Pseudomonas aeruginosa employing ciprofloxacin (10 μg/ml) as a reference standard. The zone of inhibition was measured and presented in Table 2.

The results in Table 2 indicated that all the compounds exhibited appreciable antibacterial activity, while the compounds VA2 exhibited equivalent activity with the standard ciprofloxacin against *K. pneumoniae, B. subtilis, C. ferundi, S. epidermitis and S. flexnari,* the compound VA5 exhibited equivalent activity with the standard against *K. pneumoniae* and *S. epidermitis.*

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Four Simple Spectrophotometric Determinations of Lisinopril in Pure State and in Tablets

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Four simple and sensitive procedures (methods A, B, C and D) for the assay of lisinopril in pure form and formulations are described. Methods A and B are based on the condensation of lisinopril (acyclic imino acid) with ninhydrin (indane-1,2,3-trione hydrate) in the presence of ascorbic acid (method A, λ_{max} 560 nm) or ascorbic acid (method B, λ_{max} 520 nm). Method C is based on the initial formation of water insoluble adduct involving lisinopril and phosphomolybdic acid, followed by release of phosphomolybdic acid from the adduct with acetone and color development with cobalt nitrate–ethylenediaminetetraacetic acid disodium salt complex (λ_{max} 840 nm). Method D is based on the formation of colored radical anion on treating lisinopril with 2, 3-dichloro,5,6-dicyano-1,4-benzoquinone (λ_{max} 460 nm). The variable parameters in all these methods have been optimized. The results were statistically validated.

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Lisinopril [(LP), 1-[N^2-[(S)-I-carboxyl-3-phenyl propyl]-L-lysyl]-L-proline dihydrate] is a long-acting angiotensin converting enzyme (ACE) inhibitor, indicated for the treatment of hypertension and congestive heart failure[1]. It is official in USP[2], BP[3] and EP[4]. Existing analytical methods reveal that relatively little attention was paid in developing visible spectrophotometric methods[5-7] for its determination. This paper describes four visible spectrophotometric procedures involving LP with reagents such as ninhydrin (indane-1,2,3-trione hydrate, NH) and ascorbic acid (ASA) (method A), ascorbic acid (method B), phosphomolybdic acid (PMA) and cobalt nitrate-ethylenediaminetetraacetic acid disodium salt complex (Co(II)-EDTA) (method C) and 2,3-dichloro,5,6-dicyano-1,4-benzoquinone (DDQ) (method D) by exploiting its structural features (acyclic imino acid and substituted pentyl amino group).

A Systronics 106 vis spectrophotometer and Milton Roy Spectronic 1201 UV/Vis spectrophotometers were used for absorbance measurements. An Elico LI-120 digital pH meter was used for pH measurements.

Aqueous solutions of PMA (2%, Reachem, Chennai), cobalt nitrate (3%, BDH, Mumbai), EDTA disodium salt (4%, S. D. Fine Chemicals, Mumbai) and ASA (0.1%, BDH, Mumbai, method A) were prepared in triple distilled water. NH (1%, BDH, Mumbai) solution in acetone, DDQ (0.1%, Loba Chemie, Mumbai) in chloroform were prepared. ASA (0.1%, BDH, Mumbai, method B) solution was prepared by initially dissolving 50 mg of ASA in 0.5 ml water and then diluted to 50 ml with dimethylformamide (DMF). Citrate buffer (pH 5.0) was prepared by diluting a mixture of 200 ml of 0.5 M citric acid and 200 ml of 1.0 M NaOH solution to 500 ml with distilled water and the pH was adjusted to 5.0.

A standard solution containing 1 mg/ml of LP was prepared by dissolving 100 mg of pure LP in 100 ml of distilled water and was used as it is for method C. It was further diluted to 400 μg/ml for method A. A 500 μg/ml solution of LP was prepared for method B by dissolving 25 mg of LP in 50 ml of dimethylsulphoxide (DMSO). A 100 μg/ml of LP was prepared for method D by dissolving 10 mg of LP in 100 ml of DMF.

An accurately weighed amount of tablet powder, equivalent to 100 mg of LP was tirturated with 5x5 ml portions of methanol and the combined extract was diluted to 100 ml with the same solvent to obtain 1 mg/ml LP methanolic stock solution. Portions of this stock solution was evaporated on boiling water bath and dissolved in appropriate solvent (distilled water for methods A and C, DMSO for method B, and DMF for method D) to the requisite concentration as under procedures described for bulk samples.

In method A, aliquots (0.1-0.6 ml, 400 μg/ml) of the standard LP solution were transferred into a series of calibrated tubes containing 4.0 ml of citrate buffer (pH 5.0), 1 ml NH (1%) solution and 0.5 ml of ASA (0.1%) solution. The volume in each tube was adjusted to 8 ml with distilled water and were kept in a boiling water bath. After 15 min, tubes were removed and chilled in ice water. The solution in each tube was made up to 10 ml with distilled water. The absorbance was measured at 560 nm against a reagent blank prepared similarly with in the stability period (5-60 min). The amount of LP was calculated from Beer's law plot.

In method B, aliquots (0.1-0.6 ml, 500 μg/ml) of the standard LP solution were transferred into a series of calibrated tubes and the total volume in each tube was adjusted to 1 ml with DMSO. Then 2 ml of ASA (0.1%) solution was added and the tubes were kept in boiling water bath for 15 min. Tubes were removed, cooled to room temperature and the volume in each tube was adjusted to 5 ml with DMF. The absorbance was measured at 520 nm against similar reagent blank within the stability period (5-30 min). The amount of LP was estimated from the calibration graph.

In method C, aliquots (0.5-3.0 ml, 1 mg/ml) of the standard LP solution were transferred into a series of centrifuge tubes containing 1 ml of 0.1 N HCl and the volume in each tube was adjusted to 5 ml with distilled water. Then 4 ml of PMA (2%) solution was added and centrifuged for 5 min. The precipitate was collected through filtration followed by washing with distilled water (3x1 ml) until it is free from the reagent. The precipitate in each tube was dissolved in 5 ml of acetone and transferred into a 25 ml graduated test tube. One millilitre of Co(II) (3%) and EDTA (4%) solutions were successively added and the tubes were heated to 10 min at 60°. The test tubes were cooled and the solution in each tube was made up to the mark with distilled water. The absorbance was measured at 840 nm against a similar reagent blank with in the stability period (5 min-2 h). The amount of LP was calculated from Beer's law plot.

In method D, aliquots (0.5-3.0 ml, 100 μg/ml) of the standard LP solution were transferred into a series of calibrated tubes and the volume in each tube was adjusted to 3.0 ml with DMF. Then 1 ml of DDQ (0.1%) solution was added and the total volume in each tube was adjusted to 5 ml with $CHCl_3$. The absorbance of the colored species was measured at

TABLE 1: ESTIMATION OF LP IN TABLETS.

Tablets*	Labeled amount (mg)	Amount found by proposed method**				Amount found by reference method (mg)	% Recovery by proposed methods***			
		A	B	C	D		A	B	C	D
Listil Forte	10	10.0±0.1 t=0.03 F=0.2	10.0±0.1 t=0.01 F=0.2	9.99±0.1 t=0.2 F=0.5	10.0±0.1 t=0.03 F=0.5	10.02±0.1	100.2	100.1	99.9	100.2
Lipril	10	10.0±0.1 t=0.2 F=0.3	10.0±0.1 t=0.2 F=0.2	10.0±0.1 t=0.2 F=0.6	10.0±0.1 t=0.2 F=0.2	9.97±0.1	100.2	100.3	100.1	100.3
Listil	10	10.0±0.1 t=0.1 F=0.3	10.0±0.1 t=0.1 F=0.2	10.0±0.1 t=0.2 F=0.3	10.0±0.1 t=0.03 F=0.4	10.0±0.1	100.1	100.1	100.3	100.2
Nivant	10	9.99±0.1 t=0.1 F=0.4	10.0±0.1 t=0.1 F=0.2	10.0±0.1 t=0.1 F=0.3	10.0±0.1 t=0.03 F=0.2	10.04±0.1	99.9	100.1	100.1	100.3

Listil forte and Listil are manufactured by Torrent Pharmaceuticals, Ahmedabad. Lipril is manufactured by Lupin Pinnacle and Nivant by Germen Remedies, Mumbai. **Average± standard deviation of six determinations; the t- and F-values refer to comparison of the proposed methods with the reference method. Theoretical values at 95% confidence limits, t=2.57, F =5.05; ***After adding 10 mg pure drug to the pre-analyzed pharmaceutical formulations, each value is an average of three determinations.

460 nm against a similar reagent blank during the stability period (10-40 min). The amount of drug present was calculated from the calibration graph.

The optical characteristics such as molar absorptivity (l/mol.cm), Sandell's sensitivity (μg/cm^2/0.001 absorbance unit), Beer's law limits (μg/ml) were found to be 9.849×10^3, 0.045, 4-24; 3.476×10^3, 0.127, 10-60; 1.762×10^3, 0.25, 20-120 and 2.78×10^3, 0.159, 10-60 for methods A, B, C and D respectively. Slope, intercept and correlation co-efficient (from regression analysis) and % relative standard deviation (from 6 replicates) were found to be 2.22×10^{-2}, 9.33×10^{-4}, 0.9999, 0.610; 7.817×10^{-3}, 1.4×10^{-3}, 0.9999, 0.612; 3.997×10^{-3}, -1.333×10^{-4}, 0.9999, 0.388 and 6.314×10^{-3}, -7.33×10^{-4}, 0.9999, 0.735 for methods A, B, C and D, respectively.

The utility of each method was verified by means of replicate estimation of tablets. The values obtained by the proposed and reference methods (UV) for pharmaceutical formulations were compared (Table 1) and are in good agreement. These results were compared statistically by t- and F- tests and found not to differ significantly. The results of recovery experiments by the proposed methods are also listed in Table 1.

The commonly found excipients and additives and other therapeutic component, hydrochlorothiazide (HCZ) present in certain formulations did not interfere with the assay methods. The results indicate that the methods A, B, C and D possess higher λ_{max} values than the reported methods and have advantage of broad range in Beer's law limits. The proposed methods are simple, selective, reliable and sensitive for the determination of LP in pure state and in tablets.

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Influence of Granule Size and Lubricant Concentration on the Dissolution of Paracetamol Tablets

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The effects of granule size and concentration of magnesium stearate as lubricant on the dissolution rate of paracetamol tablets were studied. The results obtained show that dissolution rate was increased as the granule size of the tablet was increased for tablets prepared with 1.5% magnesium stearate as lubricant. However, tablets prepared with different granule size, exhibited no pronounced effect on the dissolution characteristics when concentration of magnesium stearate was used as 0.75%.

The relationship between granule size and dissolution rate for a number of drugs was previously reported[1-4]. In another study, Finholt and Solvang[5] have pointed out that the dissolution rate of phenacetin tablets was increased as the particle size was decreased. Dissolution may be affected by incorporation of a lubricant[6]. Hydrophobic lubricant decreases the effective drug-solvent interfacial area, which results in reducing wettability and thereby prolonging its dissolution[7]. Hasan *et al.*[10] indicated that the dissolution time of paracetamol tablets was increased with the decrease of the granule size in presence of magnesium stearate. The present authors in their earlier study found that dissolution rate of paracetamol tablets containing 1.5% magnesium stearate increased as the granule size increased[8]. The report assumed that layer of granules undergo a breakdown during compression, yielding a larger surface area some of which are not covered by the insoluble lubricant (magnesium stearate). The present study concerns with the dissolution characteristics of compressed paracetamol tablets, prepared with three different granules and in presence of varying concentrations of a hydrophobic lubricant, magnesium stearate.

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Paracetamol IP was obtained as a gift sample from Duphar-Interfran Ltd, Mumbai. Excipients used in preparing the tablets were starch, talc, polyvinylpyrrolidone (PVP), alcohol and magnesium stearate and all were of IP grade. Weighed quantities of paracetamol, starch, and talc were mixed for 30 min and kneaded with 40% w/v solution of PVP in alcohol. The mixture was granulated by passing through sieve no. 16 followed by drying at 50-55° for 10-12 h. The dried granules were separated by sieves 16, 22 and 30 into three parts. The sized granules of each lot was subdivided into two portions and mixed with 1.5% and 0.75% magnesium stearate, respectively. The tablets were compressed on a single punch tablet machine at a constant compression force with calculated average weight of a tablet equiva-