Conclusions The present study showed that only polar constituents prevent mast-cell degranulation whereas non-polar constituents were unable to prevent mast-cell degranulation.

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Investigations on wound-healing activity of leaves of *Ocimum basilicum* L.

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Objectives Indian basil or *Ocimum basilicum* L. is a holy plant and widely used to cure various ailments including skin diseases. In the present investigations, scientific validation of the wound-healing properties of leaves of *O. basilicum* was carried out along with investigation into the quality parameters of the extracts used for the study.

Methods Fresh leaves of *Ocimum basilicum* L. were collected, dried, powdered and extracted with three different solvents (water, alcohol and hydro-alcohol (25%)) by maceration for 72 hours with occasional shaking. All the extracts were concentrated under reduced pressure and at lower temperature using a rotary evaporator; after this they were dried. High-performance thin-layer chromatography fingerprinting of the dried extracts was developed. Swiss albino mice of 25–30 g in weight were used for the experiment and approved by the ethical committee of our institute. Animals were anaesthetized under ketamine anaesthesia (intraperitoneal 10 mg/kg) and an area of approximately 4 cm^2 on the dorsal surface was clipped free of hair and swabbed with 70% ethanol. The cleared dorsal surface of the skin was marked with a sterile circular (10 mm diameter) stainless steel stencil. A full-thickness wound was created by excising the skin flap in an aseptic environment using sterile scissors and forceps. The mice were divided into five groups (n = 5). Group I was kept as a control group, group II was kept as a positive control and treated with marketed formulation (0.5% w/w povidone iodine ointment) and groups III, IV and V were treated with the aqueous, hydro-alcoholic and alcoholic *O. basilicum* extracts topically on the wound daily up to the 16th day after wounding.

Results To evaluate the wound-healing potential of *O. basilicum*, hydroxyproline content and percentage wound contraction were estimated. Hydroxyproline content is an index of collagen and measures the synthesis of neocollagen, which is an indicator of improved condition of wound healing in animals. Hydroxyproline was estimated (Woessner 1961) from granulation tissues of animals on the 16th day after wound creation. The levels of hydroxyproline were found to be 6.40 ± 1.09, 7.10 ± 2.53, 10.11 ± 1.26, 14.95 ± 1.87 and 8.52 ± 1.28 mg/g of tissue in groups I–V, respectively. Hydroxyproline level was significantly higher ($P < 0.05$) in animals treated with hydro-alcoholic extract (group IV). Wound contraction indicates the rate of reduction of an unhealed area during the course of treatment; the greater the reduction the better the efficacy of the medication (Peacock 1984). Wound contraction was measured by tracing the wound margins at 4-day intervals on transparent graph paper with a millimetre scale to an accuracy of 0.05 mm. The wound-contraction data are shown in Table 1.

Conclusions In conclusion, the hydro-alcoholic extract of *O. basilicum* leaves showed significant wound-healing properties in this excision-wound model.

Table 1 Percentage of wound healing in mice from groups I–V

Group	Wound healing (%)			
	Day 4	Day 8	Day 12	Day 16
I (control)	43.68 ± 4.55	55.46 ± 2.01	72.52 ± 1.42	79.90 ± 0.82
II (positive control)	45.35 ± 4.53	60.76 ± 1.01	75.14 ± 1.46	82.70 ± 0.66
III (aqueous extract)	43.24 ± 3.42	69.36 ± 2.44	78.10 ± 0.70	86.52 ± 0.71
IV (hydro-alcoholic extract)	43.38 ± 1.86	74.58 ± 4.25	95.55 ± 0.85	98.42 ± 0.15
V (alcoholic extract)	40.72 ± 1.90	65.42 ± 4.19	76.78 ± 1.48	83.36 ± 1.04

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SESSION 2
Analytical Chemistry

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High-performance liquid chromatography method for simultaneous determination of gallic acid and ellagic acid in herbal extract and formulations

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Objectives This study was performed for the development and validation of reverse-phase high-performance liquid chromatography (RP-HPLC) methods for standardization of two widely used herbs, the whole plant of *Phyllanthus amarus* L. and seed extract of *Syzygium cumini* L. Two marker compounds, gallic acid and ellagic acid, were quantified from the methanol extracts as well as from commercial formulations using RP-HPLC. This paper presents an isocratic elution system for the separation of gallic acid and ellagic acid. Method validation was performed as recommended in the International Conference on Harmonisation (ICH) guidelines.

Methods Reference standards of gallic acid and ellagic acid (purity 98%, w/w) were from Natural Remedies (India) and all chemicals used were of analytical grade. Methanol extracts were prepared from the whole plant of *P. amarus* and seed of *S. cumini* and their formulations from three different places. A Thermo ODS Hypersil C_{18} (250 mm × 4.6 mm, 5 μm) column was used. Separation was achieved using a mobile phase consisting of 5 mM potassium dihydrogen phosphate (pH 3.2)/acetonitrile (41:9) at a flow rate of 1.0 mL/minute. The eluent was monitored using UV detection at a wavelength of 280 nm. Calibration curves were prepared using standard solution in a range of 0.8–8 μg/mL for gallic acid and 2–20 μg/mL for ellagic acid. The validation parameters addressed were specificity, precision, accuracy, linearity, limits of detection and quantification and the stability of gallic acid and ellagic acid in the mobile phase.

Results HPLC method development and optimization were done after tracking several elution systems. The study revealed that the gallic acid and ellagic acid were well resolved from *P. amarus* and *S. cumini* extracts as well as their formulations, with retention times of 3.8 and 10.3 minutes respectively. Good linearity was achieved in the investigated ranges for both analytes. Correlation coefficients were $R^2 = 0.998$ for gallic acid and $R^2 = 0.999$ for ellagic acid. The values for limit of detection (LOD) were 0.2 and 1 and limit of quantification (LOQ) values were 0.8 and 1.6 respectively. The relative SD (RSD) values for injection repeatability, analysis repeatability and for the intra-assay and inter-assay precision were lower than 2.0% of the peak area. The percentage recovery values at three different levels of gallic acid were 101.33, 99.04 and 101.14% and for ellagic acid were 97.20, 101.38 and 99.00%. The gallic acid and ellagic acid contents found were 0.41 ± 0.03 and 0.13 ± 0.02% respectively in *P. amarus* and 1.15 ± 0.02 and 0.36 ± 0.01% in *S. cumini* respectively.

Conclusions The developed HPLC method is precise, specific and accurate for determination of both the marker compounds. In previously reported work the time required for each run was high. But the method that we have developed proves that repeatable and selective analysis of these two active components in herbal drugs as well as in pharmaceutical formulations requires less time. It can also be used in routine quality control of herbal raw materials as well as formulations containing either or both of these compounds.

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The effect of complex coordination on gallium determination using ion chromatography

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Objectives Interest in the therapeutic use of gallium is increasing due to the discovery of its effectiveness as an anti-tumour and anti-microbial agent (Bernstein 1998). However, gallium strongly coordinates with many organic and inorganic ligands and these complexes can display very different physico-chemical properties (Houghton 1979). The gallium species present may also influence the accuracy of the assay used to quantify it. To enable the design of dosage form gallium must be accurately quantified irrespective of the coordination species present. The aim of this study was to develop a simple, rapid method for determining gallium content in a range of coordination complexes in a simple vehicle and a biological matrix.

Methods An ion-exchange column (IonPac CS5A) was used to separate gallium prior to colorimetric quantification using a derivatization reaction with 4-(2-pyridylazo)resorcinol. Gallium in deionized water standards were injected on consecutive days (n = 6) to test the method precision and efficiency. Hyperquad simulation and speciation (HYSS) software was used to construct speciation profiles for gallium in aqueous buffer systems. This allowed specific vehicle pH and gallium concentrations to be identified for the investigation of gallium coordination complexes. Recovery from solutions containing two ligands was assessed using 50 mM citrate and 3.5 mM EDTA to coordinate gallium (range 0.25–0.0125 mg/mL). Gallium recovery from a mucus model prepared from ultrafiltrated pig stomach mucus was assessed (n = 3) as a representative biological matrix.

Results A single resolved peak was observed for the gallium standards (t_R = 2.55 ± 0.02 minutes). A linear calibration curve was obtained in the range 0.5–0.005 mg/mL (y = 8185.6x-19.12, R^2 = 0.9999) and the assay accuracy was 99.2 ± 1.8%. The HYSS speciation plots showed gallium to be 100% complexed by the citrate and EDTA ligands at the pH of the mobile phase (pH 4.2). Gallium was efficiently recovered from the citrate complex (100.7 ± 2.7%) but not from the EDTA complex (48.5 ± 80.1%). Gallium recovery from the mucus model was found to be linear over range 0.4–0.25 mg/mL (R^2 = 0.997) and accurate (97.0 ± 1.2%).

Conclusions A simple and rapid method for determining gallium content in coordination complexes and a biological matrix has been developed. Good recovery was obtained from the citrate complex, but the gallium–EDTA complex was too stable (log β 23.6) for efficient interaction with the ion pair reagent pyridine dicarboxylic acid and hence the column, resulting in underestimation of gallium content. This demonstrates that the coordination complex formed plays an important role in the analysis of solutes and would therefore influence formulation composition. Linear recovery from the mucus model allowed accurate gallium quantification; however, the y intercept showed a negative deviation from 0, possibly due to intermolecular protein binding which has previously been reported with the delivery of transition metals in biological systems (Hostynek et al 1993).

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Analysis of 1-aryl piperazine drugs of abuse by high-performance liquid chromatography

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Objectives Products containing 1-aryl piperazines are sold through shops, night clubs, music festivals and the internet as so-called legal highs. They have now been determined to be medicinal products and the Medicines and Healthcare Products Regulatory Agency (MHA) has recently warned that selling products containing benzylpiperazine and its derivatives through these outlets is illegal. The objective was to develop analytical methods to detect and quantify 1-benzylpiperazine and related 1-aryl piperazines in pharmaceutical formulations to support the regulation of these products in the UK. The methods were developed from an unpublished method supplied by the US Food and Drugs Administration.

Methods Samples of one tablet or capsule were sonicated with 25 mL methanol followed by dilution with aqueous acetonitrile prior to injection on each of two isocratic high-performance liquid chromatography (HPLC) systems equipped with UV diode array detection. Method 1: separation was carried out on a Phenomenex Luna C_{18}(2) (5 μm, 150 mm × 2 mm inner diameter) column with 10 mM sodium 1-hexanesulphonate (72.4%)/acetonitrile (27.5%)/acetic acid (0.1%) as a mobile phase at 30°C and 0.25 mL/minute. Injections of standards of 1-(2-chlorophenyl)piperazine, 1-(3-chlorophenyl)piperazine, 1-(4-chlorophenyl) piperazine, 1-(3-trifluoromethylphenyl)piperazine, 1,4-dibenzyl piperazine and 1-(4-trifluoromethylphenyl)piperazine at 0.2 mg/mL in aqueous acetonitrile were made with detection at 210 nm. UV spectra from 190 to 400 nm were also recorded. Method 2: separation was carried out as for method 1 but with 10 mM sodium 1-hexanesulphonate (79.5%)/acetonitrile (20.4%)/acetic acid (0.1%) as the mobile phase. Injections of standards of 1-benzyl piperazine, 1-(4-methoxyphenyl) piperazine, 1-(2-methoxyphenyl)piperazine, 1-(3-methoxyphenyl)piperazine, 1-(4-fluorophenyl)piperazine and 1-(4-methylphenyl)piperazine were made as for method 1.

Results The two isocratic methods used together provide satisfactory separation of 10 1-aryl-piperazines; a further two derivatives co-elute but can be clearly identified by their characteristic UV spectra. Validation of the method was carried out for selected compounds, giving linearity coefficients of 0.999 and injection repeatability of 0.9% relative SD.

Table 1 Analysing products from the UK market

Sample	Content (mg per dose)				
	1-benzyl piperazine	1-(4-methoxy-phenyl) piperazine	1-(3-trifluoro-methyl phenyl) piperazine	1-(3-chloro-phenyl) piperazine	1-(4-fluoro-phenyl) piperazine
1	43	34	0	0	0
2	34	11	11	0	0
5	174	0	104	0	0
7	144	0	1	0	0
10	0	7	0	0	20
13	60	0	3	0	0
15	43	12	14	0	12
16	188	0	0	0	0
17	170	0	75	0	0
19	266	0	0	22	0
20	134	0	69	0	0
21	206	0	0	0	0
23	34	4	19	6	0

Conclusions Twenty products obtained from the UK market were found to contain widely varying quantities of benzylpiperazine and other 1-aryl-piperazines (Table 1). The compounds were quantified at 210 nm and characterized with a high degree of certainty by a retention time and UV spectra.

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Compatibility studies for an opioid and anti-emetic in Graseby pump syringes

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Objectives To determine whether within-syringe compatibility of an anti-emetic/opioid (cyclizine/fentanyl) combination could be predicted from a 96-well plate precipitation assay.

Methods Cyclizine lactate (Valoid®) injection 50 mg/mL, fentanyl citrate injection 100 μg/2 mL (Mayne Pharma) and water for injection (DEMO S.A) were used. Fentanyl citrate injection and water for injection were added to wells in a 96-well plate in quantities so that, on the addition of the cyclizine lactate injection, the resulting solution would contain the nominal concentrations of fentanyl citrate injection and cyclizine lactate injection in the ranges 2–48 and 2–45 μg/mL respectively. A 96-well plate containing the diluted fentanyl solutions was then placed in a SpectraMax 340 plate reader and allowed to equilibrate to 25°C. Following this, the appropriate volume of pre-warmed cyclizine citrate injection was added, using an eight-channel multi-pipette. The plate was immediately mixed (30 seconds) and absorbance recorded at 500 nm every 2 minutes for 2 hours. The plate was mixed (30 seconds) prior to each absorbance measurement and the onset of precipitation was set at a theshold of 0.004 absorbance units. All solution combinations were run in triplicate and a phase diagram was constructed to summarize the injection compatibility. Compatibility at 10 mg/mL cyclizine and 5, 10, 15, 20 and 30 μg/mL fentanyl was also investigated in 30 mL syringes. Solutions were prepared in duplicate in volumetric flasks, and drawn up into 30 mL syringes to 48 mm, as required for Graseby pumps. Fentanyl citrate injection was added to the volumetric flask first, followed by the water; then cyclizine lactate injection was added, and the solution made up to volume with water. The syringes were stored at 4, 25 and 37°C and protected from light. At 20 minutes, 1 hour and 2, 6, 24 and 48 hours the solutions were examined visually, and a sample analysed for absorbance at 500 nm using a UV-visible spectrophotometer (Shimadzu UV-1601PC). The precipitate that formed was collected and analysed by infrared spectroscopy, dynamical simulated annealing and nuclear magnetic resonance.

Results One hundred and twenty-two combinations were investigated in triplicate in the 96-well plate experiments (Figure 1). Combinations were considered physically incompatible if the optical density at 500 nm increased over 0.004 absorbance units. Compatible combinations gave optical densities within the range –0.002–0.002 absorbance units.

Visual inspection of syringes containing 10 mg/mL cyclizine (as the lactate) at 25°C showed that 10 μg/mL fentanyl was physically compatible at 48 hours. A precipitate was observed at fentanyl concentrations of 15, 20 and 30 μg/mL at 12, 6 and 2 hours respectively. At 37°C, 20 μg/mL was compatible for 48 hours and at 4°C only the 10 μg/mL was physically compatible for 48 hours. The

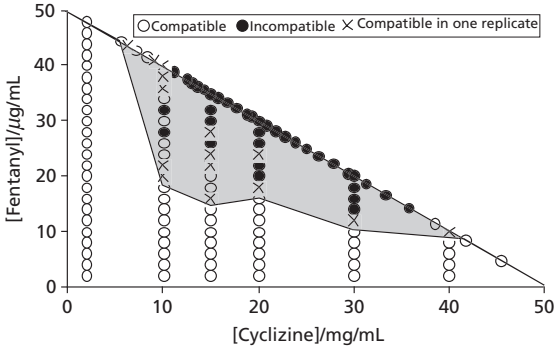

Figure 1 Compatibility of fentanyl citrate and cyclizine lactate injections at 25°C; duration = 2 hours. The shaded area indicates incompatible combinations.

precipitate was identified as cyclizine hydrochloride due to the presence of NaCl in the fentanyl injection.

Conclusions Physical compatibility boundaries for the mixtures were determined from the plate reader assay. In-syringe compatibility at 10 mg/mL cyclizine was in good agreement with the predicted compatibility.

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Simultaneous estimation of lamivudine and zidovudine by reversed-phase high-performance liquid chromatography in tablet dosage forms

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Objectives There are several UV, reversed-phase high-performance liquid chromatography (HPLC) and high-performance thin-layer chromatography methods available for simultaneous estimation of the drugs lamivudine and zidovudine but two reported methods can be used for simple, precise and fast simultaneous estimation of these drugs.

Methods Two simple, fast and precise reversed-phase HPLC methods have been developed and validated for the simultaneous estimation of lamivudine and zidovudine from tablet dosage forms. Lamivudine ((2*R-cis*)-4-amino-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-2(1H)-pyrimidinone) and zidovudine (3′-azido-3′-deoxythymidine) are well-established anti-HIV agents. Lamivudine is official in Indian Pharmacopoeia [1] and [2] and zidovudine is official in Indian Pharmacopoeia [3] and [4]. In the first method the analytes were resolved by using a mixture of buffer (sodium phosphate)/acetonitrile/isopropyl alcohol (85:10:5, by vol.) as the mobile phase on a C_{18} column as a stationary phase and UV 277 nm as the detection wavelength. The retention times of lamivudine and zidovudine were 3–4 and 6–8 minutes respectively. In the second method the analytes were resolved by using a mobile phase of potassium dihydrogen phosphate/acetonitrile/isopropyl alcohol (85:10:5, by vol.) on a C_{18} column as a stationary phase and UV 277 nm as the detection wavelength. The retention times of lamivudine and zidovudine were 3–4 and 7–8 minutes respectively. No spectral or chromatographic interference from the tablet excipients was found.

Results The calibration plot was found to be linear and obeyed the Beer–Lambert law. Both methods were validated for precision, accuracy, linearity, reproducibility and robustness. Both methods were statistically compared by analysis of variance.

Conclusions The proposed two methods can suitably be applied to the assay of commercial formulations and used for routine quality-control applications.

Biopharmaceutics

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Expedited solid-phase synthesis and utilization of affinity-based probes for the serine proteases

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Objectives Serine proteases are one of the most widely studied classes of enzymes; this is largely due to their well-characterized, widespread and diverse roles in a host of physiological and pathological processes. Many pathological disorders are caused by a dysfunction in the normally exquisite regulation of the activity of these proteolytic enzymes, resulting in abnormal tissue destruction and/or the aberrant processing of other proteins and peptides. For example, serine proteases play a critical role in a number of processes, including extracellular matrix remodelling, angiogenesis, wound healing, tumour invasion and metastasis. We and others have previously reported on the synthesis and biochemical testing of peptides and amino acid analogues of amino alkyl diphenyl phosphonates as inhibitors of the serine proteases. These inhibitors exhibit an absolute selectivity of action for the serine protease class and function as time-dependent irreversible inhibitors of their target proteinases. We now wish to report on a novel expedited solid-phase synthesis approach for the generation of active-site-directed affinity probes based upon simple aminoalkyl diphenyl phosphonates and their application for the profiling and characterization of serine proteases obtained from a broad variety of bacterial, human and recombinant sources.

Methods The synthetic scheme employs recently available NovaTag™ resin technology that enables the facile synthesis of activity probes bearing fluorescent or biotin tags and which can also incorporate pegylated spacer units, if desired. Using this approach, we have synthesized a number of affinity probes that target serine proteases with differing P1 specificities. These probes are then used to detect, via affinity-based capture, serine protease activity in various biological milieux by standard electrophoresis and western-blotting techniques employing streptavidin-HP and a chemiluminescent substrate.

Results These inhibitors are potent, selective irreversible inhibitors of trypsin-, chymotrypsin- and elastase-like serine proteases. For example, the affinity-based probe biotin-PEG-succinyl-$Lys^{P}(OPh)_2$ had an overall second-order rate constant of 0.86×10^6 M^{-1} min^{-1}. The second-order rate constant for the inactivation of 4-hydroxy-2-nonenal (HNE) by biotin-PEG-succinyl-$Val^{P}(OPh)_2$ was determined to be 1.29×10^4 M^{-1} min^{-1}. The probes were used to disclose the activity of various serine proteases from both recombinant expression systems and from a range of biological samples including bacterial, mammalian and clinical (colonoscopy) samples. These probes have thus far been utilized to detect elevated levels of proteolytic activity from bacterial pathogens, inflammatory diseases of the colon and a variety of mammalian cells. The detected proteases can then be identified via exploitation of their interaction with immobilized streptavidin, and subsequent *de novo* sequencing, using mass spectrometry.

Conclusions This study reports the rapid, facile synthesis of a range of selective, potent, affinity-based probes for the serine proteases. The utility of these probes has been demonstrated in a number of examples presented. The probes will also find utility in the detection of proteases in numerous processes, especially chonic diseases where serine protease activities can be correlated with disease stage and progression.

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Does reduced dissolution of paracetamol contribute to delayed absorption following single 60 and 90 mg/kg doses in third molar extractions?

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Objectives To investigate paracetamol dissolution using a limited-volume US Pharmacopoeia (USP) dissolution test, then to investigate paracetamol plasma concentration time profiles following 60 and 90 mg/kg doses to determine whether limited solubility may influence paracetamol absorption in a clinical trial (Zacharias et al 2007).

Methods Paracetamol capsules were prepared (500 and 600 mg) in vegetable starch capsules (Wagner Pro-Biotics, Australia) and dissolution was compared with Panadol® caplets in a standard USP dissolution test. Dissolution media volume was reduced to 250 mL and dissolution of one, five, 10 and 15 capsules of 600 mg was determined at 37°C. Dissolution of 10 and 15 capsules was also determined in 250 mL 0.05 M HCl/0.25% w/v sodium dodecyl sulphate. Paracetamol dissolved was determined by UV spectroscopy (242 nm). In the clinical study, 600 mg capsules were administered pre-operatively for third molar extraction at 60 and 90 mg/kg in a randomized, double-blind cross-over study. Plasma was analysed for paracetamol at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 8 and 24 hours by reversed-phase high-performance liquid chromatography.

Results USP dissolution test showed 80.6 ± 4.8, 79.4 ± 4.3 and 93.3 ± 3.2% dissolution in 45 minutes from 600 and 500 mg capsules and Panadol caplets respectively (n = 3). In 250 mL water, the percentage dissolved at 45 minutes was 76.5 ± 3.5, 72.1 ± 2.8, 55.6 ± 1.4 and 43.2 ± 3.0% for one, five, 10 and 15 capsules respectively. In simulated gastric fluid, the dissolution rate was lower, with 27.0 ± 4.5 and 26.5 ± 2.2% dissolved at 45 minutes for 10 and