# Pharmaceutical Technology

## 58
## Novel formulation for oral delivery of antihypertensive: chronotherapeutic combination approach

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Attempt was made to develop a novel dosage for chronotherapeutic treatment of hypertension (Smolensky & Labrecque 1997). Combination of calcium channel blocker (CCB), nifedipine and selective $\beta$1-blocker, atenolol; with nifedipine as sustained release mini-tablet and atenolol as controlled onset extended release (COER) pellets with an aim of combining the advantages of both drugs. Calcium channel blockers (CCB's) lower hypertension by directly decreasing the total peripheral resistance by blocking the influx of calcium ions and inhibiting the contractile processes of cardiac and vascular smooth muscles. They are also reported to retard the development and progression of atherosclerosis. However, calcium antagonists have poor clinical outcome with little effect on the frequency or the total duration of ischemic episodes. Also, they have also been reported to activate SNS *in vivo* which may increase myocardial oxygen requirement in the early morning. The extrinsic activation of SNS triggered by CCB's overlaps with intrinsic activation set by circadian cycle would lead to severe cardiac disturbances. The $\beta$ blockers are reported to effectively inhibit SNS and rennin-angiotensin system thus exerting antihypertensive effect during the morning vulnerable period and reducing the occurrence of cardiovascular events. Solid dispersions of nifedipine were prepared by common-solvent evaporation, hot-melt and liquid molecular dispersion methods. Fast dissolving mini tablet containing loading dose was prepared by direct compression using dicalcium phosphate and sodium starch glycolate, while the maintenance dose containing tablet was prepared using ethyl cellulose (8–25%). Atenolol drug-loaded non-pariel seeds (NPS) was coated with pH-independent polymers, Eudragit RL and RS 100 in combination and further coated with enteric coating polymer Eudragit S-100; drug coated by powder layering technique and Eudragit coating by spray coating (Shivakumar et al 2002). Nifedipine solid dispersions containing drug and PVP in ratio of 1:1 and drug, PVP, MCC in ratio of 2:2:6 had increased solubility of 6 and 10 folds, respectively. Increase in aqueous solubility would increase its bioavailability considering it belongs to Class 11 BCS system. The sustained release mini-tablet of nifedipine released 80% of the drug within 8 hrs of administration. In atenolol COER pellets, Eudragit RL and RS 100 in 0.5:1 ratio; 8% w/v ethanolic solution coated to obtain 6% weight gain was found to be optimum, optimized by $2^3$ factorial design, and had controlled release of drug for 4 hrs. Further coated with Eudragit S-100 to prevent release of drug below pH 6.8; 6% w/v ethanolic solution coated to obtain 5% weight gain was found to be optimum. This coating prevented the release of the drug until it reached the colon when it began to slowly release the drug. A total of 12 hrs of release was obtained in pH 7.4 buffer as determined by in-vitro dissolution studies. The SEM of nifedipine solid dispersions showed an amorphous uniform distribution of drug in the matrix of the polymer while the SEM of atenolol pellets confirmed the uniformly of coating on the core of the drug loaded pellet. A combination of two important anti-hypertensive drugs was successfully formulated having different release characteristics based on chronobiology of hypertension (Sarasija & Patak 2005)

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## 59
## Effect of different formulation variables on the drug release PLGA microspheres of olanzapine prepared by solvent evaporation method

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PLGA microspheres of Olanzapine, an atypical antipsychotic agent, were prepared by single emulsion and double emulsion solvent evaporation methods. The objective of the proposed study was to optimize different formulation variables for the fabrication of the extended release microspheres. The effect of surfactant, external phase volume and osmotic agent in the external phase was studied on the microsphere formulation and drug release behaviour. Ten different emulsifiers viz., Poly vinyl alcohol (PVA), Polyvinyl pyroliidione, Tween 80, Cremophore EL, Poloxamer F68, Poloxamer 407, Tyloxapol, Vit E TPGS, Dextran sulfate, cyclodextrin were used for preparing the emulsion. Effect of concentration of surfactants, osmotic agent and volume of external phase on the drug entrapment, particle size and shape of the microspheres were also investigated. Drug content of the microspheres was determined by HPLC method, particle size was determined by laser diffraction technique and their morphology was studied by Scanning Electron Microscopy (SEM). It was observed that as the surfactant concentration is increased, the stickiness and particle size of the microspheres decreases and the drug entrapment is reduced. In the case of PVA when surfactant concentration was increased from 0.2% to 2.5% the drug entrapment decreases from 76% to 32%. The initial burst release was increased with increase in surfactant concentration. It was also observed that when partially hydrolyzed PVA was used as the surfactant then particle size and drug entrapment was better. With other surfactants either small particle size or spherical shape was not obtained on lower concentration. When the volume of external phase was increased the drug loading was decreased and burst release was increased. This effect would be attributed to increase in the porosity of the formed microspheres as supported by SEM studies. When the volume of external phase was reduced then drug loading was increased and burst release was reduced. The drug release was suppressed on further reduction of external phase. The addition of osmotic agent (mannitol, sodium chloride, dextrose) increases the entrapment efficiency of the microspheres with reduced burst release. On the basis of above finding it was possible to formulate microspheres of olanzapine with desired particle size and drug release profile up to 14 days.

## 60
## In vitro and in vivo characterization of buccoadhesive bilayered tablets of propranolol hydrochloride

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Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration (Gibaldi 1985). It provides direct entry into the systemic circulation thus avoiding the hepatic first-pass effect. This study was designed to study the mucoadhesive bilayered buccal tablets of propranolol hydrochloride (PRO-HCL) using combination of bioadhesive polymers sodium alginate (Na-alginate), carbopol-934 (CP) and ethyl cellulose (EC) as an impermeable backing layer. Buccoadhesive bilayered buccal tablets ($1.5 \pm 0.18$ mm thickness,150 mg weight, disc shaped flat surface) were prepared by direct compression and consisted of an adhesive layer containing drug with bioadhesive polymers carbopol-934, sodium-CMC and PVP-K30, and mannitol in different ratios with an impermeable backing layer of ethyl cellulose. The swelling index was determined on 2% agar gel plate with the adhesive layer of tablet facing the gel surface (Kemken et al 1991). Ex vivo buccoadhesive strength *was* measured on sheep buccal mucosa using a modified physical balance (Gupta et al 1994). In vitro drug release studies were undertaken using a USP XXIII dissolution rate test apparatus 2 (50 rpm, 37°C, phosphate buffer pH 6.8.) with samples analysed spectrophotometrically at 290 nm. In vitro drug permeation studies were performed at $37 \pm 1$°C on sheep buccal mucosa using 12.5 ml of phosphate buffer pH 7.4 in a Keshary-Chien diffusion cell (Kurosaki et al 1989). An in vivo pharmacodynamic study was undertaken using buccal tablets applied to rabbit oral mucosa (Kemken et al 1991) and monitoring of inhibition of isoprenaline-induced tachycardia. Bilayered tablets were prepared by different ratios of Na-alginate and Carbopol (6:1, 5:1, 4:1; 3:1, 2:1, 1:1, 1:2, 1:3, and 1:4). Tablets were optimized by 30%, 8% and 2% of PVP-K30, D-mannitol and PEG-4000 respectively. Tablets containing Na-alginate and CP in the ratio of 5:1 were chosen for optimized tablets. They gave the maximum percentage of in-vitro drug release without disintegration in 12 hours. The mechanism of drug release was found to be non-Fickian and followed first order kinetics. Optimized tablets showed good bioadhesive strength ($28.9 \pm 0.99$ g.), high in vitro drug permeation ($68.65 \pm 3.69$% for 12 hr). Stability study of optimized tablets was determined in natural human saliva, and it was found that both drug and buccal tablet were stable in human saliva. Swelling index was directly proportional to Na-alginate and inversely proportional to CP content. The surface pH of all tablets was within satisfactory limits (pH $7.0 \pm 1.5$) and hence these tablets should not cause irritation in the buccal cavity. The optimized tablet was applied to rabbit oral mucosa and inhibition of isoprenaline-induced tachycardia was achieved. The studies conducted in rabbits confirmed the sustained release as compared with intravenous administration. The optimised buccal bilayered tablets showed significant mucoadhesion in contact with sheep buccal mucosa, and good swelling and drug release characteristics. In vivo study in rabbits confirmed both good bioavailability and the sustained release of drug from the tablet. Mucoadhesive buccal tablets of PRO-HCL may provide advantages in bypassing hepatic first pass metabolism of this drug.

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## 61
## Mannitol crystallisation in freeze dried dosage forms

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Zydis is a fast dissolving dosage form and is used in a range of pharmaceutical products. Zydis is manufactured through freeze drying to obtain the porous structure, which gives the "melt on the tongue" effect. The Zydis matrix is composed of many materials designed to achieve a number of objectives. Polymers such as gelatin, dextrans or alginates are required to form a glassy amorphous structure which imparts strength and resilience during handling. Saccharides such as mannitol or sorbitol give crystallinity, hardness and elegance (Seager 1998). Mannitol is used as a bulking agent in Zydis, and indeed many other freeze dried products as a filler. The extent to which mannitol crystallises during freezing and freeze drying is important to ensure the physical integrity of the product (e.g. reduced shrinkage, unit cracking and collapse). This study was carried out to assess the process and formulation factors that can affect mannitol crystallisation and unit appearance during Zydis manufacturing. Drug M was used as a model drug for this study. Drug M is normally presented as a hydrochloride salt. In this study, both the free base of drug M (obtained through a neutralisation step) and the HCl salt were incorporated in matrix system comprising gelatin and mannitol. The HCl salt is freely soluble in water to give a solution, whereas the free base is readily precipitated out to give a suspension. The Zydis manufacturing process comprises the steps of mixing, unit dosing, freezing and freeze drying. The effect of annealing on mannitol crystallisation was also studied. The frozen units of the free base (suspension) product were held at −25°C for up to 24hrs. The crystallinity of mannitol was determined by X-ray diffraction, DVS (Dynamic Vapour Sorption) and DSC. The results have shown that a significant proportion of mannitol from the solution product comprising the HCl salt is in the amorphous state, whereas the mannitol from the suspension product (free base) is largely in the crystalline state. This suggests that mannitol is much more freely crystallised out during freezing and freeze drying from a suspension product than from a high strength solution product. It is postulated that this is likely related to the higher glass transition temperature of the frozen solution. It is also possible that the presence of suspended particles facilitates the crystallisation process. We also showed that annealing of the frozen units has a significant impact on the crystallinity of the finished products as shown by XRD and DSC analysis. There is evidence that tablets with increased crystallinity have a more elegant surface appearance and also a reduced tendency to unit cracking during freeze drying. Annealing presents a useful means of improving the unit appearance.

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## 62
## In vitro deposition from a dry powder inhaler and its correlation with surface energy of amorphous fine particle surfaces

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Dry powder inhaler (DPI) drug products are composed of a device and a dry powder formulation. The latter often consists of a micronised drug (1–5 $\mu$m) suitable for deep lung deposition and an inert coarse carrier particle, typically lactose, to aid the flow and dispersion of highly cohesive drug particles (Zeng et al 2000). The aim of this project was to test the hypothesis that the adhesion between fine particles and the carrier should correlate with the surface energy, if the morphology of all samples were identical. To investigate this it was necessary to test the in vitro deposition of spherical particles with different surface energy, using the same carrier lactose and inhaler. Polymers were used to create spherical model "drugs" by spray drying. Surface energy has been correlated with the fine particle fraction of drugs previously (Cline et al 2002), however in unpublished results we have not seen such correlations. Polyacrylic acid (five batches), polyvinyl alcohol and salbutamol sulphate were spray-dried using the SDMicro spray dryer to produce material with a geometric size between 1 and 5 $\mu$m. A solution of 10% w/v of each compound and 0.04% w/v of Triamterene (UV marker for polyacrylic acid and polyvinyl alcohol) was prepared in ethanol. The morphology and geometric size of the spray-dried particles was then assessed by scanning electron microscopy (SEM) and formulated with lactose monohydrate (Respitose SV008) in a Turbula mixer (45 rpm/30 minutes) to produce a 1% w/w polymer/lactose blend. In vitro deposition of each formulation was determined using a twin stage impinger (TSI) and involved the aerosolisation of the contents of ten capsules, each containing a dose of 100 mg (total blend) at 60 l/min, via the Aerolizer. Quantitative recovery of material from deposition sites was achieved through ethanol wash and UV analysis. The emitted dose (ED) was the amount of polymer deposited in the upper and lower stages of the TSI. The fine particle dose (FPD) was the amount of polymer recovered from the lower stage (particles < 6.4 $\mu$m). Fine particle fraction (FPF) was the FPD as a percentage of the ED. The surface properties of the materials were investigated using pulse inverse gas chromatography (IGC) using infinite dilution to determine the dispersive component of the surface energy. Experiments were performed at 30°C/0% RH using a helium carrier flow rate of 10 mLmin$^{-1}$. The dispersive surface energy was determined by eluting 0.04% v/v injections of an homologous series of alkanes (hexane, heptane, octane, nonane, decane). The IGC data and FPF for the materials used as model drugs are shown in Table 1 and indicate that increasing the surface energy of particles decreases the FPF of the formulations. This may be related to a decrease in cohesive and adhesive forces by reducing the surface energy. These results show a non-linear decrease in FPF with increasing surface energy compared with a linear increase in FPF with surface energy reported previously by Cline et al (2002).

**Table 1** Impact of surface energy of different model drugs on fine particle fraction

| Polymer (model drug) | Dispersive surface energy (mJm$^{-2}$) | FPF (%) (n = 2) |
|---|---|---|
| Polyvinyl alcohol | 31.8 ± 2.5 | 35.2 ± 3.6 |
| Polyacrylic acid (batch 1) | 35,6 ± 1,1 | 32.1 ± 5,2 |
| Polyacrylic acid (batch 2) | 33.6 ± 0.3 | 25.5 ± 0.9 |
| Polyacrylic acid (batch 3) | 36.4 ± 1,9 | 23.9 ± 1.3 |
| Polyacrylic acid (batch 4) | 36.9 ± 0.5 | 22 ± 4,6 |
| Salbutamol sulphate | 40.3 ± 0.9 | 21.8 ± 0.3 |
| Polyacrylic acid (batch 5) | 41.9 ± 0.2 | 17.9 ± 1.8 |

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## 63
## Particle size distribution of nasal pMDIs: an alternative approach using an adapted simplified model of the human nose

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The current regulatory guidelines (Draft Guidelines 2003) recommend a number of in-vitro tests for analysis of pressurised Metered Dose Inhalers (pMDIs) for topical nasal administration, including uniformity of delivered dose through life, droplet size distribution and particle size distribution. This study investigates the relevance of determining the residual particle size produced from an MDI for nasal delivery. The currently recognised test for analysis of particle size distribution is to couple a 1L expansion chamber to a Cascade Impactor (CI). This forces the evaporation of the droplets into residual particles prior to entering the CI. However, in the clinical setting it is improbable that droplets emitted from a nasal pMDI will have evaporated in the short distance between the actuator exit orifice and the structures of the nasal cavity. It is more likely that the droplets will impact before there is sufficient time for evaporation, preventing deposition beyond the nose and especially into the respirable region of the lung. An alternative method to evaluate nose and lung deposition is suggested and evaluated. The method substitutes the expansion chamber for a simplified adapted replica of one side of the human nose without any of the internal nasal structures (Hallworth & Padfield 1986). The drug deposition profile is compared for the expansion chamber and the nose at the regulatory recommended flow rate of 28.3 L/min. This flow rate is widely accepted for inhalation via the oral cavity; however data is published to suggest that a sniff through a single nostril is approximately 40 L/min (Sobel et al 2000), and sedentary breathing is approximately 10 L/min. Furthermore, inhalation rates may vary significantly between patients due to person to person variability and the effects of allergic rhinitis. The study addresses the appropriateness of the flow rate of 28.3 L/min for in-vitro analysis of nasal pMDIs. Additionally, it may be beneficial for the patient not to inhale at all, or inhale gently during or immediately after administration of the dose. The effect of flow/inhalation rate is therefore investigated. Using the glass nose coupled to the Andersen CI, drug deposition using flow rates of 0, 10, 28.3 and 40 L/min is compared.

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**64**

## Mucoadhesive buccal films: swelling, mechanical and bioadhesive properties

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Mucoadhesive systems have been developed as potential drug delivery systems for the gastrointestinal (GI)-tract to provide a prolonged resisdence time and sustained drug release. In this study, mucoadhesive buccal films as a candidate vehicle were developed and formulated with various viscosity-matched hydrophilic celluloses as a matrix, including methyl cellulose (MC), hydroxyethyl cellulose (HEC), hydroxypropylmethyl cellulose (HPMC); with glycerol as a plasticizer and miconazole nitrate as a model drug. The mechanical and physical properties, such as tensile strength, swelling ratio, residence time and erosion rate, were characterized to investigate the possibility and suitability of this buccal delivery system. A texture analyzer was used to measure the tensile strength of the films as well as elongation and elasticity. The residence time was measured as the time taken to detach the film from a moist agar surface due to washing with phosphate suffered saline (pH7.4; 1 $mLmin^{-1}$) to mimic saliva flow. The swelling ratio measured the rate of swelling of the films on a moist agar surface over time; the ratio of swelled diameter to initial diameter was used to assess this property. It was demonstrated that both MC and HPMC films showed higher tensile strength compared with HEC films ($4.9 \pm 0.1$ and $12.3 \pm 2$ versus $1.8 \pm 0.1$ mPas $mm^{-2}$) (Table 1). Moreover, when glycerol was increased from 5% v/v to 10% v/v in all films, there was a decrease in tensile strength and an increase in elongation, indicative of a more elastic, more flexible and softer film. In the swelling study, HEC and HPMC films swelled far more than MC films (40 and 70% compared with 5%). This finding correlated to the hydrophilicity of cellulose derivatives, HEC is the most hydrophilic followed by HPMC then MC (Rodriguez et al 2000). The in vitro residence time for the films was inversely linked to the swelling of the polymers, particularly apparent for the MC films. The in vitro residence time for MC films was more than three times longer than HEC and HPMC films (210 versus 60 and 50 min). Because of the hydrophilicity, HEC and HPMC films were very water soluble and dissolved when washed by PBS buffer (pH 7.4); on the other hand, MC films were more difficult to wash off as they absorbed water forming strong hydrogen bonds between the polymer and the surface to increase the residence time of these films. Overall these films show potential as formulations for buccal drug delivery with MC films showing the most appropriate physical characteristics.

**Table 1** Tensile strength, swelling ratio and residence time of mucoadhesive buccal films

| Formulation | Swelling (%) | Residence time (min) | Tensile strength (mPas $mm^{-2}$) |
|---|---|---|---|
| MC5%G | 5 | 210 | 4.9 |
| MC10%G | 15 | 150 | 2.0 |
| HEC5%G | 40 | 60 | 1.8 |
| HEC10%G | 30 | 75 | 0.6 |
| HPMC5%G | 70 | 50 | 12.3 |
| HPMC10%G | 60 | 60 | 8.1 |

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**65**

## Process optimisation for a modified release (MR) tablet using production data

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Investigations into the production of oral drugs have shown that a large number of factors, including the physicochemical properties of the raw materials and the manufacturing processes, influence the drug release behaviour from the final product dissolution. Dissolution is a critical quality parameter for MR tablets (Furlanetto et al 2006). While processing parameters are optimised during process development; they may subsequently not be optimal at full production scale. Improving process understanding is of great relevance to industry. This is being increasingly recognised; FDA is currently promoting a system for designing, analyzing and controlling manufacturing through timely measurements the so-called Process Analytical Technology (PAT) initiative. The objective of this project is to apply an engineering approach to investigate the influence of processing parameters on the dissolution of a particular MR drug, and to identity optimisation strategies. The work was based on happenstance data compiled from 105 manufacturing batch records. Selection of relevant process factors was based on thoroughly mapping the process; however, some factors could not be studied because variability with respect to the set point was very small (a coefficient of variance greater then 10% was used as the acceptance criteria). Tablet dissolution rate distribution was analysed with the Kolmogorov-Smirnov test. Investigation on the effect of the process factors was performed using a Pareto analysis; given the nature of the data, calculations were based on polynomial regression using Statistica 7.0 (StatSoft, Inc 2004). Identification of combinations of process factors that would lead to dissolution within the specifications was done using Microsoft Excel. Tablet dissolution data showed a normal distribution (2 h, 4 h and 12 h), which rarely fell outside specifications, however the mode value was at the lower end of the specified dissolution range. The influential process factors at a 95% significance level were: powder mixing duration prior to wetting [13 min]; impeller torque at the end of granulation [7.4%]; maximum vacuum during drying [52 hPa]; granulate drying duration [133 min]; granulate cooling duration [14.8 min]; storage between granulation and tabletting duration [6,192 min]; and average main compression force during tabletting [6.0 kN]. The process values obtained from the model which would lead to tablet dissolution with an average close to the mid specification value and within the specification limit for these factors are presented in the square parenthesis. Some interaction effects were also significant. The results of this study showed that engineering quality tools allow for dynamic process improvement, even when only happenstance data are available. Future work will focus on the production of batches at semi-pilot scale, using process factors set at levels specified according to a robust design of experiments (DOE), and further validation at industrial scale.

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**66**

## A study into the effect of additional learning activities on the use of sunscreens in the MPharm degree at the University of Brighton

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Due to the changing climate conditions in the UK it has been estimated that there will be around 5000 additional cases of skin cancer per year (Diffey 2004). Therefore it is likely, in the future the pharmacist may have an increasingly important role in advising the general public on the correct type and use of sunscreens to help prevent this. Recent studies have found that pharmacists demonstrate low levels of personal sun protection behaviour (Souvignier et al 1996). Previously we have reported that the pharmacy students' perceptions on the use of sunscreens were similar to students studying non-health care related courses (Ingram et al 2004). To increase pharmacy students' perception and understanding of sun awareness and the use of sunscreens, a lecture series was introduced covering a broad range of topics on sun awareness, structure and function of sunscreens and the types, prevalence and treatment of skin cancer in the dermatology module taught in year one of the MPharm programme. This additional learning activity has now been in place for 3 years. General feedback within this module has reported that these activities perform well within the dermatological module. Current work is to investigate specifically if these learning activities have had an effect on pharmacy students' perceptions compared with the previous study. The study involved the distribution and collection of questionnaires during lectures to MPharm students. The questionnaire consisted of 10 questions relating to sunscreens uses; strength of sunscreen (SPF type), habits of reapplication of sunscreens, economic considerations, skin type, and environmental factors. The questionnaire was approved by the University of Brighton ethics committee, all data collected were anonymous. In the previous study, approximately 53% of pharmacy students used sunscreens. This current study has determined that across the total MPharm cohorts now approximately 70% of MPharm students use sunscreens. While this does show an increase of awareness, a longer term study is required to establish if didactic lectures are the best mechanism of raising awareness of sunscreen usage. The other demographical information assessed by the questionnaire had not changed significantly. In addition to this, the delivery of this learning activity has resulted in a novel way to introduce chemical structure activity relationships associated with the activity and protection of the sunscreens molecules. Therefore students have chemistry taught from a non-traditional route which fits into a clinical application. We are currently investigating if this clinical use of chemistry teaching can be applied to other aspects such as practical activities.

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## 67
## Evidence for flocculation-controlled microcrystallisation of salmeterol xinafoate

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The therapeutic management of pulmonary disease depends upon the efficient delivery of aerosolized drug particles with an aerodynamic diameter of 2.5–6 $\mu$m (Pritchard 2001). Particles for such aerosols are routinely produced by jet milling, which can lead to the generation of amorphous regions on the surface or polymorphic conversion. An alternative strategy to directly crystallize the drug and limit subsequent particle growth, would provide the opportunity to avoid potential crystal modification during processing. Precipitation at high supersaturation produces primary particles in the low micron size-range, but secondary growth frequently follows the aggregation and agglomeration of these primary particles (Yu et al 2005). The aim of this study was to investigate the control of crystal growth of salmeterol xinafoate (SX) during crystallization from an aqueous phase. Three separate batches of SX were crystallized by reverse addition antisolvent crystallization according to Murnane et al (2005), by adding 1 part of a 3.5% w/w SX solution to 11.6 parts water (supersaturation, $\sigma$, of 26.9) with overhead propeller stirring (IKAwerk, Germany). Crystallization was monitored using the Lasentec S400 focused beam reflectance measurement (FBRM) probe, and image capture was achieved using the Lasentec PVM camera (Mettler-Toledo Autochem, UK). De-supersaturation was monitored by sampling the crystallization medium, and assaying the filtrate using a validated HPLC method. The filtered crystals were dried in a vacuum oven at 50°C for 10 h, before sizing using a Malvern Mastersizer X in a dispersant solution of SX-saturated 0.1% w/v Span 80 in cyclohexane. There was a statistical difference in the final median particle diameter (MD) (range 3.40–6.07 $\mu$m) (ANOVA, $P < 0.05$) between the three batches, but not between the cumulative 90% undersize (ANOVA, $P > 0.05$). HPLC analysis showed delayed crystallization with $\sigma = 7.13 \pm 0.25$ at 1 min post-addition and $1.75 \pm 0.03$ after 5 min. FBRM shows a rapid rise to high counts of fine particles (1–5 $\mu$m) by the end of the addition of the drug solution (20 s), while PVM showed many small particles, which were highly cohesive. The initial MD was $4.75 \pm 0.10$ $\mu$m. During the period of delayed de-supersaturation, there was a decrease in the count of fine particles in the range of 1–10 $\mu$m, with a concomitant increase in the mean particle diameter. This showed the aggregation of SX crystals, complete within 5 min, to create low counts (small numbers) of large 'particles' ($118.56 \pm 11.30$ $\mu$m). FBRM showed a decrease in counts of particles of chord length 102–500 $\mu$m, as the aggregates underwent attrition during crystallization. Increasing the shear rate led to a decrease in the mean particle diameter, which displayed the friable nature of the agglomerates, as they broke down to form primary particles. There was no significant difference between the initial MD by FBRM and the dried SX crystals ($P = 0.97$). In situ particle characterization has shown that the highly cohesive nascent micron-sized particles of SX may be stabilized against precipitate-aging by undergoing reversible flocculation.

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## 68
## The influence of alcohol on aspirin release from hypromellose matrix tablets

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The potential impact of concomitant alcohol consumption on in vivo release of drugs from modified release oral dosage forms is currently evincing much interest following the suspended marketing of Palladone (FDA Alert, July 2005). Human volunteer studies involving co-administration of drug and significant amounts of alcoholic beverages pose ethical and operational challenges. Consequently, in vitro studies, providing insight on release mechanisms in hydro-ethanolic media could guide formulation programs such that the potential for alcohol related "dose dumping" is avoided. The aim of this investigation was to assess the influence of ethanol on release of aspirin from hydrophilic matrix tablets. Tablets, comprising 149.5 mg Hypromellose (Methocel 2208, K4M; Dow Chemicals Co., USA), 149.5 mg aspirin (acetyl salicylic acid; Sigma Aldrich, UK) and 1 mg magnesium stearate (BDH, UK) were prepared by direct compression on a Manesty F3 single punch tablet press fitted with 8.95 mm diameter, flat punches. Tablets were obtained at crushing strengths (Dr Schleuniger 6D tablet tester) of 5.5–6 kP. Drug release experiments were carried out using B.P. Apparatus 1 at rotation speed 50 rpm in 500 ml of medium at 37°C. Media comprised 500 ml of acetate buffer (B.P.) with 0, 10, 20, 30 and 40% v/v ethanol. For each medium, 6 tablets were tested and drug release was monitored spectrophotometrically at 265 nm. With the exception of the medium containing 40% ethanol (medium v), profiles suggested near-zero order release. Release rates were proportional to the ethanol levels in the medium, although a "dose dumping" effect was not evident. Release profiles in medium (v) were characterized by an initial rapid release with rate progressively reducing over time, suggesting that a diffusion controlled release mechanism predominated. The high standard deviation for the 40% ethanol data could be indicative of non-uniform gel layer generation causing inconsistency in release. This study has shown that hydro-ethanolic media can affect the kinetics and mechanism of drug release from matrix-based controlled release formulations in a manner related to the ethanol content and has highlighted the need for further investigation in this area.

**Table 1** Aspirin release from hypromellose matrix tablets in various hydro-ethanolic media

| Time (min) | Media | | | | |
|---|---|---|---|---|---|
| | i | ii | iii | iv | v |
| 5 | 1.2 ± 0.8 | 0.1 ± 0.3 | 0.5 ± 0.1 | 0.1 ± 0.7 | 8.4 ± 3.8 |
| 15 | 1.9 ± 1.1 | 0.6 ± 0.2 | 2.0 ± 0.2 | 1.8 ± 0.8 | 11.4 ± 5.2 |
| 30 | 3.0 ± 1.1 | 1.9 ± 0.3 | 4.0 ± 0.4 | 4.3 ± 0.9 | 15.7 ± 5.9 |
| 60 | 5.7 ± 1.1 | 4.4 ± 0.5 | 8.3 ± 0.6 | 9.6 ± 1.0 | 24.1 ± 6.5 |
| 90 | 7.9 ± 1.2 | 7.6 ± 0.6 | 11.9 ± 0.4 | 14.4 ± 1.2 | 30.9 ± 7.4 |
| 120 | 10.2 ± 1.2 | 10.4 ± 0.6 | 15.3 ± 0.5 | 18.5 ± 1.4 | 37.0 ± 7.9 |
| 240 | 18.8 ± 1.8 | 21.4 ± 1.1 | 28.3 ± 1.4 | 33.1 ± 2.0 | 56.4 ± 9.3 |
| 360 | 27.4 ± 2.3 | 31.9 ± 1.7 | 39.4 ± 2.2 | 45.1 ± 2.6 | 69.9 ± 9.9 |

(% released ± s.d. n = 6 for each data set).

U.S. Food and Drug Administration alert for healthcare professionals (2005)

## 69
## The use of Dynamic Mechanical Analysis (DMA) to determine film properties in-situ on pharmaceutical pellets

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The production of single-unit dosage forms as modified release preparations using film-coated pellets is not a straightforward process and many factors must be taken into consideration when formulating such a dosage form. The ultimate success of the single-unit dosage form is dependent on the properties of the drug containing pellets, the cushioning excipients used and the properties of the film coating. The mechanical properties of the film coating have traditionally been assessed on so-called "free" or "cast films", however it is questionable to what degree such films can accurately represent the "true" properties of the film. In a recent study, Podczeck & Almeida (2002) have shown that in principal it is possible to use Dynamic Mechanical Analysis (DMA) to investigate the mechanical properties of films on pellets. Therefore these principal findings formed the basis of this research, which involves the investigation of the mechanical properties of several film coating formulations in-situ on drug-containing pellets using DMA. Non-osmotic pellets (Microcrystalline cellulose (MCC) & Theophylline) and osmotic-pellets (MCC/Glucose/Theophylline) were produced using a process of extrusion and spheronisation, which were then subsequently coated using a Uni-Glatt bottom spraying (Wurster system) technique (Glatt GmbH, Dresden, Germany) with a polyvinyl acetate dispersion stabilized with povidone and sodium lauryl sulphate (Kollicoat SR 30D) (BASF Aktiengesellschaft, Ludwigshafen, Germany) a plasticizer, Eudraflex (Triethyl Citrate, Röhm GmbH, Darmstadt, Germany) and a fluorescent dye, Fluorescein Sodium (Sigma-Aldrich, St Louis, USA) according to central composite design. The variables in the design were coating film thickness and percentage plasticizer (Table 1). The film thickness was initially estimated by calculating the amount of coating required per gram of pellets, taking into account the mean diameter and surface are of the pellets and the calculated volume and density of the coating layer. Once coated the film coating thickness for each pellet batch was verified using Confocal Laser Scanning Microscopy (CLSM) (Omnichrome Corp., California, USA). The mechanical properties of the pellets were then studied using a DMA7 (Perkin Elmer Corp., High Wycombe, UK) with a parallel geometry (5 mm diameter of the top moving plate). During the testing procedures, samples were equilibrated at $20 \pm 0.1$°C and purged with Helium (20 ml min$^{-1}$), and the results are the mean and standard deviation of 10 pellets. Static scans were performed on all pellet batches,

**Table 1** Central composite design for pellet film-coating

| Batch | | % Plast. | Film thickness ($\mu$m) | |
|---|---|---|---|---|
| | | | Target | Achieved |
| 1 | low × centre (−1.414, 0) | 0 | 60 | 55.18 ± 2.52 |
| 2 | low × low (−1, −1) | 2 | 35 | 36.44 ± 0.94 |
| 3 | centre × low (0, −1.414) | 5 | 20 | 21.81 ± 0.83 |
| 4 | high × low (+1, −1) | 8 | 35 | 35.17 ± 0.93 |
| 5 | centre (0,0) | 5 | 60 | 57.85 ± 1.12 |
| 6 | high × centre ( + 1.414, 0) | 10 | 60 | 58.89 ± 1.02 |
| 7 | low × high (−1, + 1) | 2 | 85 | 81.45 ± 2.29 |
| 8 | high × high ( + 1, + 1) | 8 | 85 | 81.49 ± 1.04 |
| 9 | centre × high (0, + 1.414) | 5 | 100 | 96.24 ± 1.61 |

**Table 2** Young's Modulus data for osmotic & non osmotic pellet batches

| Batch No. | Young's Modulus (MPa) | | | |
|---|---|---|---|---|
| | 10% Osmotic | 20% Osmotic | 10% Non Osmotic | 20% Non Osmotic |
| 1 | 6.69 ± 0.21 | 7.53 ± 0.29 | 8.19 ± 0.67 | 8.48 ± 0.33 |
| 2 | 6.58 ± 0.33 | 5.44 ± 0.44 | 6.73 ± 0.30 | 7.81 ± 0.38 |
| 3 | 6.59 ± 0.33 | 6.59 ± 0.46 | 7.50 ± 0.40 | 6.52 ± 0.31 |
| 4 | 6.72 ± 0.33 | 6.93 ± 0.53 | 7.66 ± 0.27 | 8.42 ± 0.28 |
| 5 | 6.95 ± 0.37 | 5.65 ± 0.29 | 6.47 ± 0.40 | 7.83 ± 0.54 |
| 6 | 6.60 ± 0.22 | 6.46 ± 0.33 | 4.66 ± 0.24 | 6.50 ± 0.37 |
| 7 | 4.73 ± 0.31 | 6.43 ± 0.33 | 6.37 ± 0.42 | 7.19 ± 0.48 |
| 8 | 6.61 ± 0.35 | 5.40 ± 0.40 | 5.19 ± 0.29 | 6.29 ± 0.36 |
| 9 | 5.58 ± 0.38 | 5.59 ± 0.35 | 3.73 ± 0.24 | 5.77 ± 0.33 |
| 10(un/c) | 7.59 ± 0.28 | 5.97 ± 0.48 | 6.47 ± 0.86 | 6.94 ± 0.60 |

un/c = uncoated control (% refers to the amount of drug).

the modulus of elasticity was calculated from the slope of the linear portion of the stress-strain curves and are presented in Table 2. Analysis of variance (ANOVA) showed that both the plasticizer concentration and film thickness are interacting influence factors on the elasticity of the films. ANOVA also showed that the elasticity values obtained on coated pellets are significantly different from control values obtained from uncoated pellets, demonstrating that the method indeed assesses film properties.

Podczeck, F., Almeida, S. M. (2002) *Eur. J. Pharm. Sci*. **16**: 209–214

## 70
## Colonic drug delivery: an investigation into the use of starch as a coating material

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Starch is a complex polysaccharide composed mainly by the essentially linear amylose and the branched amylopectin. When starch is heated in an excess of water above its glass transition temperature (Tg), the starch granules swell to many times their original size and a gel structure is formed. Upon cooling this gelatinized, non crystalline starch begins to reassociate into a crystalline structure via a phenomenon known as retrogradation (Ring et al 1988). This retrograded starch resists hydrolysis by pancreatic amylase but stills undergoes digestion in the colon (Englyst & Cummings 1987). Dosage forms coated with retrograded starch can therefore be of great interest in the targeting of drugs into the colon. Previous studies using glassy amylose have proven its efficacy in the colonic delivery of 5-aminosalicylic acid both in vitro and in vivo (Milojevic et al 1995). However, for it to be used as a film coating material, organic solvents were required and its swelling properties in aqueous media had to been controlled by mixing it with ethylcellulose, a water insoluble polymer. In this study, simple aqueous dispersions of different starches of pharmaceutical use (Hylon VII, Hylon V and IM-DS acetate starch), pure resistant amylose and amylopectin plasticized with dibutyl sebacate were mixed with a insoluble polymer-Surelease in a ratio of 1:5 related to the weight of the dry polymers and applied as coating material onto pellets containing 5-aminosalicylic acid as a model drug. The potential of these systems was assessed in vitro, in both 0.1 N HCl (pH 1.2) and phosphate buffer (pH 7.2). The systems that did not show any drug release in any of the medias over a period of 8 h were further assessed in artificial gastric and intestinal juices containing commercially available pepsin and pancreatin, respectively. Additionally, $\alpha$-amylase from hog pancreas dissolved in phosphate buffer, pH 7.2 was used in the formulations that showed resistance to be digested in the artificial intestinal juice. This was also performed over a period of 8 h. The pellets coated with the starches and pure resistant amylose showed no drug release at both pH values tested. However, when amylopectin was used as a coating material the rate of drug release was very high. In the artificial gastric juice again the formulations did not show any significant drug release. When tested in the artificial intestinal juice all formulations showed a minor drug release after 4 h. From the above results it can be argued that the tested starch coatings can be use in colonic drug delivery since no significant drug release can be expected in the upper gastrointestinal tract. However future studies in colonic conditions will prove the feasibility of these coatings in colonic drug delivery.

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## 71
## Small scale high shear wet granulation as a screening technique to evaluate processing differences in dicalcium phosphate dihydrate from two suppliers

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Dicalcium phosphate dihydrate (DCPD) is an insoluble diluent with low hygroscopicity and good mechanical strength on compression. Its manufacturing process has been shown to affect crystal size, structure, shape and propensity to dehydrate at low temperatures and high humidity (Carstensen 1988). Therefore, it is possible that pharmaceutical processing (e.g. wet granulation) could be subject to batch-to-batch or supplier variability. Three batches each of two sources of DCPD were compared in this study – Calipharm D (Rhodia) and Dicalcium Phosphate Powder (Astaris). Their certificates of analysis highlighted no apparent differences, which was supported by preliminary laser diffraction particle size analysis (Sympatec). To investigate the wet granulation of these materials, duplicate 50 g samples were granulated at 250 mL scale (MiPro, ProCepT) at three water levels (10 mL, 12 mL and 14 mL). DCPD was granulated on its own to eliminate the introduction of sources of error from other excipients. As would be expected, increased granulation water content resulted in differences in the impeller torque-time profiles for each material. Within supplier batch-to-batch variability was not detected. However, differences between the profiles of the Rhodia and Astaris material were noted, which are most easily represented by the area under the torque curve (AUC) (Table 1). Furthermore, the granulation products were visibly different (Table 2). To determine the source of these differences, some preliminary characterisation was performed. BET surface area (Gemini, Micromeritics) for the Astaris material was found to be 2.2 (± 0.2) $m^2$/g, as opposed to 3.7 (± 0.3) $m^2$/g for the Rhodia samples. It is possible that the Astaris material's lower surface area caused increased surface saturation by water, resulting in its tendency to overgranulate with less water. Subjecting the samples

**Table 1** Torque-time curve AUCs

| Water level (mL/50 g) | AUC (Nm s) (n = 6) | |
|---|---|---|
| | Rhodia | Astaris |
| 10 | 16.6 (± 0.9) | 15.9 (± 0.8) |
| 12 | 16.4 (± 0.7) | 19.1 (± 0.6) |
| 14 | 19.3 (± 0.1) | 22.9 (± 2.1) |

**Table 2** Wet mass visual evaluation

| Water level (mL/50 g) | Observations | |
|---|---|---|
| | Rhodia | Astaris |
| 10 | Undergranulated fines | Discrete granules |
| 12 | Discrete granules | Larger aggregates |
| 14 | Larger aggregates | Paste |

to a two cycle moisture sorption-desorption isotherm (0–95–0% RH, 25°C) (Dynamic Vapour Sorption, Surface Measurement Systems) showed that the Rhodia material undergoes a much slower cycling through each moisture uptake and loss cycle (~28 h), as compared with the Astaris material (average cycle time = ~14 h). The Rhodia samples also displayed hysteresis in failing to return to their original dry mass after either moisture sorption cycle, presumably due either to the retention of sorbed moisture within the particle or a re-crystallisation event (although there was no other evidence of this). The difference in surface area between the two materials is not thought sufficient to fully explain this behaviour. Further characterisation of both materials is planned, particularly focusing on their surface properties. This work has demonstrated the value of screening excipients for wet granulation at small scale to identify potential differences. These findings indicate that changing DCPD supplier for an established formulation might not be trivial, although studies on the formulation itself would be required to confirm this.

Carstensen, J. T. (1988) *Drug Dev. Ind. Pharm.* **15**: 1927–1969

## 72
## Characterisation of gelatin films and correlation with dissolution of gelatin film-coated caplets

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An alternative film coating technology for solid dosage forms employing aqueous solvents has been reported (Laru et al 2006). Manipulation of the film formulation can be used to minimise lag times prior to onset of dissolution, which could delay the onset of action. The aim of this study was to investigate if a decrease in dissolution rate, or an increase in lag time, for a free-film used in the coating process would have a corresponding effect on tablet dissolution once coated onto the tablet. Ingredients for the films were mixed at 40°C prior to casting with a Multicator 411 casting knife. Dried and conditioned (52% RH) films were placed within a rigid wire mesh prior to dissolution in phosphate buffer, pH 5.8. Samples were analysed by microviscometry (Anton Paar). Mechanical properties of free-films (films prior to coating) were studied using Hounsfield Test Equipment (Laru et al 2005). The films for the coating procedure were prepared as above and once dried, they were heated to their transition temperature (determined using DSC) to induce flexibility. A vacuum was then applied and the films pulled around paracetamol tablets forming a thin film coating. The weight gain was measured and the tablets stored in a desiccator until use. Drug dissolution from coated tablets was studied in a USPII dissolution bath (phosphate buffer pH 5.8, 50 rpm). Simple formulations containing a mixture of gelatin and glycerol were cast at different thicknesses. They showed a lag time of $1.02 \pm 0.33$ min at a thickness of 0.05 mm but a thicker film had a delay in onset of $3.61 \pm 0.34$ min. A scatter plot of thickness versus lag time for a variety of free-film formulations ($n = 35$) showed a weak positive correlation ($R^{2=}0.464$), therefore lag time is not dependent on thickness alone. A film formulation was developed using gelatin, glycerol and additional $MgCO_3$. In isolation, it had a lag time of $2.55 \pm 0.26$ min at pH 5.8. The elastic modulus was low ($0.57 \pm 0.18$ MPa) indicating the film was soft and plasticized possibly due to intermolecular forces being reduced between the polymer molecules (Aulton 1995). The film thickness was $0.100 \pm 0.006$ mm, which is higher than the average (0.06 mm). The mechanical properties of this film made it impossible to use in the coating technology so the formulation was modified by increasing the plasticizer and including a surfactant, Brij 35. The extended lag time was maintained when tablets were coated with this film: $4.37 \pm 0.22$ min for paracetamol tablets coated with this film, compared to a lag time of only $0.93 \pm 0.34$ min for a HPMC-coated formulation. Thus the preliminary tests to measure dissolution properties of the film in isolation can predict the subsequent effects on a coated solid dose formulation and can therefore be used in a screening process. This is a great advantage as similar direct correlation is not possible for conventionally pan-coated formulations.

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Laru K. J. et al (2005) *J. Pharm. Pharmacol*. **57**: S227

Laru K. J. et al (2006) *Proceedings of Helsinki Drug Research 2006*, In press for *Eur. J. Pharm. Supp*.

## 73
## Making the best ice cream: it's all in the mix

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Ice cream represents an oil-in-water emulsion based on milk fat, where the fat globules are coated with protein/emulsifier layer (Goff 1997). To improve the quality of an ice cream emulsion, it is important to define the main factors affecting their physico-chemical properties, since the components of a mixture and certain processing parameters can greatly determine the behaviour of emulsions upon emulsification, processing and storage (Granger et al 2003). The aim of this study was to investigate the effect of varying different components involved in ice-cream manufacture on the physico-chemical characteristics of the resulting emulsion, and hence determine the ingredients needed to formulate the best ice cream. Oil-in-water emulsions based on a protein mixture (skimmed milk powder (SMP) 10% w/v) were prepared by the two-step homogenisation process, similar to that described elsewhere (Granger et al 2005). Three types of emulsifiers (saturated and polyunsaturated mono-di-glycerides, and polysorbate 80, 0.3% w/v), four oils (castor, peanut, mineral and vegetable, 8% w/v) and three viscosity modifiers with locust bean gum 0.2% w/v (glycerol, sucrose and trehalose, 12% w/v) were studied. All emulsions were characterised in terms of mean fat globule size, viscosity and the effect of ageing for 24 h at 4°C, and compared with commercially available ice creams. Initially, emulsions based on polysorbate 80 were studied, and those formulated with vegetable oil exhibited significantly ($P < 0.05$) smaller globule sizes ($5.5 \pm 0.6\ \mu$m) when compared with emulsions formulated with castor, peanut and mineral oil ($14.1 \pm 0.9\ \mu$m, $11.4 \pm 1.9\ \mu$m and $11.1 \pm 0.9\ \mu$m, respectively). Upon ageing, all formulations showed an increase in globule size as a consequence of coalescence. The remainder of the prepared emulsions were thus based on vegetable oil. Upon the addition of viscosity modifiers in combination with locust bean gum to the formulation, much smaller globule diameters were seen (glycerol: $2.9 \pm 0.2\ \mu$m, sucrose: $2.4 \pm 0.1\ \mu$m, trehalose: $2.9 \pm 0.1\ \mu$m), as well as increased viscosity. Although ageing promoted slight aggregation of the particles, these emulsions displayed only creaming instability over the measured time period, in contrast to the previous emulsions, which had coalesced, suggesting greater emulsion stability. Presence of both saturated mono-di-glycerides (SMDG) and partially unsaturated mono-di-glycerides (PUMDG) promoted increased viscosity, in comparison with the emulsion based on polysorbate 80, although PUMDG exhibited a significantly ($P < 0.005$) smaller mean globule size ($2.3 \pm 0.1\ \mu$m) than SMDG ($3.0 \pm 0.04\ \mu$m). Once again, ageing led to creaming of the emulsions, yet the globule size remained almost constant, particularly for the PUMDG formulation ($2.3 \pm 0.1\ \mu$m), and viscosity increased, suggesting that these emulsions were well stabilised in comparison to the other formulations tested. In addition, the characteristics exhibited by the PUMDG formulation correlated well with commercially available products ($2.6 \pm 0.1\ \mu$m mean globule size). Overall, these results demonstrated the interaction occurring between emulsifier, oil and sugar content of the mix, with the characteristics and the suitability of the emulsions for use as ice creams being very much dependent on the ingredients used.

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## 74
## Effect of granulating conditions in the preparation of hypromellose (HPMC) matrix tablets using ethanol-water as granulation fluid

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An aqueous alcoholic solution is one of the suitable solvents to prepare hydrophilic matrix tablets using hypromellose (HPMC) by wet granulation. Because HPMC is a water-soluble viscous polymer with high water uptake capacity, process control using aqueous wet granulation tends to be difficult. In this study, the effect of ethanol-water ratio and granulation time was examined. The basic formulation was: theophylline 26.4 mg/tab HPMC (type 2208, 4000 mPa·s) 64.5 mg/tab and magnesium stearate 1.5 mg/tab (total tablet weight 330 mg). The HPMC used in this study was METOLOSE 90SH-4000SR (Shin-Etsu Chemical Co., Ltd), which had a specification of the mean particle size between 40 and 60 micrometers. The granules for tableting were prepared by wet granulation using a high shear mixer. Alcohol content in the granulation liquid has a strong influence on the wet granulation process, especially on the formation of aggregates. Lower content of ethanol (high water content), increases the average particle size. The granules prepared with high ethanol content showed many pores, but the granules prepared by high water content were compacted. Particle structure can affect the tablet hardness. Higher tablet hardness was observed in the case of high ethanol content in the granulation liquid. However, the ethanol content has no effect on the dissolution profiles. The formation of granules will typically continue with granulation time, but this is not the case with 80 % ethanol. The initial aggregates seem to be formed by liquid bridge and then gradually drying. This is due to insolubility of HPMC in 80 % ethanol. After 20 min, average particle size decreased but certain densification was observed. This particle structure can affect the tablet hardness. Higher tablet hardness was observed in the case of short granulation time. However there is no difference of the dissolution profiles. Ethanol content and granulation time in wet granulation process for hydrophilic matrix tablets were examined. To avoid excess granulation, aqueous alcoholic solution with 80 or 90% ethanol were found to be effective. No further granulation takes place due to insolubility of HPMC in 80% ethanol. The dissolution of the matrix tablets produced consistent results, with almost no difference in dissolution profile. This

suggests that it will not be difficult to optimize the wet granulation process during scale up. In conclusion, a solution of 80 or 90% ethanol is recognized as the optimal granulation solution for hydrophilic matrix tablets.

**75**

## Influence of low-substituted hydroxypropyl cellulose (L-HPC) on drug release from nifedipine-HPMCAS (hypromellose acetate succinate) solid-dispersion granules and tablets

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In our previous study, HPMCAS (hypromellose acetate succinate) was found to be an effective carrier for solid dispersions of a poorly-soluble drug Nifedipine (Tanno et al 2004). To study on more convenient dosage forms, we prepared granules and tablets of NP-HPMCAS solid dispersions using L-HPC (low-substituted hydroxypropyl cellulose) as a disintegrant and evaluated properties of these dosage forms. The materials were as follows. Carrier for solid dispersions: hypromellose acetate succinate (HPMCAS, Shin-Etsu AQOAT, Shin-Etsu Chemical, Japan) Tablet excipients: low-substituted hydroxypropyl cellulose (L-HPC, LH-B1, Shin-Etsu Chemical, Japan), croscarmellose sodium (cl-CMC-Na, Ac-Di-Sol, FMC), microcrystalline cellulose (MCC, Avicel PH-101, FMC), Mg stearate (Kyoudo Yakuhin, Japan). Preparation of solid-dispersion granules and tablets: NP and HPMCAS were dissolved together in ethanol–water (8:2 w/w). By spraying this solution as a granulation binder, a mixture of lactose and cornstarch was granulated in a fluidized-bed granulator. L-HPC was added internally (i.e. granulated together with lactose and cornstarch) or externally (i.e. added after granulation). The obtained granules were sieved and compressed into tablets after dry-blending with a lubricant (Mg stearate). For comparison with L-HPC, a combination of MCC/cl-CMC-Na was also tested. For granules, drug dissolution from the obtained solid dispersions was improved compared with the physical mixture (approx. 3–9 fold). Granules with L-HPC showed even faster and higher drug dissolution, especially by internal addition. This is probably because the L-HPC incorporated in granules enhanced the wettability and facilitated the dispersal of the drug particles resulting in increased surface area. A combination of MCC and cl-CMC-Na was also effective by internal addition. Although the drug dissolution from the solid dispersions was improved compared with the physical mixture (approx. 2–8 fold), the tablets showed lower dissolution than those from granules due to decrease of surface area and slow disintegration. However, tablets with disintegrant showed greater drug dissolution. The external addition of L-HPC was the most effective for the drug dissolution, since L-HPC accelerated the tablet disintegration and dispersed the drug finely. In the case of the internally-added L-HPC, the disintegration time of the tablet was longer than that with external-addition. In the case of tablets, the external addition was more effective, while the internal addition was more effective for granules. All tablets had similar hardness (approx. 90 N). In conclusion, using L-HPC as a disintegrant, it is possible to prepare tablets of NP-HPMCAS solid dispersions with improved dissolution and unique characteristics.

Tanno et al (2004) *Drug Dev. Ind. Pharm*. **30**: 9–17

**76**

## Comparison between direct compression and wet granulation method in the preparation of hydrophilic matrix tablets using hypromellose (HPMC)

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The objective of this study was to compare direct compression and wet granulation for preparation of hydrophilic matrix tablets using Hypromellose (HPMC). Two mixtures with the same basic formulation were prepared separately using wet granulation and dry mixing. Tablet productivity using a rotary tablet machine was investigated, specifically for tablet weight deviation. Tablets from each method were examined with respect to tablet properties and drug release profiles. The basic formulation was: theophylline 26.4 mg/tab, HPMC (type 2208, 4000 mPa·s) 64.5 mg/tab and magnesium stearate 1.5 mg/tab (total tablet weight 330 mg). The HPMC was METOLOSE 90SH-4000SR (Shin-Etsu Chemical Co., Ltd), which had a specification of the mean particle size between 40 and 60 micrometers. For the wet granulation method, the granules for tableting were prepared by wet granulation with a high shear mixer using 80% ethanol as granulating liquid. For the direct compression method, the theophylline powder was granulated with a fluid-bed granulator using HPMC, type 2910, 6 mPa·s (Pharmacoat 606, Shin-Etsu Chemical Co., Ltd) as a binder to improve flowability. The hardness of the tablet prepared from wet granulation was lower than from direct compression. It appears that the densification of the compressive stress that occurs during wet granulation reduced compressibility. Wet granulation produced less tablet weight deviation although that of direct compression is acceptable for practical use. The granules prepared from wet granulation had better flowability and high density compared with those from direct compression. The dissolution profile of the tablet from wet granulation was slightly lower than from direct compression. It is therefore assumed that the granules prepared from wet granulation were more compact. However, such a slight difference can be controlled through modification of the formulation, which can be done by increasing the Hypromellose content in direct compression. Theophylline tablets made by both direct compression and wet granulation method were evaluated. Small differences were observed in the tablet properties and productivity from the comparison of both methods using the same formulation. However, both tablets showed almost the same dissolution profile in spite of a slight difference in hardness. In conclusion, there was no significant difference between the two methods under the conditions used in this study.

**77**

## Targeting improvement of Tat-derived peptide based gene delivery using laminin receptor binding ligand (YIGSR)

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Cell specificity is one of the major obstacles for efficient gene transfer. Recently, cell penetrating peptides (CPPs) have been widely used to facilitate the internalization of different bioactive molecules across the plasma membrane (Gupta et al 2005). Tat-derived peptide one of the most characterized CPPs has been shown to mediate gene delivery. Due to its highly cationic nature, however, the cellular selectivity of Tat-derived peptide is generally regarded non-specific relying mainly on electrostatic interaction with negatively charged membrane components, which eventually may hinder its clinical application in gene therapy (Suzuki et al 2002). In an attempt to improve the selectivity of CPPs, Tat-derived peptide sequence was combined with a laminin receptor-binding domain to construct Tat-YIGSR analogue. The cellular uptake of both peptides namely Tat and Tat-YIGSR in two different cell lines including HT1080 and HT29 was assessed by confocal microscopy and flow cytometry FACS using live (unfixed) cells. The ability of both peptides to bind and condense DNA was examined using YOPRO-1 fluorescence assay. Transfection efficiency of both peptides was evaluated using a luciferase reporter gene. Flow cytometry data indicates that almost all the cells were able to internalise the peptide but uptake was heterogeneous. HT1080 cells exhibited ~4 fold higher uptake of the Tat-YIGSR sequence compared to HT29 cells. Conversely, both cell lines responded almost equally well to Tat-derived peptide. Confocal microscopy analysis did not reveal any obvious differences in the intracellular localisation of both peptides displaying a diffused fluorescent signal throughout the cell in both cell lines tested. Even as low as 1 N/P ratio, both peptides showed efficient DNA condensation displaying little residual fluorescence. In the case of HT1080, a significant improvement in gene transfection was achieved using Tat-YIGSR compared with Tat peptide at different N/P ratio charge ratios reaching ~ 27 fold increase at the highest N/P ratio. By contrast, a decreased level of gene expression was observed in HT29 cells using Tat-YIGSR compared to Tat. In summary, despite the reduced level of internalization of Tat-YIGSR peptide in both cell lines tested compared to Tat, its ability to selectively enhance the gene expression in laminin receptor positive cell line -HT0180- was apparent. These findings demonstrate that Tat-YIGSR peptide can potentially be utilized to enhance gene expression and selectivity to HT1080 cells.

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**78**

## Multi-particulate process miniaturisation

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Multi-particulate dosage form development (including drug and functional polymer coating) is routinely conducted by fluid bed processing methods. For a number of development type machines, batch sizes of > 500 g are generally required to run an efficient process and achieved the desired product quality. For product enhancement entities or generic API's (Active Pharmaceutical Ingredient) this is generally not an issue due to API availability and cost. However, for early research formulation and process development processing at this scale is not ideal due to limited API quantities, high consumption of API relative to conventional tablet dosage form and long processing times. Therefore, work was conducted to identify a laboratory scale fluid bed processor capable of manufacturing small-scale, high quality, development and cGMP multi-particulates. Three laboratory scale fluid bed processors were chosen for assess-

ment, Aeromatic Strea-1 (Huettlin processing chamber), Glatt MiniGlatt and a Glatt GPCG-1 (3.5″ insert chamber). To assess the machine performance three known coating processes were trialled: Opadry II cosmetic coat, L-aspartic acid aq suspension (model for poorly soluble drugs) and Eudragit RS/RL30D (proprietary aq polymethacrylate polymer system for controlled release membranes). The coating processes at this scale were controlled by product temperature and a visual assessment of bead fluidisation using batches sizes recommended by the manufacturer. Post processing, the multi-particulates were compared for quality against multi-particulates produced at the kilo scale looking at process responses including spray efficiency and process time. Multi-particulate quality was compared by determination of assay (titrometric), morphology (SEM) and drug release (in-vitro dissolution). From these experiments comparable coating quality was achieved to that at the kilo scale using all three coating machines. Target assay and similar porous coating morphology was achieved for L-aspartic acid. Similarly coating morphology and total drug release and rate for the Eudragit RS/RL30D coated multi-particulates were comparable to the kilo scale process. This was achieved at 50 g scale for both the Glatt MiniGlatt and Aeromatic Strea-1 (Huettlin processing chamber) as well as 225 g scale for the Glatt GPCG-1 (3.5″ insert chamber). Spray efficiencies for all machines were not as high as at the kilo scale, especially for Eudragit RS/RL30D (43–69% vs 96%), however, this was considered to be due static build-up and subsequent variable fluidisation. Processing times were similar to the kilo scale process as slow spray rates were required to maintain product temperature. In conclusion it was demonstrated that the Glatt MiniGlatt and Aeromatic Strea-1 (Huettlin processing chamber) could be used to manufacture relatively complex drug and polymer coated multi-particulates at the 50 g scale. This would allow multi-particulate development and cGMP manufacture using significantly reduced quantities of API and subsequent rapid evaluation of clinical proof-of-concept.

**79**

## An approach to maximise drug loading for oral tablets via formulation and process design

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Compound A is a highly viscoelastic API that has good compression properties and is formulated as a low dose, immediate release tablet using a dry granulation approach. To increase the drug loading without excessively increasing the tablet size, a change of granulation approach was warranted based on previous poor compression performance. Therefore a study was conducted to investigate alternative dry granulation and High Shear Wet Granulation (HSWG) approaches to achieve high drug (approx. 50% w/w) loading tablets demonstrating acceptable in-vitro drug release and processing performance. For the HSWG approaches a number of formulations were investigated, each with a different diluent, binder or disintegrant. Eight formulations (2 dry granulation, 6 HSWG) were assessed in total via nine characterisation techniques at each stage of tablet core manufacture. The tests included: blend – compression profiling (compaction simulation) and true density (i.e. roller compacted ribbon solid fraction); granules – compression profiling (compaction simulation), flow (Flodex and axial shear cell) and morphology (scanning electron microscopy, mercury porosimetry and particle sizing); tablet cores – in-vitro performance (USP I dissolution and disintegration) and tablet morphology (x-ray microtomography). HSWG granules exhibited excellent flowability and narrow particle size distribution. SEM revealed round consolidated agglomerates typical of HSWG. Conversely, the dry granulated granules exhibited inconsistent particle size distributions and very poor flow behaviour. Compaction simulator testing showed that relatively strong, robust tablet cores were produced as a result of the HSWG process, with croscarmellose sodium (Ac-Di-Sol) identified as the disintegrant of choice. However, a reduction in the compression properties of wet granulated tablet cores when compared to the roller compacted formulations was seen (dry gran RTS = ~ 3.7 MPa c.f. HWSG RTS = ~ 1.8 MPa at 15 kN compression force). For HSWG, dissolution testing in pH 6.8 phosphate buffer and mercury porosimetry indicated that the Ac-Di-Sol containing tablets were superior to those containing sodium starch glycolate (Explotab), with a ~ 10% increase in release during dissolution within 30 min. Thus, it was shown to be the preferred disintegrant. From this study it was shown that using a HSWG formulation approach, 50% w/w drug loading could be readily manufactured to deliver acceptable tablet performance. Resultantly, tablet size may be significantly reduced using this approach to potentially aid patient compliance and optimise market image. Additional studies are recommended to optimise the HSWG formulation and process to improve the compression performance of the granules and ensure appropriate tablet core process robustness at scale.