the transfer standard measured on A and B or C respectively. These corrected spectra were then used to predict the paracetamol content using a model developed on A.

Results A three-factor partial least squares regression (PLSR) calibration model (1100–2498 nm) using SNV + first-derivative spectral pre-treatment on instrument A gave an RMSEP of 0.57% m/m. Direct transfer of spectra from instrument B gave an RMSEP of 0.81% m/m. Corrected spectra gave slightly better results: for example, avicel PH101 in vial (0.95% m/m), avicel PH101 in cell (0.60% m/m), paracetamol in vial (1.14% m/m), sucrose in vial (0.58% m/m), sucrose in cell (0.81% m/m) and mean sample spectrum (0.56% m/m). Transfers between different instrument types (A and C) were less successful: direct transfer (0.97% m/m), avicel PH101 in vial (0.75% m/m), avicel PH101 in cell (1.60% m/m), paracetamol in vial (0.54% m/m), sucrose in vial (1.07% m/m) and sucrose in cell (1.03% m/m). However, correction using the mean sample spectrum was best (0.52% m/m). Many factors influenced the success of transfer. Model selection was important; for example, increasing the level of smoothing during spectral pre-treatment generally improved transfer. Matching the transfer standard dimensions to that of the paracetamol tablets was also an important factor. In general the transfer standard needs to closely match the sample both chemically and physically.

Conclusions Transfer using simple pure compounds, while useful, was not to be preferred over mean sample spectrum correction.

Biologics

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Synthesis and evaluation of an affinity-based probe for fibroblast-activation protein α (seprase) activity

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Objectives Fibroblast-activation protein a (FAPα; also known as seprase) is a 170 kDa serine gelatinase and prolyl dipeptidyl peptidase that consists of two identical N-glycosylated 97 kDa subunits embedded in and integral to the cell membrane. FAPα is expressed during tumour cell invasion at the invasive fronts of melanoma cells and breast carcinoma cells, in gastric carcinoma and also in rheumatoid arthritis. FAPα belongs to a family of post-proline-cleaving proteases, many of which share a high degree of homology and/or substrate specificity. This is particularly true of dipeptidyl peptidase IV (DPP-IV), another therapeutically important protease. The purpose of this study was to design, synthesize and evaluate an affinity-based probe for the selective disclosure of FAPα activity in biological milieux where other closely related peptidase activities are present.

Methods The affinity-based probe, Bio-PEG-T-S-G-$P^P(OPh)_2$, was synthesized by a combination of solid- and solution-phase synthesis. The amino acid sequence was based on previous work by our group which indicated that Gly-$Pro^P(OPh)_2$ was a potent irreversible inhibitor of both DPP-IV and FAPα (Gilmore et al 2006), and a recent report indicating that FAP could cleave extended substrates (Edosada 2006), thus permitting the design of selective inhibitors which do not target closely related peptidases such as DPP-IV. The inhibitor was evaluated by continuous fluorimetric assay against FAP, DPP-IV, DPP2 and DPP7. Labelling of peptidases was conducted as described by Gilmore et al (2007) using standard electrophoresis and western-blotting methodologies. Labelled peptidases were detected by streptavidin-HP chemiluminescence on photographic film.

Results The inhibitor probe Bio-PEG-T-S-G-$P^P(OPh)_2$ was found to be a moderately potent but highly selective inhibitor of FAPα, having an overall second-order rate constant (k_i/K_i) of 3.8×10^3 M^{-1} min^{-1}. Importantly, Bio-PEG-T-S-G-$P^P(OPh)_2$ exhibited no inhibitory activity against DPP-IV, DPP2 or DPP7. The probe was subsequently used to label recombinant FAPα and shown to be directed by the active site, since incorporation of the probe was blocked by pre-incubation of the enzyme with pefabloc.

Conclusions In this report we detail the synthesis of a moderately potent, selective affinity-based probe for the disclosure of FAPα activity in complex biological milieux even where closely related peptidase activities are present. This probe may have utility in further elucidating the role of this peptidase in diseases such as cancer and rheumatoid arthritis.

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Chemistry

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Photothermal microspectroscopy: a new technique for spatially differentiating between crystalline and amorphous materials

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Objectives This study demonstrates the ability of photothermal microspectroscopy (PTMS), a new technique (Hammiche et al 2004), to differentiate between both the physical and chemical nature of a model GlaxoSmithKline drug in its amorphous and crystalline forms.

Methods The model GlaxoSmithKline drug was used as received in its crystalline form. The amorphous form was prepared using a Büchi Mini-Spray Dryer B-290. Compacts of the samples were formed using a 13 mm infrared sample press with an applied pressure of 1 ton. PTMS was performed by interfacing a Caliber AFM equipped with a Wollaston wire thermal probe to a Bruker FTIR spectrometer. Local thermal analysis experiments were conducted with an underlying heating rate of 10°C s^{-1} from 60 to 200°C. Infrared spectra were collected using 200 scans and a resolution of 8 cm^{-1}, across the range 4000 to 500 cm^{-1}. Modulated-temperature differential scanning calorimetry (MTDSC) and attenuated total reflectance-Fourier transform infrared spectroscopy were used to validate the PTMS results.

Results PTMS demonstrated its ability to distinguish between the pure amorphous and crystalline surfaces. The topography of the crystalline and amorphous surfaces showed clear differences although it was not possible to state which surface represents which material from topography alone. Local thermal analysis, whereby the temperature of the tip is raised and the temperature of penetration noted (Royall et al 2001), was able to discriminate on the basis of the glassy or melting behaviour of the system. This agrees with the MTDSC response seen. For the first time we were also able to differentiate via the photothermal infrared spectra using PTMS, shown in Figure 1, with spectral differences noted in terms of peak broadening and disappearance in the 3500–2000 cm^{-1} region. This broadening is due to non-specific intermolecular bonding in the amorphous material.

Conclusions PTMS was shown to be a highly promising new technique for determining and differentiating between pure amorphous and crystalline materials at precise topographic locations. Subsequent work is focused on mixed systems and results to date are highly encouraging.

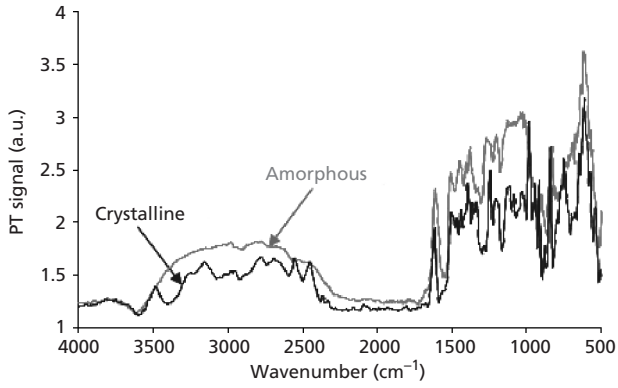

Figure 1 Photothermal IR spectra of the amorphous and crystalline samples.

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Synthesis, characterization, *in vitro* hydrolysis and biological evaluation of amino acid methyl ester conjugates of valproic acid: a prodrug approach

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Objectives Valproic acid (VPA) is an extensively used anti-epileptic drug for the treatment of various kinds of epilepsies and administered orally several times a day due to short half-life. It has been proven to possess the life-theatening side effects of hepatotoxicity, teratogenicity and gastric irritation (Sobol et al 2004, Bryant and

Dreifuss 1996). Glycine, glutamic acid and cysteine derivatives of VPA were synthesized to reduce the dosing frequency and side effects of the parent molecule.

Methods The conjugates of VPA were synthesized through esterification of amino acid using methanol with thionyl chloride followed by activation of the free carboxyl group of VPA with thionyl chloride. The acyl chlorides of VPA and the free amino groups of esterified glycine, glutamic acid and cysteine were conjugated to produce VPA amino acid methyl ester conjugates (VGyM, VGuM and VCyM respectively). The synthesized conjugates were characterized by UV, infrared, ^{1}H-nuclear magnetic resonance (NMR) spectroscopy and elemental analysis, then subjected to *in vitro* hydrolysis and *in vivo* pharmacological screening studies.

Results *In vitro* hydrolysis studies of VPA conjugates showed negligible hydrolysis in acidic medium (pH 1.2). The rate constant (K) and the half-life ($t_{1/2}$) of the synthesized conjugates VGyM, VGuM and VCyM in pH 7.4 buffer were found to be 0.1072 (6.46 hours), 0.082 (8.45 hours) and 0.0954 (7.26 hours) respectively and showed a slow rate of hydrolysis following the first-order kinetics, whereas the rate constant and the half-life of the synthesized conjugates in pH 9.0 buffer was found to be 0.011 (63 minutes), 0.00824 (84.1 minutes) and 0.0097 (71.44 minutes) respectively and showed a faster rate of hydrolysis. In anti-convulsant activity, VGyM and VGuM conjugates showed maximum anti-convulsant activities with protection of 100 and 83.33% respectively, whereas VCyM conjugates showed 66.67% protection. The hepatotoxicity of these synthesized conjugates was determined through enzymatic (serum glutamic pyruvic transaminase (SGPT), serum glutamicoxaloacetic transaminase (SGOT) and alkaline phosphatase (ALP)) estimation. The SGPT enzyme level was found after treatment of VPA, VGyM, VGuM and VCyM to be 98 ± 7.432, 86 ± 6.256, 68 ± 4.583 and 80 ± 2.954 Units/Ml respectively and SGOT enzymatic level found to be 89 ± 6.230, 75 ± 3.421, 63 ± 4.503 and 75 ± 3.122 Units/Ml respectively. The serum level of ALP was also determined as 21.23 ± 3.305, 16.63 ± 2.016, 12.24 ± 2.146 and 15.92 ± 1.989 Ka Units respectively. The ulcerogenic indices of VPA and their amino acid conjugates were found to be 31.4 ± 1.14 (VPA), 7.66 ± 0.45 (VGyM), 4.44 ± 1.31 (VGuM) and 6.55 ± 0.62 (VCyM). All the synthesized conjugates showed less hepatotoxicity and ulcerogenicity than the parent drug VPA.

Conclusions This study suggests that VPA amino acid conjugates can be employed successfully as a promoiety/carrier for VPA to reduce its hepatic toxicity and ulcerogenicity.

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Development of novel inhibitors and substrates for *Pseudomonas* elastase, a potential anti-biofilm target in *Pseudomonas aeruginosa*

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Objectives It has been demonstrated that *Pseudomonas* elastase (LasB, pseudolysin) is essential for secretion of alginate, the structural substance of the pseudomonal biofilm (Kamath et al 1998). Biofilm growth is accountable in some of the more resistant modes of bacterial growth in infection, and thus LasB represents a potential therapeutic target in biofilm-based disease.

Methods Accordingly, this work reports the solid-phase synthesis, kinetic characterization and biological evaluation of a combinatorial library of small-molecular-weight inhibitors of *Pseudomonas* elastase as putative anti-biofilm compounds. To assess LasB inhibition, a set of novel fluorogenic substrates has been generated with a greater sensitivity than their commercially available counterparts, for kinetic evaluation of LasB, and related metallo-proteases (Nishino and Powers 1980). The most potent LasB inhibitors were then used for biological screening of anti-biofilm activity using the MBEC assay (Ceri et al 1998). Additional work presented here has involved recombinant expression of nucleoside diphosphate kinase (NDK). This is the natural LasB substrate in the proposed biofilm pathway, and thus can be used to validate inhibition of this pathway.

Results Kinetic evaluation of this library of 400 compounds has distinguished potent inhibitors, with i_i values in the mid-nanomolar range. Preliminary biological evaluation of the most potent of these using the MBEC assay has produced statistically significant reduction in biofilm growth. The most potent inhibitors have also been demonstrated to protect NDK against LasB-mediated activation, further validating the activity of these inhibitors within the biofilm pathway.

Conclusions We envisage that inhibitors capable of reducing biofilm growth will have utility in prevention of *Pseudomonas* biofilm formation on indwelling medical devices by either direct incorporation or surface modification of the biomaterial.

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Substrate–haem complex approach: the derivation of a representation of the active site of 4-retinoic acid hydroxylase (CYP26)

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Objectives We have previously reported the substrate–haem complex (SHC) approach in an effort to gain further information regarding the active site of a number of cytochome P450 enzymes (Ahmed and Davis 1995, Ahmed 2004). Retinoic acids, in particular all-*trans*-retinoic acid (ATRA), has been shown to play a major role in cellular development and differentiation; however, it is metabolized by CYP26 to 4-hydroxyATRA. It has been shown that the inhibition of the hydroxylation of ATRA results in anti-proliferative effects across a wide range of cancers. However, the crystal structure of this enzyme is not currently available although workers have used homology-based modelling techniques to produce an approximate model (Gomaa et al 2007). Here we have utilized the SHC approach in an attempt to obtain a different perspective on the active site of CYP26. We therefore report the initial development of the SHC-based model of CYP26 and the rationalization of a number of recently reported inhibitors of CYP6.

Methods The structures of the porphyrin and ATRA (as well as the small range of inhibitors within the current study and potential hydrogen-bonding groups considered to exist at the active site) required for the construction of the SHC were all constructed within CaChe molecular modelling software on an IBM PC-compatible microcomputer. In the construction of the SHC, we used the previously reported approach (Ahmed and Davis 1995). It is postulated that there is an involvement of a ferroxy radical; as such, the attacking species would be expected to be positioned at an appropriate distance and angle about the ATRA backbone such that the C-4 position can be attacked. We therefore attached the haem to the C-4 of ATRA, via the ferroxy oxygen. We also postulated that the ATRA would undergo hydrogen bonding at the active site so as to hold the substrate in a specific manner, allowing stereospecific hydroxylation. We attached a representative hydrogen-bonding group and undertook the minimization of the 'complex' to give the CYP26 SHC. Inhibitors were then superimposed onto the overall complex using three or more pairs of atoms.

Results The results of the present study suggest that groups able to interact with both the haem and the potential hydrogen-bonding group within the active site result in increased inhibitory activity. Binding inhibitors to the complex, we observe that the inhibitors containing large spacer units, so as to mimic the long conjugated chain of ATRA, are able to undergo the extra polar–polar interaction whereas inhibitors containing smaller spacer groups only have a single Fe–N interaction stabilizing the inhibitor haem complex.

Conclusions In conclusion, we have developed a novel model, using which we have been able to propose a range of features that may be considered important in the further design of novel inhibitors of CYP26.

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Investigation into the mechanism of oestrone sulphatase: the development of a biomimetic study into the hydrolysis of a number of sulphonate derivatives of 4-hydroxyphenyl ketones

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Objectives We have previously reported the synthesis of a number of inhibitors of the enzyme oestrone sulphatase (ES); in particular, compounds based upon 4-hydroxybenzoic acid (Owen et al 2002), one of which has proved to be more potent than 667-COUMATE (Patel et al 2004). From the consideration of a wide range of inhibitors, we proposed a novel mechanism of action of inhibitors involving the attack of the sulphonate moiety by the gem-diol functionality at the active site of ES (Ahmed et al 2002). In our mechanism, we proposed that all sulphonate-based inhibitors would also undergo a hydrolysis reaction. In an effort to study other functionalities which may possess inhibitory activity, we considered the development of a non-enzyme-based system which would allow us to study the hydrolysis of aromatic sulphonated compounds. Here, we therefore report the synthesis of a range of sulphonate derivatives of 4-hydroxyphenyl ketone and the development of the biomimetic 'assay'.

Methods In the synthesis of the target compounds, we followed literature procedure (Ahmed et al 2002). In the development of the biomimetic assay, we initially determined the best concentrations for the detection of the phenoxide ion (so as to be within the limits of the spectrophotometer); the concentration of the

NaOH required to produce full hydrolysis of the majority of the compounds; the time required so as to observe full hydrolysis. As such, the compounds were exposed to the basic conditions and 'assay' run until the complete hydrolysis of the compounds, and the half-life of each compound determined from the plot of absorbance against time.

Results In the development of the assay, we considered the hydrolysis reaction and, in particular, the half-life of the compounds under basic conditions. That is, we concluded that the mimicking of the gem-diol within the active site of ES is best undertaken through the use of HO^- (e.g. through the use of alcoholic NaOH). As such, we considered the time taken for the full hydrolysis of the sulphonate moiety and therefore monitored the production of the phenolic product. From our results, we discovered that the previously reported acetate- and formate-based inhibitors possess a greatly reduced half-life in comparison with the methanesulphonate derivatives (for example, the half-life for the methanesulphonate derivative of 4-hydroxyacetophenone was approximately 77 minutes whereas for the acetate derivative it was approximately 5 minutes; it should be noted that the time for the aminosulphonates was found to be less than 1 minute). As such, this would appear to suggest that the mechanism of action of these two ranges of compounds is similar; that is, hydrolysis of the sulphonate/carboxylate moieties.

Conclusions We have therefore provided a novel non-enzymatic methodology that has been utilized successfully in the study of the mechanism of different ranges of inhibitors of ES.

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Patel, C. K. et al (2004) *Bioorg. Med. Chem. Lett.* **14**: 605–611

Drug Delivery

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An investigation into the use of clathrates in metered-dose inhaler formulations

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Objectives Clathrates are crystalline compounds consisting of a lattice of one type of molecule which hosts a second type of guest molecule within its structure. Guest molecules in clathrates are packed (in channels and cages) in coordination compound frameworks. Clathrates are thermodynamically unstable and tend to dissociate rapidly when removed from the stabilizing medium, due to the presence of large empty cavities at the core of their structure. The guest molecules prevent the collapse of the open framework structure and render the structure more thermodynamically stable. The aim of this study is to investigate and characterize the physico-chemical properties of beclomethasone dipropionate (BDP) crystallized from trichloromonofluoromethane (CFC-11). Although CFC-11 will shortly be phased out of use, the BDP–CFC-11 clathrate is a stable entity and thus easy to use for our initial investigations (Vervaet et al 1999).

Methods BDP is a widely used corticosteroid for the treatment of asthma. It is formulated in metered-dose inhalers (MDIs) in the presence of propellant and other formulation ingredients. Since the solid-state chemistry can significantly alter the therapeutic effect of the formulation, it is crucial to determine the most stable crystalline form in the presence of the propellant. Crystal growth of anhydrous BDP in CFC-11 was examined. The crystal investigated in this study was grown in 0.1 and 0.5% w/w BDP in CFC-11 at ambient room temperature. Under these conditions, BDP crystallizes with a channel structure that allows the insertion of CFC-11 molecules (Kuehl et al 2003). The structure is held together through hydrogen bonding. Anhydrous BDP suspended in CFC-11 resulted in spontaneous crystal growth. The structure of the BDP–CFC-11 clathrate was determined using direct methods such as X-ray photoelectron spectroscopy and X-ray powder diffraction. Atomic force microscopy was used for the determination of surface energy (primarily the dispersive component). In addition, 3M Drug Delivery Systems also supplied an isopropyl alcohol (IPA) clathrate of BDP for investigation.

Results The dispersive surface energy of anhydrous BDP was 47.5 ± 4.9 mJ m^{-2} whereas the dispersive surface energy of the BDP–IPA clathrate was 66.5 ± 6.7 mJ m^{-2}.

Conclusions The higher dispersive surface energy observed for BDP–IPA clathrate is most likely attributable to its non-anhydrous nature, since the IPA associated with the BDP–IPA solvate can promote hydrogen bonding. Thus the surface of BDP will be more 'active' compared with anhydrous BDP. This has implications when considering interparticulate interactions, since a higher surface energy typically results in greater cohesive and adhesive properties. However, the greater dispersive surface energy may not be detrimental to the overall shelf life of the formulation. The surface energy and adhesive interactions of the BDP–CFC-11 clathrate are currently still under investigation and will be reported.

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Physico-mechanical characterization of multipolymeric monolayered films for buccal delivery of propranolol hydrochloride

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Objectives For optimal controlled release and mucoadhesivity of a buccal delivery system, the blending of polymers and drug of opposing solubilities may be required for the formation of monolayered films. The preparation technique of such a system comprising polymers and drug of opposing solubilities presents a challenge since the drug and polymers cannot be dissolved in a single vehicle to form a solution to be cast as a monolayered film. Further, conventional casting onto teflon-coated trays to be cut into films of desired sizes has been shown to suffer from poor drug-content uniformity (Perumal et al 2008). The aim of this study was therefore to prepare and characterize monolayered multipolymeric films comprising a hydrophilic drug (propranolol hydrochloride; PHCl) and polymers of opposing solubilities using a specially designed silicone moulded compartmentalized tray for film casting.

Methods Multipolymeric monolayered films (MMFs) containing PHCl and the hydrophilic polymer chitosan (CHT) and the hydrophobic polymer Eudragit® RS100 (EUD100) with plasticizer (30% w/w) were prepared in various ratios, by a modified emulsification/solvent evaporation method (Perugini et al 2003) and then cast by a new approach using a silicone moulded tray with individual wells. Films were characterized in terms of drug content (UV-1650PC spectrophotometer; Shimadzu), drug release (shaking water bath; Memmert), mucoadhesion and textural analysis (Texture Analyser XT2*i*; Stable Microsystems). Film thickness (electronic digital micrometer), film-surface morphology (Nikon Coolpix 5.1 digital camera and Jeol JSM scanning electron microscope), swelling, erosion and surface pH were also evaluated.

Results MMFs with a hydrophilic drug and polymers of opposing solubilities, i.e. comprising PHCl with EUD100 and CHT (PHCl/EUD100/CHT, 2:20:1), could be successfully prepared. Reproducibility studies demonstrated uniform drug content ($100.71 \pm 2.66\%$), thickness (0.442 ± 0.030 mm), mucoadhesivity (401.40 ± 30.73 mN) and no significant differences between the batches ($P > 0.05$). The films also showed controlled drug-release profiles that were reproducible ($f_2 > 50$). Drug release followed Higuchi's square-root model ($r^2 = 0.9426$). Maximum swelling of the films occurred after 1 hour and 28.26% of the films eroded during the 8 hour test period. Mechanical testing in terms of tensile strength, elongation, elasticity and toughness revealed that the MMFs displayed a greater abrasion resistance, were more elastic and also required more energy to break, rendering them tougher and more suitable for buccal delivery when compared with the monopolymeric PHCl/EUD100 film. The more porous surface morphology of the MMF was attributed to the inclusion of CHT into the PHCl/EUD100 film. The surface pH of the films remained constant at neutral pH throughout the test period.

Conclusions Monolayered multipolymeric films with drug and polymer of opposing solubilities, i.e. PHCl/EUD100/CHT (2:20:1), could be reproducibly prepared. The characterization data obtained in this study confirmed the potential of this MMF system as a promising candidate for the controlled buccal delivery of PHCl.

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Co-delivery of 5-aminolevulinic acid and the novel hydroxypyridinone iron chelator CP-94 from bioadhesive patches for enhanced topical photodynamic therapy

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Objectives In photodynamic therapy (PDT) a combination of a photosensitizing drug and visible light causes selective destruction of neoplastic cells. Administration