacity from a few grams of material (such as a press feed hopper used in a tabletting facility) to tons capacity (such as raw material storage hopper). The vast quantities of bulk solids that are handled would suggest that the area is well understood but unfortunately it is not. Many of the problems associated with bulk materials handling are encountered during discharge from hoppers. The hopper gives rise to several operational problems, such as flow blockages due to arching, reduced capacity due to rathole formation and segregation which can affect the subsequent plant operation (Jenike 1964). Powder characterisation and knowledge of the flow properties of the powder is essential for the smooth operation of the production plant. In this work, an attempt is made to understand the influence of the different processing stages on the flow properties of powder. The important flow properties are the angle of internal friction, angle of wall friction, Flow Function and bulk density. The bulk material handled in the different processing equipment namely, blender, granulator and tabletting press was measured using a Schulze Ring Shear Tester (Schulze 1994) to understand the influence of the process parameters on the powder flow properties. The Flow Function (FF) results obtained using the shear tester can be used to classify the flow behaviour of the powder (Table 1). The flow properties of two typical excipients, namely microcrystalline cellulose (Avicel PH102) and di-calcium phosphate (DCP), were measured initially. A placebo blend with a composition of 2:1 ratio of Avicel PH102 and DCP and 0.5% magnesium stearate was prepared to investigate on the influence of dry granulation on the powder flow behaviour. The placebo blend was granulated using a mini-scale roller compactor at set granulation conditions (Roll force 3 kN, Roll gap 2 mm, Roll speed 2 rpm and tamp/feed ratio 150%). The flow properties of the placebo blend and granules were measured (Table 2). The results were used to map the change in flow properties of the particulate powder due to various pharmaceutical processes. It was found that the flow properties of the powder changed significantly with different processing steps. Further work will be carried out to identify the influence of the dry granulation process parameters, namely roll force, roll gap and roll speed, on the flow properties of the granules.

Table 1 Classifying flow behaviour powders using Flow Function value

Flow function (FF)	Powder flow behaviour
< 1	Hardened
1–2	Very cohesive
2–4	Cohesive
4–10	Easy flowing
> 10	Free flowing

Table 2 Flow properties of excipients, blend and granules

Processing stage	Material	FF
Blender feed	Avicel PH102	6.63
Blender feed	DCP	8.69
Granulator feed	Placebo blend	14.97
Granulated product	Placebo granules	16.92
Tablet press feed	Lubricated placebo granules	20.20

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134
Rational development of a pharmaceutical extrusion spheronisation formulation: application of the solid-liquid-interaction classification and image analysis based pellet characterisation

C. Seiler, N. O. MacPhail and S. Fitzpatrick

Merck Sharp & Dohme Ltd, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK. Email: Christian_seiler@merck.com

Extrusion spheronisation is the most popular method for producing pellets and consists of four processing stages: preparation of the wet mass (granulation), shaping of the wet mass into cylinders (extrusion), breaking up and rounding of the extruded wet mass (spheronisation) and drying of the produced spherical pellets (Vervaet et al 1995). Commercially available pellet formulations are mainly coated with a polymer film to obtain a controlled release effect (Vervaet et al 1995). In the in-house development programme described in this abstract, defined API dissolution rates had to be achieved by varying the amount of coat applied to the pellets. Since the thickness-to-mass ratio of the coat, and hence the API dissolution rate, is directly linked to the core pellet size, control of the core pellet size was a key formulation objective. Different studies (e.g. Bains et al 1991; Chatchawalsaisin et al 2005) have shown that the fluid is an important parameter in the extrusion spheronisation process and that pellets of acceptable quality can be achieved within a lower and upper fluid limit. Bains et al (1991) found for a simple formulation that the water content relative to the quantity of microcrystalline cellulose (MCC) was more important than the absolute quantity of water, but offered no specific explanation for this. Chatchawalsaisin et al (2005) studied formulations containing MCC, glyceryl monostearate (GMS), different APIs and water, but limited their discussions to the experimental observations. The in-house formulations also contained MCC, GMS, API and water and one objective was to explain the interactions between the solid ingredients and water. The central hypothesis was that the sorption potential and solubility of the materials determine their

interactions with fluids and thus the pellet properties. To rationalise this, the so-called Solid-Liquid-Interaction (SLI) classification was devised, which involved grouping materials according to their solubility and sorption potential. Pellet formulations were prepared using high shear wet granulation, screen extrusion, spheronisation and fluid bed drying. For the evaluation and optimisation of pellet size and shape, an image analysis based pellet characterisation method was developed, which required dried pellet samples of not more than 0.5 g in weight. A spinning riffler was used to ensure that these samples were representative. The results confirmed the predominance of the MCC-to-water ratio for both fixed and varied water levels. As shown in Table 1, the mean pellet size only increased significantly at low MCC to water ratios (39%) and decreased slightly at high ratios (85%), whereas the relative standard deviation (RSD) for pellet size increased exponentially with MCC-to-water ratio. These observations can be explained by the different sorption potentials of the formulations (Table 1), using the SLI-concept. Since narrow pellet size distributions with a consistent mean size were required, it was concluded that there was a relatively narrow window for overall formulation optimisation. It was also concluded that the SLI-concept and detailed characterisation data, allow a more rational development of extrusion spheronisation formulations.

Table 1 Mean pellet size and pellet size RSD as a function of MCC to water ratio

MCC/water	Sorption potential	Mean size (mm)	RSD (%)
39%	Low	1.66, 2.03, 2.50	14, 16, 16
43%	Low	1.44, 1.63	17, 22
57%	Medium	1.51, 1.59	20, 28
85%	High	1.21, 1.48	47, 51

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135
Freeze-dried protein nanoparticles suitable for pMDI formulation

B. K. Nyambura, I. W. Kellaway and K. M. G. Taylor[1]

The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX and [1]University College London Hospitals, Camden and Islington Pharmaceutical Services and The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, UK. E-mail: bildad.nyambura@ulsop.ac.uk

The efficacy of protein medications via the inhaled route depends on the particle size and retained biological activity of the inhaled drug. Freeze-drying is frequently used when developing drugs with stability issues for human use (Greiff 1971). However, freeze-drying can also be used to form drug nanoparticles. Non-ozone-depleting hydroflourocarbons (HFA) propellants now replace ozone depleting chlorofluorocarbon (CFC) propellants (Pischtiak et al 2001). Due to different physical properties between CFCs and HFAs (e.g. higher polarity of the HFA-propellants), a direct substitution into existing pMDIs has proved to be difficult, leading to formulations involving co-solvent systems. The most widely used co-solvent for such formulations is ethanol (Hickey & Evans 1996). The aim of this work is to produce stable bioactive protein nanoparticles suitable for pMDI formulation. Nanoparticles containing lactose and lysozyme were prepared using a nano-precipitation method. Lysozyme and lactose (100 mg total weight) were weighed into glass vials to form a composition of 80% w/w, 85% w/w, 90% w/w and 95% w/w lysozyme. 1 mL of 50 mM phosphate buffer (pH 7) was added into each vial and powder dissolved to form an aqueous phase. Egg lecithin (0.2 g) was weighed into a separate vial and dissolved into 5 mL of ethanol to form an oily phase. Each aqueous phase was put into the oily phase drop-wise while homogenising at 24 000 rev min^{-1} for 5 min. The nano-precipitates formed were then snap-frozen to immobilise the suspension into a solid state using liquid nitrogen and freeze-dried overnight to remove water from the frozen suspension. Excess lecithin was removed by dispersing the freeze-dried matter in absolute ethanol followed by centrifugation to recover the nanoparticles. Particle size was determined using photon correlation spectroscopy. Retention of biological activity of lysozyme was determined using a turbidimetric method (http://www.sigmaaldich.com, method no. EC 3.2.1.17) using UV/VIS spectrophotometer (Model UV-1601, Shimadzu Corporation) at 450 nm. The nanoparticles were filled into glass pMDI vials with HFA 134a and suspension stability was visually assessed with time. Retained biological activity of lysozyme increased with increasing lactose concentration over the range investigated (Table 1). There was no clear trend between nanoparticle size, Polydispersity Index and lactose concentration (Table 1). However, high concentration of lysozyme (i.e. 95% w/w) produced the largest nanoparticle size and highest Polydispersity Index (Table 1). The nanoparticles formed a stable suspension with time in HFA 134a. In conclusion, a freeze-drying process produced stable lysozyme-containing nanoparticles of the appropriate size for peripheral lung deposition. They are characterised by high retention of biological activity and tight size distribution. They can form a stable suspension in HFA 134a, therefore making them a suitable system for aerosol drug delivery.

Table 1 Effect of lactose concentration on nanoparticle size, polydispersity index and retained biological activity

% w/w Lactose	Size (nm)	Polydispersity index	% Retained activity
5	358 ± 14	0.28 ± 0.038	67 ± 3
10	246 ± 1	0.10 ± 0.013	75 ± 4
15	266 ± 2	0.16 ± 0.015	83 ± 2
20	288 ± 18	0.16 ± 0.019	99 ± 4

Data are means $\pm$ s.d., $n = 3$.

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136
Solid-liquid-interaction concepts for the rational design of pharmaceutical formulations prepared by high shear wet granulation

C. Seiler, N. O. MacPhail and S. Fitzpatrick

Merck Sharp & Dohme Ltd, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK. E-mail: Christian_seiler@merck.com

High shear wet granulation is a process that is widely used in the pharmaceutical industry as the initial stage in the preparation of solid oral dosage forms. It involves intensive mixing of powders and fluid, which results in the formation of enlarged new solid entities, referred to as granules. The type and amount of fluid is a critical component in the preparation of granulations with properties that fall into an acceptable processing window. Improper granulation causes problems in down-stream processes, including caking, segregation and poor tableting performance (Iveson et al 2001). It has been observed that different formulations prepared by the same process can require significantly different amounts of fluid to yield product of similar granule size. The central proposal of the work described in this abstract is that differences in the sorption potential and solubility of solids are responsible for their different interactions with granulating fluids. A formulation with high sorption potential is expected to require more fluid to achieve a certain extent of granulation than one with a lower sorption potential. Material solubility is, upon drying, thought to be responsible for solid bridge formation, which provides granule strength during down-stream processing. The objective was thus to define concepts for the rational selection of fluid levels. One developed concept, which involved grouping materials according to their solubility and sorption potential, was labelled as Solid-Liquid-Interaction (SLI) classification. To probe the developed concepts, formulations containing varying levels of API, hydroxypropyl methylcellulose (HPMC), croscarmellose sodium (CC Na) and microcrystalline cellulose (MCC), granulated with different levels of a hydro-alcoholic solution, were studied. The granulator power consumption had been monitored for each experiment, which is a widely used technique (Faure et al 2001), and the data were used as a surrogate for the extent of granulation. Particle size data were generated to back up this approach. The SLI-classification concept was then used to systematically analyse and explain the granulator power data. As shown in Table 1, a low formulation sorption potential (determined by low MCC and CC Na levels) in conjunction with a high fluid level correlated to high granulator power, and vice versa, with fluid level modulating the effect of the formulation sorption potential. A separate analysis for the effect of the binder HPMC, belonging to the (1,1) SLI-classification of high solubility and high sorption potential, suggested that either the sorption potential or the solubility predominated, depending on the amount of fluid used for granulation. The overall conclusion from this study was that a good fundamental understanding of the solid-liquid-interactions has the potential to

minimise the need for experimentation and maximise the probability of success of the wet granulation process. This is of particular relevance in the early stages of pharmaceutical development, when formulations are changed frequently. Further work is on-going to develop tools for the quantitative prediction of appropriate fluid levels from first principles.

Table 1 Granulator power end-point for formulations with different sorption potentials granulated at different fluid levels

MCC	CC Na	Sorption potential	Fluid	Power
Low	Low	Low	High	118 W
High	High	High	High	75 W
High	Low	Medium	Low	75 W
Low	High	Medium/High	Low	66 W

Note: MCC and CC Na belong to the (0,1) SLI-classification of low solubility and high sorption potential.

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137
Application of electrical impedance analysis for investigation of emulsion stabilisers in the frozen state

C. Martin, A. J. Ingham[1], K. R. Ward[1] and H. O. Alpar

Vaccine Delivery Group, Centre For Drug Delivery Research, University of London, School of Pharmacy, 29–39, Brunswick Square, London, WC1N 1AX and [1]Biopharma Technology Limited, Biopharma House, Winn all Valley Road, Winchester, SO23 0LD, UK. E-mail: oya.alpar@ams1.ulsop.ac.uk

The aim of these experiments was to investigate the stability of guar gum-sunflower oil emulsions at below ambient temperatures by examination of impedance response to an applied fixed-frequency electric field while varying temperature, a form of dielectric spectroscopy. Dielectric spectroscopy examines the polarisation-relaxation response of materials when exposed to an electromagnetic field, which is dependent on both structural and molecular properties as well as the ratio of components in mixed systems (Goff 1995). Guar gum is a natural product derived from seeds of the guar plant, *Cyamopsis tetragonolobus*. It is composed of a straight backbone chain of D-mannopyranose units with side branches of D-galactopyranose every other unit. The gum is used as a binding and disintegration component in tabletting in the pharmaceutical industry, as well as a thickener and viscosity promoter in various food products. Analysis was conducted with Lyotherm2 (Biopharma Technology Limited), a thermal analyser capable of assessing impedance during cooling and warming of materials and gives an indication of molecular mobility changes (as a result of events, such as softening, relaxation, crystallisation, rearrangement or melting), which may be applicable to reduced temperature operations for such materials, such as cold storage and freeze drying. Emulsions were prepared by high speed mixing from aqueous solutions of 1.0% m/v guar gum and sunflower oil in three different volumetric ratios: 1:1, 5:1 and 10:1. Cooling to $> 40^{\circ}C$ below the maximum impedance temperature was provided within the liquid nitrogen chamber and the samples were reheated to $0^{\circ}C$ (at $1.5^{\circ}C\,min^{-1}$). The data was exported directly to Microsoft Excel for analysis of the warming profile to determine the temperature of significant events, which may be due to increases in molecular mobility or relaxation. The T_{Zonset} values (onset point of elevated mobility) shown in Table 1 for the 5:1 and 10:1 aqueous:oil emulsions indicate that the system remains immobile until the temperatures rises above $-20^{\circ}C$ (-13.19 and $-15.22^{\circ}C$, respectively). In terms of cold storage, this data indicates that these emulsions could safely be retained in a standard $-20^{\circ}C$ freezer with minimal molecular mobility. Comparing T_{ZL} values (temperature point at which sample begins to deviate from maximum impedance, 5625 kΩ, under an applied field frequency of 1 000 Hz) in Table 1, there is a dramatic decrease in T_{ZL} between the 1:1 and 5:1 emulsions, indicating the enhanced molecular mobility of the latter. The 5:1 and 10:1 emulsions have similar T_{ZL} values (-51.73 and -59.56 kΩ, respectively), indicating that the major difference seen in the system is due to variations in the ratio of aqueous and oil phases (Moran et al 2000). At increased ratios of the aqueous guar phase, impedance is reduced as a function of the conducting properties of water molecules (McCrystal et al 2002). Concurrently decreasing the proportion of oil also leads to a reduction in impedance because the sunflower oil acts to decreases the effective electric field due to enhanced permittivity, thus increasing the capacitance of the system. In conclusion, these results may indicate that the storage of guar gum to minimise molecular mobility (below $0^{\circ}C$), can be achieved at $-20^{\circ}C$. This may have stability advantages for the processing, storage and transport of drug delivery systems incorporating guar.

Table 1 Summary of thermal events accompanying the reduction in impedance values approaching $0^{\circ}C$ three different aqueous 1% m/v guar gum-sunflower oil emulsions (1:1, 5:1, 10:1 v/v)

Sample	Thermal event	Change	Impedance event (°C)
1:1	Melt	T_{ZL}	−2.77
		T_{onset}	−0.50
		T_{end}	−0.40
		T_{Zmelt}	−0.17
5:1	Melt	T_{ZL}	−51.73
		T_{onset}	−13.19
		T_{end}	−11.33
		T_{Zmelt}	−9.04
10:1	Melt	T_{ZL}	−59.56
		T_{onset}	−15.22
		T_{end}	−12.60
		T_{Zmelt}	−9.08

T_{ZL}, temperature point of deviation from the maximum impedance (5625 kΩ) under an applied field of frequency 1000 Hz; T_{onset}, onset point of an elevated mobility region; T_{end}, end temperature point of elevated mobility region and T_{Zmelt}, point of sudden onset of mobility indicating a thermal melting event.

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Poster Session 2 – Biopharmaceutics

138
The use of discriminant analysis to identify molecules with potential as enhancers of percutaneous absorption

W. J. Pugh, R. Wong, F. Falson[1], B. B. Michniak[2] and G. P. Moss[3]

Welsh School of Pharmacy, Cardiff University, Cardiff, UK, [1]Faculty of Pharmacy, Lyon University, 69373 Lyon, France, [2]Department of Pharmacology and Physiology, New Jersey Medical School, University of Medicine & Dentistry, Newark NJ 07103, USA and [3]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth PO1 2DT, UK. Email: pugh@cf.ac.uk

Various methods have been used to enhance percutaneous absorption, including the co-formulation of enhancer chemicals, where the enhancer may be the formulation vehicle itself, such as ethanol or propylene glycol, or a chemical dissolved in the vehicle. Such chemicals have been variously termed penetration enhancers, accelerants or sorption promoters. They may be grouped into various chemical categories, such as terpenes, and variations on the Azone (N-dodecylazacycloheptan-2-one) lead molecule. In this study enhancing power (ER) is quantified as the ratio of drug permeated after 24 h relative to control. The standard approach uses regression to yield QSAR equations that predict ER. Discriminant analysis assigns novel compounds to one of a set of groups with a predetermined range of properties and has been successfully applied to the prediction of maximal flux from unenhanced aqueous vehicle (Magnusson et al 2004). We report the success of this approach in predicting whether a novel compound will have an ER value > 10. Data are available for 73 enhancers of hydrocortisone permeation from propylene glycol across hairless mouse skin from the same laboratory. Enhancers had chain lengths (CC) from 0 to 16 carbon atoms, 1 to 8 H-bonding atoms (HB), MW 60 to 450, octanol/water partition coefficients (P) and molar aqueous solubility (S) were calculated. LogP ranged from -1.7 to 9.7 and logS from -7.8 to 0.7. These predictive properties were chosen because of their ready availability. ER values ranged from 0.2 to 25.3. Multiple regression analysis failed to predict activity, with 'good' enhancers (i.e. ER > 10) being underestimated. Simple guidelines suggest that high ER is associated with CC > 12 and HB 2–5. This was refined by multivariate analysis to identify significant predictors. Discriminant analysis using CC,