of the MAA was increased the degree of swelling increased, with maximum swelling occurring with films containing 70% HEMA/30% MAA. The gentamicin loading capacity followed a similar trend. 100% HEMA formulations displayed minimal swelling and consequently a low gentamicin loading and release was achieved.

**Conclusions** Following development of a quick and reliable assay method, this study has shown that, through copolymerizing MAA into poly(HEMA) networks, gentamicin can be successfully incorporated into and released from these hydrogels. Gentamicin levels achieved were in excess of known bactericidal concentrations of obtained clinical endophthalmitis isolates. Increasing crosslink density within the copolymers had a significant effect on decreasing the rate of diffusion of gentamicin from the hydrogel matrix, thus improving the controlled-release nature of the delivery system.

Arcelloni, C. et al (2001) *J. Chrom. B.* **753**: 151–156
Isoherranen, N., Soback, S. (2000) *Clin. Chem.* **46**: 837–842

### 63
### Modification of poly(vinyl chloride) biomaterials to yield surface-immobilized hydrogel layers

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**Objectives** Poly(vinyl chloride) (PVC) is one of the most common polymeric biomaterials currently in use in healthcare devices such as endotracheal tubes and catheters (Pritchard 2002). As is often the case, bacterial colonization of the PVC surface represents a major issue, contributing to poor patient outcomes, increased hospital stays, and increased costs. A prime example of this is the implication of the endotracheal tube in the development of ventilator-associated pneumonia (Vincent 2003). Adherent bacteria readily colonize such surfaces, surrounding themselves with thick exopolysaccharide matrix to form biofilms, which are difficult to treat. In the biofilm form, bacteria become much more resistant to conventional antibiotic therapies, making treatment of resultant ventilator-associated pneumonia difficult (Adair et al 1999). This work will use a surface modification approach to graft a hydrogel layer on to PVC which can be used for local antibiotic delivery to treat infection, while improving the durability of the hydrogel over current coating methods and retaining the bulk mechanical properties required for device performance.

**Methods** Thiol-mediated chemical functionalization was used to covalently attach allyl mercaptan to PVC. PVC (3 cm × 3 cm × 200 $\mu$m) was immersed in a mixture of dimethyl formamide/water (5:1 v/v) with allyl mercaptan (0.01 mol) and stirred at 60°C for 6 hours. The PVC sample was removed, washed and dried before further use. Further modification was achieved by polymerization of 2-hydroxyethyl methacrylate (HEMA) across the vinyl-functionalized PVC surface, using azoisobutyronitrile (AIBN) as an initiator. The surface of these materials was examined throughout the process using attenuated total reflectance (ATR)-Fourier-transform infrared (FTIR) spectroscopy and Raman spectroscopy. Initial drug-loading and -release studies have been performed.

**Results** Both ATR-FTIR and Raman spectroscopies confirm the initial modification with allyl mercaptan and the subsequent attachment of the hydrogel layer on to PVC. Raman mapping shows complete surface coverage of PVC with poly(HEMA). Initial study of the drug-delivery potential of the material shows promise, indicating successful drug uptake and release from the hydrogel layer.

**Conclusions** An efficient method for functionalization of PVC surfaces with a hydrogel layer has been demonstrated. Such modification has been shown to represent a potential method for the creation of a permanent drug capture-release coating for delivery of antibiotics directly to the site of the bacterial biofilm.

Adair, C. G. et al (1999) *Intens. Care Med.* **25**: 1072–1076
Pritchard, G. (2002) *PVC World Markets Prospects* **16**: 109–114
Vincent, J. L. (2003) *Lancet* **361**: 2068–2077

## Pharmaceutical Technology

### 64
### Development and validation of a near-infrared method to monitor the loss on drying within commercial single-pot processors

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**Objectives** Development and validation of two non-invasive near-infrared (NIR) chemometric calibrations for rapid monitoring of the online percentage loss on drying (% limit of detection, LOD) of a potent product to allow reduced operator exposure was required. Successful calibration models must target a percentage LOD value of 4.6% w/w, with sufficient accuracy to ensure that the predicted NIR result was within the specification limits of 3.8–5.4% w/w.

**Methods** An ABB Bomem Fourier-transform NIR spectrometer (ABB Bomem, FTPA2000–260-NetworkIR) was installed with two multiplexed diffuse reflectance probes. These probes were fitted to two separate single-pot processors (SPPs, Ultima 300, Collette, N.V, Wommelgem, Belgium). Development and validation spectra were collected external to the SPPs, due to the difficulties of safe operator access within the SPPs with a sample interface designed to mimic the probe's optical configuration within the body of the SPP. An external relative reflectance standard (99% relative reflectance standard) was used for all spectral background measurements. Samples throughout the drying run from five different development batches were removed directly from the SPP, their spectra collected and the registered reference analysis method performed. These spectra were then distributed between a calibration and internal validation set. Each sample's spectra were collected in triplicate over the wavelength range 10000–4000 $cm^{-1}$ and the sample was stirred between replicate spectra. A resolution of 16 $cm^{-1}$ and 64 co-averaged spectra were selected. Correct operation of spectrometer was verified before use with AIRS software (ABB Bomem, AIRS version 3.1 QA/QC data-acquisition and reporting package) and spectral collection was accomplished with GRAMS/AI software (Thermo Galactic, GRAMS-AI7 data-acquisition and spectroscopic package).

**Results** Spectra and reference results from the calibration sets were used to develop two separate quantitative calibration models for each SPP within the quantitative PLS/IQ software of GRAMS. This enabled accurate prediction of samples with a percentage LOD content of between 2.5 and 8.0% w/w. Predicted spectra that resulted in a $F$ ratio of more than 4.04 (95% probability of being spectrally dissimilar from the calibration model) due to incorrect sample presentation during spectral collection or reference analysis error were rejected (Haaland and Thomas 1998, Mark 1986). The average error of the reference method was determined as 0.4% w/w and was equivalent to the standard error of calibration from the two NIR calibration models. The standard error of prediction was calculated as 0.4 and 0.3% w/w for the two separate SPPs' internal accuracy prediction and 0.7 and 0.3% w/w for an independent sample lot. Spectra from two validation lots on each SPP were predicted with the calibration models and successfully met acceptance criteria for accuracy, linearity, precision, intermediate precision and robustness.

**Conclusions** The calibration models were successfully validated with a high degree of confidence that at the target value the result would meet the specification and offer reduced exposure, rapid quantification and equivalent accuracy to the registered method.

Haaland, D. M., Thomas, E. V. (1988) *Anal. Chem.* **60**: 1202–1208
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### 65
### Process optimization of aqueous ethylcellulose (Surelease®) film-coated paracetamol pellets with and without a hypromellose pore-forming agent (Opadry®) assessed using accelerated stability testing

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**Objectives** Sustained release can be achieved by coating with a water-insoluble polymer (ethylcellulose). However, for poorly soluble active agents insufficient control of dissolution is achieved with ethylcellulose. Typically, stability of the films is assured by curing, although this is not essential. This study investigated the effect of coating spray rate on the stability of aqueous ethylcellulose film-coated paracetamol pellets, applied using a MPMicro fluid-bed drier with a Wurster column. Pellets coated with Surelease® combined with a hypromellose pore-former (Opadry®) were also investigated. Each sample was stored at accelerated stability conditions (40°C/75% relative humidity (RH)) for 28 days to assess the physical stability of the film, which was measured by dissolution rate before and after storage. Some samples were cured at 50°C for 12 hours, and the effect of curing was assessed by dissolution rate.

**Methods** Samples (25 g) of paracetamol (BN9930166) pellets, formed by extrusion spheronization, were prepared by the method described by Chopra et al (2001). They were fluidized and warmed to 37°C in a MPMicro chamber fitted with a Wurster column. The inlet temperature was kept at 65°C for all coating runs. The column height was adjusted so that the pellets 'bubbled' and were fluidized throughout the coating column. Spray rates of 0.55, 0.70, 0.80 and 1.1 g/minute were used to apply the coating solution to the core pellets. Samples coated with 10% w/w ethylcellulose at spray rates of 0.55 and 1.1 g/minute were cured at 50°C for 2 hours. The purpose of the curing process is to thermally seal the film coat and make it physically stable. Dissolution testing was performed before and after

**Table 1** Drug-dissolution rates of Surelease/Opadry-coated paracetamol pellets (mean of n = 3; ± SD)

| Ethylcellulose coat (w/w) | Spray rate (g/minute) | Initial release at 10 hours (% released) | 28 day release at 10 hours (% released) | Ethylcellulose/ Opadry coat (w/w) | Initial release at 2 hours (% released) | 28 day release at 2 hours (% released) |
|---|---|---|---|---|---|---|
| 10% | 0.55 | 14.61 ± 1.26 | 15.69 ± 2.17 | 9%;1% | 13.33 ± 1.83 | 5.45 ± 0.22 |
| 10% | 0.8 | 12.36 ± 1.40 | 90.71 ± 1.71 | 8%;2% | 39.85 ± 1.64 | 65.75 ± 2.38 |
| 9% | 0.80 | 35.80 ± 1.96 | 95.83 ± 0.95 | | | |
| 6% | 0.80 | 60.39 ± 0.98 | 82.28 ± 0.07 | | | |

curing. Samples coated with 6 and 9% w/w ethylcellulose were coated at a 0.80 g/minute spray rate. Samples coated with ethylcellulose and hypromellose mixtures (80/20 and 90/10% w/w) were coated at spray rates of 0.70 g/minute. The samples were placed a stability chamber at 40°C/75% RH for 28 days. Pellets were assayed using in a US Pharmacopoeia (USP) II dissolution method (paddles) in 900 mL phosphate buffer, pH 5.8 (USP), 37°C, using online UV analysis at 293 nm. The mean of three individual determinations is reported.

**Results** The curing process appeared to have no effect on drug dissolution rate. The *in vitro* drug release remained at 15% release after 10 hours with or without curing. Samples coated with 10% w/w ethylcellulose at a spray rate of 0.55 g/minute produced no change in drug dissolution rate after storage at 40°C/75% RH for 28 days. The *in vitro* drug release remained unchanged with 15% release after 10 hours. For samples coated with 6, 9 and 10% w/w ethylcellulose and/or hypromellose at higher spray rates of 0.70 and 0.80 g/minute, a significant change in *in vitro* release rate were observed (see Table 1). This indicates that the coating conditions used for these pellets were sub-optimal and led to a deterioration in the film quality after storage at 40°C/75% RH. In all cases, except sample 8%:2% (ethylcellulose/hypromellose), drug-release rate increased after 28 days' storage. The film coat increases in porosity over time, leading to increases in drug release, possibly due to migration of the hypromellose through the film. Sample 8%:2% exhibited a reduction in drug-release rate after 28 days' storage, the mechanism of which is yet to be determined.

**Conclusions** It has been shown that curing is not a definitive way to assure film coat stability and that spray rate is also an important coating parameter that determines aqueous film-coating quality and affects long-term physical stability of the film. However, spray rates will be defined by the equipment and scale being used; therefore it should be fully investigated prior to starting a manufacturing campaign.

Chopra, R. et al (2001) *Drug Dev. Technol.* **6**: 495–503

## 66
## The effect of organic acid salts on hydroxypropyl methylcellulose matrices

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**Objectives** The presence of organic salts, incorporated as drug counter-ions or buffers in hydroxypropyl methylcellulose (HPMC) matrices, is often overlooked. This study investigates their influence on matrix drug release in relation to their effect on polymer hydration.

**Methods** The sol–gel transition temperature with respect to salt concentration ($\Delta CPT$, in °C/M) was determined turbidimetrically (Cloud-Point Apparatus, Nottingham, UK) on solutions containing 1% w/v HPMC (Methocel™ E4M-CR). Matrices, 8 mm diameter, 250 mg, containing 30% HPMC, 10% caffeine anhydrous and 60% w/w organic sodium salts were manufactured at 160 MPa using a Manesty F3 press (Liverpool, UK). Drug release was investigated using US Pharmacopoeia (USP) apparatus I, 100 rpm in 900 mL water at 37 ± 0.5°C. Results were expressed as $\Delta T_{50}$, the change in the time to 50% release ($T_{50\%}$) with respect to a control containing 60% dextrose. Experiments were performed in triplicate.

**Results** For monovalent salts, drug release showed a significant linear correlation with $\Delta CPT$ ($r = 0.938$, $P < 0.01$), but not with organic salt solubility ($r = 0.409$, $P > 0.10$) or matrix sodium ion content ($r = 0.6447$, $P > 0.10$). $\Delta CPT$ reflects the ability of the anion to disrupt or enhance polymer hydration and is a function of ionization and hydrophobicity, which oppositely affect polymer hydration-sheath stability (Richardson 2006). Drug-release results suggest that these anions may also have significant impact on the gel layer, in which water–polymer interactions play an important role. For example, when polymer water affinity is high, enhanced swelling leads to rapid gel-layer formation and good retardation of drug release. With reduced water affinity, the gel layer forms more slowly, with more extensive medium penetration of the matrix, and poorer extended-release properties. Divalent anions (circled on Figure 1) were more

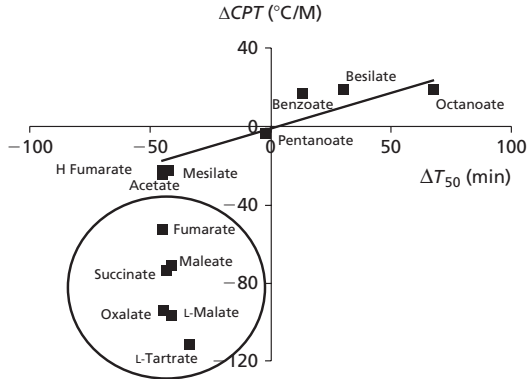


**Figure 1** The relationship between $\Delta CPT$ (°C/M) and $\Delta T_{50}$ for different organic salts (n = 3).

potent in depressing *CPT* than single-valency anions, and all caused accelerated drug release, reflecting the similar effects of multivalent inorganic salts (Alderman 1984).

**Conclusions** This study suggests that organic acid salt high loadings incorporated in HPMC matrices have the potential to influence drug release, in a rank order that reflects their modulation of the HPMC polymer hydration sheath in solution.

Alderman, D. A. (1984) *Int. J. Pharm. Tech. Prod. Manuf.* **5**: 1–9
Richardson, J. C. (2006) *Carbo. Poly.* **65**: 22–27

## 67
## Evaluation of simple quality-control tests for the determination of counterfeit medicines

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**Objectives** The prevalence and impact of counterfeit medicines are widespread. Most counterfeit products are sold on the black market or via the internet and do not enter the legitimate supply chain. They are imported into a country, passing through customs and excise. Therefore, both customs and excise officers and pharmacists need to be educated on identifying counterfeit products. There is a need, especially within developed countries, where advanced analytical techniques are not readily available, for simple first-line detection tests that can be performed by untrained personnel. This work investigated whether quality-control tests such as tensile strength can be deployed as alternatives to more elaborate methods in the identification of counterfeit medicines.

**Methods** Paracetamol tablets were produced by wet granulation with decreasing amounts of paracetamol. Lactose was deployed as a diluent to adulterate the tablets. The tablets produced underwent quality testing for uniformity of weight, tensile strength, friability, rate of disintegration and dissolution. All tests conformed to the British Pharmacopoeia. UV absorbance was also performed for quantitative assessment. Results were analysed by one-way analysis of variance using Minitab 15.

**Results** The results shown in Table 1 imply that a combination of weight and tensile strength can provide the means for assessing counterfeit products. Reduction of paracetamol content from 125 mg to 25 mg more than tripled the time taken for the paracetamol tablets to disintegrate and the tensile strength of the same tablets increased from 0.79 to 1.50 MPa.

**Conclusions** This study demonstrated that tensile strength was able to provide accurate results even with small differences in active ingredient. Tensile strength

**Table 1** Values for thickness, weight, tensile strength, friability and disintegration

| Paracetamol content per tablet (mg) | Thickness (mm) | Weight (mg) | Tensile strength (MPa) | Friability (% change) | Disintegration (seconds) |
|---|---|---|---|---|---|
| 500 | 4.52 ± 0.01 | 522.83 ± 3.86 | 1.01 ± 0.06 | 0.90 | 46 |
| 375 | 4.48 ± 0.01 | 524.06 ± 3.41 | 0.63 ± 0.05 | 0.41 | 48 |
| 250 | 4.50 ± 0.01 | 550.48 ± 4.56 | 0.60 ± 0.06 | 0.46 | 57 |
| 125 | 4.50 ± 0.02 | 596.67 ± 7.54 | 0.79 ± 0.08 | 0.40 | 73 |
| 50 | 5.03 ± 0.01 | 748.89 ± 2.74 | 1.35 ± 0.10 | – | 170 |
| 25 | 5.14 ± 0.03 | 780.91 ± 5.19 | 1.50 ± 0.10 | – | 237 |
| 5 | 5.37 ± 0.01 | 834.15 ± 4.04 | 1.69 ± 0.18 | – | 464 |
| 0 | 5.44 ± 0.03 | 840.27 ± 7.12 | 1.61 ± 0.06 | 0.25 | 486 |

can be performed quickly and without expensive instrumentation. It is possible to measure tensile strength using a small, portable hardness tester, which is both cheap and easy to use. Such instrumentation could be provided to pharmacists, customs and excise and field workers and hence aid in the global struggle to prevent the proliferation of counterfeit medicines.

## 68

### Physico-chemical, rheological and drug-release characteristics of quinine and hydroxypropyl cellulose prepared by hot-melt extrusion

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

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

**Results** This investigation highlighted the differences in solubility and interaction between quinine base and quinine hydrochloride with HPC, a hydrophilic cellulosic polymer. The results show that quinine hydrochloride has greater solubility in HPC than quinine base since HPC is hydrophilic and solubulizes more aqueous soluble active pharmaceutical ingredients. DMTA results show that the glass transition temperatures of the extrudates are influenced by drug loading and salt form, with an increase in quinine base resulting in a higher tan $\delta$ and higher storage modulus ($G'$) value before the glass transition. DVS results show that HPC matrix blends are very hygroscopic (mass increase up to 15% w/w) with the inherent polymer behaviour dominating the effects of either the quinine base or quinine hydrochloride in the matrix. DVS results also show that HPC surface area is important with milled samples reaching equilibrium moisture content faster than hot-melt extrudate material that had not been milled.

**Conclusions** Hot-melt extrusion technology allows solid dispersions of quinine to be produced in a HPC matrix in a single manufacturing process. The results show that drugs can act as plasticizers for polymers or as anti-plasticizers when there is little miscibility, solubility or chemical interaction between the drug and the polymer. The propensity for HPC to absorb moisture also draws attention to the potential long-term stability of quinine–HPC matrix formulations, particularly when the drug is in a metastable state. An understanding of solid-state characteristics and how these affect the processing characteristics of polymers shows that consideration must be given to the physical properties of solid dispersion formulations. This study helps to link thermal and chemical characteristics of drug–polymer blends to develop our understanding of their relationship to polymer flow and process parameters.

## 69

### Solubility enhancement of flurbiprofen by salt formation

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**Objectives** Salt formation is the most common method of increasing solubility for basic and acidic drugs. There is, however, limited information available on prediction of the properties of salt forms and factors governing their selection for pharmaceutical development. Amine salts of flurbiprofen (F), a poorly soluble weak acid, were prepared to study possible relationships between the resultant salts and the properties of the counterion. This study uses four amines with an increasing number of hydroxyl groups as the counterion: *tert*-butylamine (Tbut) was the starting molecule and hydroxyl groups were progressively added to determine the effect of hydrophilicity of the counterion: 2-amino-2-methyl-1-propanol (AMP1), 2-amino-2-methyl-1,3-propanediol (AMP2) and trimethamine (Tris). The salts were characterized and their saturated aqueous solubilities were measured.

**Methods** Salts were prepared in a 1:1 molar ratio by mixing equal proportions of flurbiprofen and the counterion dissolved in acetonitrile. The precipitate was removed by filtration and dried overnight at 40°C under vacuum. Salt formation was confirmed by infrared spectroscopy and nuclear magnetic resonance. Saturated aqueous solubilities were obtained by adding excess solid to 20 mL of water and stirring at 500 rpm for at least 48 hours until saturation was reached.

**Results** Solubility was improved in all cases by salt formation. Counterions increased solubility from 25 to nearly 3000 times. There is a good correlation between the pH of the resulting saturated solution and the logarithm of the solubility (Figure 1). However, there is a lack of dependence between the solubility and the increasing number of hydroxyl groups in the Tbut series. The order of solubility within this series is: F-AMP2 (0.17 M) > F-Tris (0.052 M) = F-AMP1 (0.046 M) > F-Tbut (0.015 M). Other factors apart from hydrophilicity of the counterion are therefore important in determining the solubility of the salt forms of flurbiprofen.

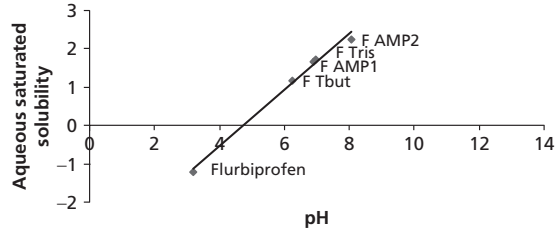


**Figure 1** pH plotted against saturated solubility.

**Conclusions** As expected, salt formation can be used to increase the solubility of flurbiprofen. The final pH of the saturated aqueous solution correlates with the increase in solubility.

**70**

## The influence of supercritical carbon dioxide in enhancing the dissolution rate of celecoxib from polyvinylpyrrolidone hot-melt-extruded tablets

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**Objectives** Hot-melt extrusion (HME) is a viable technology in producing solid molecular dispersions to enhance the oral bioavailability of poorly soluble drugs. HME produces too dense a structure, which might delay the drug-release rate especially from the extruded tablets. The aim of this work was to investigate the ability of supercritical carbon dioxide ($scCO_2$) to enhance the drug-release rate from hot-melt-extruded tablets.

**Methods** CX-PVPK25 (3:7 w/w ratio) was hot-melt extruded at 170°C and a screw speed of 100 rpm. The prepared melt extrudates were exposed to $scCO_2$ at 100 bar and 40°C. After 24 hours the chamber was evacuated rapidly of carbon dioxide and the samples were either cut into tablets or milled and sieved through mesh with a pore size of 250 $\mu$m. The samples of melt extrudates before and after $scCO_2$ exposure were characterized using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier-transform infrared (FTIR) spectroscopy and scanning electron microscopy (SEM). *In vitro* drug-release studies were done using simulated gastric fluid, adding 0.1% w/v Triton® X100 to provide sink conditions, and samples of equivalent weight of 50 mg celecoxib (CX) tablets and milled extrudates were tested.

**Results** The dissolution rate of CX from poly(vinyl pyrrolidone) (PVP) hot-melt-extruded tablets was enhanced significantly after $scCO_2$ exposure by around 2-fold after 2 hours compared with the non-exposed tablets. The milled tablets showed no significant difference in drug release either before or after $scCO_2$ exposure, while significant enhancement in drug-release rate was achieved compared with the corresponding physical mixture and CX powder. PXRD of melt-extruded samples showed a complete loss of CX crystallinity, with a single glass transition ($T_g$) appearing in the DSC. FTIR showed a significant shift in the carbonyl peak of PVP in the extruded samples. Samples exposed to $scCO_2$ showed significant porosity in SEM compared with the non-exposed samples, while there were no significant changes in the DSC, PXRD and FTIR results (Figure 1).

**Conclusions** $scCO_2$ enhanced significantly the release rate of solid molecular dispersions of CX from PVP hot-melt-extruded tablets by acting as an efficient pore-forming agent.

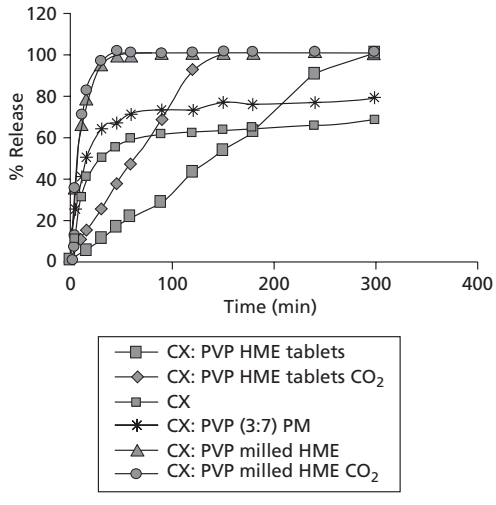


**Figure 1** Drug release profiles of Celecoxib (CX) from hot melt extruded tablets before and after $scCO_2$ treatment compared with the physical mixture (PM) and the celecoxib (CX) powder. PM, physical mixture.

**71**

## Sodium calcium alginate as a matrix component of modified-release dosage forms: an evaluation of raw-material source change

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**Objectives** The biopolymer sodium calcium alginate is a modified-release matrix component for a range of monolithic oral dosage forms. Assessment of a proposed change to the raw-material source necessitated comprehensive physico-chemical and functional qualification to assure continued performance in the finished dosage form.

**Table 1** Dissolution profile comparability analysis

| Product | $f_2$ similarity factor | |
|---|---|---|
| | High shear | Low shear |
| Clarithromycin MR | 80.1 | 91.8 |
| Buflomedil CR | 80.5 | 84.6 |

**Methods** For an alginate-based, modified-release dosage form, any significant change in alginate source, particularly to the seaweed feedstock, has potential to adversely impact dissolution performance of the finished dosage form. To qualify an alternative source, comprehensive comparative studies were performed including physico-chemical characterization and comparison. However, for dosage forms with multiple, complex mechanisms of release, prediction of final performance by means of simple physico-chemical comparison may be limited. Thus dissolution profile comparison (using $f_2$ similarity factor) from product manufactured on the pilot scale was utilized to complement physico-chemical comparability of key parameters including viscosity and calcium content, considered to directly influence functionality.

**Results** Particle-size analysis determined some small but potentially significant (Liew et al 2006) differences between sources. Physico-chemical comparison of sodium calcium alginate from an alternative source with that of the original source demonstrated a calcium content showing an apparent shift to a higher level. However, pilot-scale studies (Clarithromycin MR) using sieve fractions of an alternative source of sodium calcium alginate, screened above and below 63 $\mu$m, confirmed no statistically significant impact of particle-size distribution upon dissolution profile ($f_2$ similarity factor 65.2). Following pilot-scale manufacture using a range of production technologies, dissolution profiles for product containing an alternative source of sodium calcium alginate that reflected the extremes of the specification range for key physico-chemical parameters (viscosity, calcium content) were compared with original material. Despite minor differences in key physico-chemical parameters, resultant *in vitro* dissolution profiles show excellent similarity (Table 1).

**Conclusions** Despite differences in key physico-chemical parameters, *in vitro* dissolution comparability demonstrated no functional impact of a change in sodium calcium alginate source. Prediction of functional equivalence for differing sources of modified-release excipient also requires qualification by dissolution studies.

Liew, C.V. et al (2006) *Int. J. Pharm.* **309**: 25–37

# Pharmacology

**72**

## Pharmacokinetics of clozapine in patients with schizophrenia

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**Objectives** The pharmacokinetic parameters of clozapine and its main metabolite, norclozapine, were evaluated in 37 selected chronic schizophrenic inpatients during long-term treatment. The dose–plasma-level relationship and inter- and intra-individual variability of plasma levels during maintenance treatment with clozapine were also investigated. The study had the approval of the university's ethics committee.

**Methods** Patients were all non-smokers and otherwise healthy males, aged 18–48 years, on clozapine monotherapy. All patients met DMS-IV criteria for diagnosis of schizophrenia and received clozapine every 12 hours (stable daily doses of 300–600 mg) for up to 2 years prior to the study. Serial blood samples were collected from each patient before the administration of the morning dose and 30 minutes and 1, 2, 3, 4, 5, 8 and 12 hours after. Plasma and red blood cell (RBC) drug concentrations were determined by high-performance liquid chromatography. All plasma drug concentrations were corrected for baseline (steady-state) values. The pharmacokinetic parameters were calculated from both non-compartmental and compartmental approaches with zero-order input rate using a kinetic model for simultaneous fit of clozapine and norclozapine concentrations.