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Chapter

Interaction Studies of ACE Inhibitors with Antidiabetic Drugs

Safila Naveed and Halima Sadia

Abstract

Angiotensin converting enzyme (ACE)-inhibitors are effective in patients with mild to moderately severe hypertension, collagen vascular and cardiovascular disease. They are also used in the prevention and treatment of myocardial infarction and in the management of cardiac arrhythmias. Patients with cardiovascular diseases are generally on multiple medicines that's why it is imperative to study drug–drug interactions of medicines which are commonly taken together in any given case, as combined administration of different medicines can significantly influence the availability of drugs. In the present study we investigated the "*in vitro*" interactions of ACE inhibitors (enalapril, captopril and lisinopril) with frequently prescribed and co-administered drugs in simulated human body environments. These interactions were monitored by means of UV spectrophotometry and separation technique as RP-HPLC. Prior to start of actual drug interactions, the method of analysis of each drug was established and its various parameters validated for considering its use in testing of drug *in vitro* as well as in human serum. For this purpose, an attempt was made to develop a number of new HPLC methods for determination of ACE inhibitors (enalapril, captopril and lisinopril) and simultaneously with interacting drugs. These methods were optimized, validated and then successfully employed for the quantitation of enalapril, captopril and lisinopril and selected drugs in interactions studies. As a result, new methods for the quantitation of individual as well as multiple drugs were developed. The interacting drugs selected were antidiabetic drugs (metformin, glibenclamide, glimepride and pioglitazone. Interaction consequences revealed that the availability of enalapril was not affected in presence of antidiabetic drugss whereas the availability of captopril and lisinopril were altered in presence of NIDDMs.

Keywords: ACE Inhibitors, Antidiabetics, Interaction studies, HPLC, Method development

1. Introduction

1.1 Angiotensin converting enzyme

Angiotensin Converting Enzyme is an ectoenzyme and a glycoprotein with an appreciate molecular weight of 170,000 Do. Human angiotensin converting enzyme contains 277 aminoacid residues and has two homologous domains, each with a catalytic site and a region for binding Zn^{+2} [1, 2]. The degradation of bradykinin to inactive peptides occurs via action of ACE, thus ACE not only produces a potent vasoconstricton but also inactivates a potent vasodilator [3].

In 1965, Ferreira [4] studied the physiological effects of snake poisoning and discovered a specific component from the venom of the pit viper, *bothrops jararaca*, which inhibits degradation of the peptide bradykinin and potentiate hypotensive action of bradykinin. These factors originally designated as bradykinin potentiating factors (BPFs), were isolated and found to be a family of peptides containing 5–13 amino acid residues. Bakhle [5] reported that these same peptides had an inhibitory activity on ACE of dog lung homogenate and inhibited the enzymatic conversion of angiotensin I to angiotensin II. Hans Brunner and John Laragh [6] administered it to hypertensive patients and showed that it was extremely effective in lowering blood pressure. The structural requirements for substrates of angiotensin converting enzyme to cleave a substrate are found similar to those observed with carboxypeptidase A of bovine pancrease [7, 8]. The substrate specificity and other properties of angiotensin converting enzyme suggested that it was a zinc metallopeptidase, similar in mechanism to carboxypeptidase A, an enzyme whose active site had been well characterized by x-ray crystallography and other methods [9]. In 1970, Ferreira and Greene [10] isolated and characterized the first peptide, a bradykinin-potentiating pentapeptide that they called BPP5a; it also inhibited ACE and transiently lowered blood pressure in animal models. The significance of ACE in the pathogenesis of hypertension was not fully appreciated until 1977's, when Ondetti [11] first isolated and then synthesized the naturally occurring nonpeptide, teprotide. He proposed a hypothetical model of the active site of ACE and used it to predict and design compounds that would occupy the carboxy- terminal binding site of the enzyme [12]. Cushman and Ondetti first created succinyl-L-proline, which showed slight positive activity. Inhibitory activity increased 15 to 20 times when they substituted a methyl group in the 2 position of succinyl group. Finally to enhance the binding capacity of substrate structure and zinc of the enzyme they replaced succinyl COOH with sulfhydryl, a 2000 times increase in inhibitory potency was achieved. ACE inhibitors entered the antihypertensive drug market during the 1980. Manolio [13] explored new types of drugs in preventing cardiovascular mortality. Captopril, a specific potent inhibitor of ACE, showed excellent anti-hypertensive properties in clinical trials and had a major impact on the treatment of cardiovascular disease [14].

1.1.1 Chemistry

The most thoroughly studied of the peptide inhibitors of converting enzyme is the nonapeptide known as teprotide, having the structure, Pyoglu-Tro-Arg-Pro-Glnlle-Pro-Pro.Teprotide acts as a competitive inhibitor of converting enzyme, with an affinity for the enzyme much higher than that of angiotensin I. It is not itself a substrate for the enzyme. Although converting enzyme will cleave many different C-terminal dipeptide residues, it will not cleave peptides with proline in the penultimate position. As noted, the penultimate proline in angiotensin II, indeed, is responsible for its refractoriness to further cleavage by converting enzyme. Moreover, the presence of Pyro Glu at the N-terminus renders teprotide refractory to amino peptidases; this confers further stability and effectiveness in vivo. Nevertheless, teprotide has a relatively short duration of action and must be given parentally to be effective [11]. The optimum pH of angiotensin converting enzyme was found to vary with the substrate employed and to be influenced by the presence or absence of chloride ion. With longer peptide substrates such as angiotensin I or bradykinin in the presence of chloride ion, the optimal pH for hydrolytic action of the converting enzyme was about 7.5; with tripeptide substrates such as Z-Phe-His-Leu, Hip-His-Leu, or Hip-Gly-Gly, it was about pH 8.5 [15, 16]. Studies of the hydrolysis of synthetic substrate of ACE [17, 18] and hippuryl di and tripeptides [19] shows that enzyme tolerate changes at antepenultimate position of a peptide

substrate especially aromatic amino acids such as phenylalanine which contributes greatly to the overall affinity for the enzyme. A tripeptide with an acylated terminal amino group is the simplest peptide cleaved by the enzyme. However, the tripeptide Z-Phe-His-Leu, analogous to the terminal tripeptide sequence of angiotensin I, binds to the active site of angiotensin converting enzyme as well as the intact decapeptide. Peptides such as angiotensin II with a penultimate proline residue [20]. The orally effective ACE-inhibitor was developed by a rational approach that involved analysis of the inhibitory action of teprotide, inferences about the action of converting enzyme on its substrates, and analogy with carboxy peptidase A, which was known to be inhibited by d-benzylsuccinic acid. Ondetti and Cushman urged that inhibition of converting enzyme might be produced by succinyl amino acids that corresponded in length to the dipeptide cleaved by converting enzyme. This proved to be true and led ultimately to the synthesis of a series of carboxy or mercapto alkanoyl derivatives that acted as competitive inhibitors of the enzyme [21].

1.1.2 Mechanism of action

These drugs block the angiotensin converting enzyme that cleaves the terminal two peptides from angiotensin I (decapeptide) to form the potent vasoconstrictor angiotensin II (octapeptide) [22, 23] and lower the BP by reducing peripheral vascular resistance without reflexly increasing cardiac out put rate, and contractility [22]. They also inhibit the rate of bradykinin inactivation thus resulting in vasodilation, they also decrease the secretion of aldisterone resulting in decrease of sodium and water retention.

1.1.3 Pharmacokinetics

ACE-inhibitors are given by mouth, the oral bioavailability of this class of drugs ranges from 13–95% [24, 25]. Most of the ACE inhibitors are administered as prodrugs that remain inactive until esterified in the liver [26]. Fosinoprilate is excreted via biliary duct, elimination of the diacid is polyphasic and there is a prolong terminal elimination phase, which is considered to represent binding to ACE at saturate binding site. This bond fraction does not contribute to accumulation of drug following multiple doses [27, 28].

1.1.4 Therapeutic use

ACE-inhibitors are effective in patients with mild to moderately severe hypertension, with normal or low plasma renin activity, with collagen vascular disease, with cardiovascular and in anephric disease [29–36]. They cause a reduction in left ventricular hypertrophy, and in plasma fibrinogen level [37, 38]. They are also used in the prevention and treatment of myocardial infarction [39, 40], and in the management of cardiac arrhythmias [41, 42]. They can decrease the progression of atherosclerosis [43], microalbuminuria [44] and diabetic retinopathy [45–47] and produce beneficial effect in Bartter's syndrome [48].

1.1.5 Adverse effects

Pronounced hypertension may occur at the start of therapy with ACE-inhibitors particularly in patients with heart failure, and in sodium or volume depletion patients [49–51]. They cause hyperkalemia in patients with renal insufficiency or in patients taking k + −sparing diuretic, k + −supplement, beta blockers or NSAID's [23, 52] and produce cough in hypertensive patient [53, 54]. Altered liver function,

cholestatic jaundice, hepatitis, hepatotoxicity [55] and aplastic anemia [56] have also been reported. They can produce a complex and contradictory effect on kidney and induce renal insufficiency in patients having bilateral renal artery stenosis, heart failure or diarrhea [57–61]. Angioedema is a rare but potentially life-threatening side effect of ACE inhibitors [62–68] can cause a number of fetal anomalies [69, 70]. Scalded mouth syndrome [71] and drug induced pulmonary-infiltration with eosinophilia syndrome (PIE-syndrome) is a rare complication [72]. With use of ACE inhibitors, anaphylactoid reactions are also reported [73, 74].

1.1.6 Contraindications

Experimental and clinical data conclude that use of ACE inhibitors should be avoided in all trimester of pregnancy [75, 76]. Patients with peripheral vascular disease are at high risk of renal failure with this therapy [77] also contraindicated in known hypersensitivity to any ACE inhibitors [78].

1.1.7 Overdosage

There have been reports of over dosages with captopril and enalepril [79–81], the main effect is hypotension [82, 83] which usually responds to supportive treatment and volume expansion, pressor agents are rarely required. Infusion of angiotensin amide may be considered if hypotension persists [84, 85].

1.1.8 Drug interactions

Hypotensive effect of ACE inhibitors decreased when given in combination with non-steroidal anti-inflammatory drugs [86] but this effect is enhanced with calcium-channel blockers [87] and beta-blockers [88]. Granulocytopenia occurs after combine therapy of ACE inhibitors and interferones [89], the nitritoid reaction occurs with concomitant use of gold salt and ACE inhibitors [90]. Cytokines antagonize the hypotensive effect of ACE inhibitors [91], severe hypokalaemia occurs with potassium depleting diuretics [92] and potassium-sparing diuretics produced hyperkalaemia [93–95]. ACE inhibitors could increase potassium levels in the body [96, 97]. Alpha-blockers enhance hypotensive effect of ACE inhibitors [98]. Iron supplementation successfully decreases cough induced by ACE-inhibitors [99] and can interfere with the absorption of ACE inhibitors [100]. Hypoglycemic effect is enhanced with antidiabetics and insulin [101, 102]. Azathioprine and ACE inhibitors combination is associated with anemia [103]. Marked hypotension occurs in patients receiving general anesthetics and ACE inhibitors [104]. The risk of bone marrow depression is increased in patients taking concomitant therapy of ACE-inhibitors and immunosuppressive agents [76]. **Table 1** shows some example of ACE Inhibitors.

1.2 Antidiabetic drugs

Type II or non insulin dependent diabetes mellitus (NIDDM) formerly known as maturity-onset or adult-onset diabetes. Approximately 95% of patients are being affected by the type II form [105, 106]. NIDDM are being increasingly diagnosed as its importance as a risk factor for the development of cardiovascular disease and many drugs has been known to interfere with glucose control. The greatest effect was seen with propranolol and the least with cardioselective and less lipophilic beta-blockers, nifedipine has been associated with deterioration in glucose control but verapamil has been found to have a beneficial effect on glucose control. Antihypertensive drug clonidine has not been shown to result in deterioration in

glucose control when used in NIDDM. Long term therapy with the more specific agonist guanfacine was reported to have a beneficial effect on glucose tolerance [107]. **Table 2** shows, examples of antidiabetic drugs.

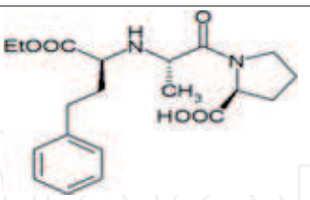
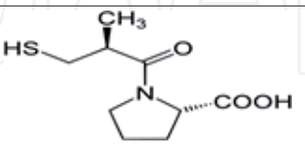
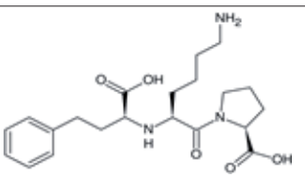
Drugs	Nomenclature	Structure
Enalapril	(S)-1-[N-[1-(ethoxycarbonyl)-3-phenyl propyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt	
Captopril	1-(3-mercapto-2-dmethyl-1-oxopropyl)-1-proline (S,S)	
Lisinopril	((S)-1-[N2-(1-carboxy-3-phenylpropyl)-1-lysyl]-1-proline dehydrate	

Table 1.
Examples of ACE inhibitors.

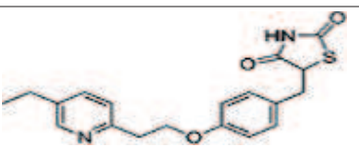
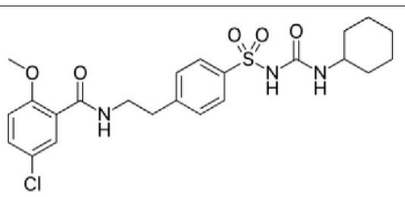
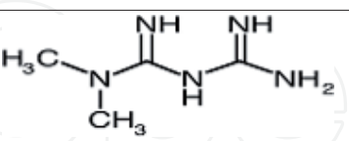
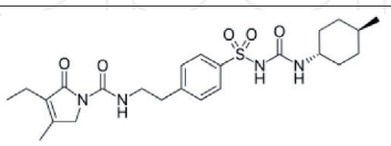
Drags	Nomenclature	Structure
Pioglitizone	(±)-5-[[4-[2-(methyl-2-pyridinylamino) ethoxy]phenyl] methyl]-2,4-thiazolidinedione, (Z)-2-butenedioate(1:1)	
Glibenclamide	1-[[4-[2-[(5-chloro-2-ethoxybenzoyl) amino]ethyl]phenyl]sulphonyl]-3-cyclohexylurea, $C_{23}H_{28}ClN_3O_5S$	
Metformin	N,N-dimethyl-imido-di-carbonimidic diamide hydrochloride	
Glimepride	[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyyroline-1-oxamide)ethyl] phenyl] sulfonyl]-3-(trans-4-methylcyclohexyl) urea,	

Table 2.
Examples of anti-diabetic.

2. Experimental

2.1 Materials

Raw materials used were of pharmaceutical purity and were obtained from different Pharmaceutical Companies (**Table 3**). Tablets were purchased from local

Class	Drugs	Brands	Potency (mg)	Pharmaceutical industry
ACE inhibitors	Enalapril	Renitec	10	MSD
	Captopril	Capoten	25	Bristol Meyers Pvt. Ltd
	Lisinopril	Lisinopril	5	Atco Laboratories Ltd
Antidiabetic	Metformin	Neodipar	250	Sanofi Aventis (Pakistan) Ltd
	Glimepride	Amaryl	2	Sanofi Aventis (Pakistan) Ltd
	Pioglitazone	Poze	45	Ali Goliar Pharmaceuticals (Pvt
	Glibenclamide	Diazet	5	Safe Pharmaceutical (Pvt) Ltd

Table 3.
Drugs, brands and manufacturers.

pharmacy and each product was labeled and expiry date not earlier than two years, at the time of these studies were noted.

2.1.1 Reagents

Analytical grade reagents were used during the whole experimental procedures. Methanol and acetonitrile were of (HPLC grade) (TEDIA®, USA). Other reagents include hydrochloric acid, sodium hydroxide, sodium chloride, potassium dihydrogen orthophosphate, disodium hydrogen orthophosphate, ammonium chloride, 10% NH_3 solution, phosphoric acid 85% (Merk, Germany). Organic solvents used were methanol, ethanol, ethyl acetate, chloroform, acetronitrile, triethylamine and DMSO (Merck Grade).

2.1.2 Equipments

UV visible spectrophotometer (Model 1601, Shimadzu, Japan) with 10-mm path length connected to a P-IV computer loaded with Shimadzu UVPC version 3.9 software was used in these studies. Deionizer, Stedec CSW-300 used for deionization of water. The dissolution equipment was the B.P. 2009 standards. Chromatographic studies were carried out by using two Shimadzu HPLC systems, one equipped with LC-10 AT VP pump, SPD-10 A VP UV–*vis* detector and other HPLC system was equipped with LC-20AT and SPD-20A UV/VIS detector utilizing Hypersil, ODS, C18 (150 × 4.6 mm, 5micron) and Purospher® STAR RP-18 column. Chromatographic data were recorded using a CBM-102 Shimadzu. Shimadzu Class-GC 10 software (version 2) for data acquisition and mathematical calculations.

IR studies were carried out by FTIR Prestige-21 spectrophotometer Shimadzu. Spectral treatment was performed using Shimadzu IRsolution 1.2 software. The H^1-NMR spectra were recorded on a Bruker AMX 500 MHz spectrometer using TMS as an internal standard. Melting points were recorded by Gallenkamp melting point apparatus.

2.2 Methods

2.2.1 Preparation of simulated gastric juice and buffers

0.1 N hydrochloric acid was prepared by diluting 9 mL hydrochloric acid of analytical grade (11 N) in a liter volumetric flask and the volume was made up to the mark with de-ionized water. Chloride buffer of pH 4 was prepared by dissolving

3.725 g of potassium chloride in deionized water in one liter and 0.1 N HCl was used for pH adjustment. For preparation of phosphate buffer of pH 7.4, 0.6 gm of potassium dihydrogen orthophosphate, 6.4 g of disodium hydrogen orthophosphate and 5.85 g of sodium chloride were dissolved in sufficient deionized water to produce 1000 mL and the pH adjusted. For preparation of ammonia buffer of pH 9, 4.98 g of ammonium chloride was dissolved in 1000 mL of deionized water and pH adjusted with 10% ammonia.

2.2.2 Construction of the calibration curve of drugs

The above prepared working standard solutions of all drugs were scanned in the region 200–700 nm against the reagent blank and absorbance maxima was recorded as shown in **Table 4**. Calibration curves were constructed between concentration and absorbance. Epsilon values and linear coefficients were calculated in each case at all above described pH values. Beer Lambert's law was obeyed at all concentrations and pH.

2.2.3 Monitoring of drug interactions of enalapril, captopril and lisinopril by high performance liquid chromatography

HPLC methods for simultaneous determination of enalapril, captopril and lisinopril with NSAIDs, H_2-receptor antagonist, statins, antidiabetic drugs, metals and antacids in raw materials, pharmaceutical dosage forms or in human serum are developed and validated according to ICH guidelines. These methods were then applied to drug–drug, drug metals and drug antacid interaction studies.

2.2.4 Chromatographic conditions

The isocratic elution was performed at ambient temperature with two different types of columns. Hypersil, ODS, C18 (150 × 4.6 mm, 5micron) and Purospher® STAR RP-18, for assay of enalapril, captopril and lisinopril and simultaneous determination of these drugs with interacting drugs respectively. The mobile phase, flow rate, wavelength UV detection were varied as cited in **Table 5**. Sample volume of 20 μL was injected in triplicate onto the HPLC column and elute was monitored at different wavelengths.

2.2.5 Preparation of standard solutions

Stock reference standard solutions of all drugs were prepared daily by dissolving appropriate amounts of each drug in mobile phase to yield final concentrations

Class of drugs	Analytes	Wavelength (nm)	Cone.range (m Mole)
ACE inhibitors	Enalapril	203, 206, 207, 208	1–9 x 10^{-5}
	Captopril	203, 204, 206	5–14 x 10^{-7}
	Lisinopril	206	1–10 x 10^{-5}
Antidiabetic drugs	Metformin	205, 223	0.01–0.1
	Glimepride	240	0.01–0.1
	Glibenclamide	231, 238, 246	0.01–0.1
	Pioglitazone	225, 269	0.01–0.1

Table 4.
Absorbance maxima.

Drugs	Mobile phase			pH	Flow rate	Detection
	MeOH	ACN	H_2O		$mLmin^{-1}$	Nm
Enalapril assay	70	—	30	3.5	1	215
Enalapril+Antidiabetic drugs	70		30	2.8	1	230
Captopril	50	—	50	2.9	1	220
Captopril +Antidiabetic drugs	70		30	3	1	230
Lisinopril	80	2.5	17.5	3	1	225
Lisinopril+Antidiabetic drugs	80		20	3	1	225

Table 5.
Chromatographie conditions of HPLC methods.

300 μg mL^{-1}. For the calibration standards, calibrators of each drug were prepared by making serial dilutions from stock solutions. All solutions were filtered through 0.45 μm filter and degassed using sonicator.

2.2.6 Preparation of pharmaceutical dosage form samples

Pharmaceutical formulations of the respective brands, commercially available in Pakistan were evaluated. In each case, groups of twenty tablets were individually weighed and finely powdered in a mortar. Weighed portion of the powder equivalent to the suitable amount of drug (according to the labeled claimed) was transferred into a 100 mL volumetric flask completely dissolved in mobile phase and then diluted with this solvent up to the mark, a portion of this solution was filtered through a disposable 0.45 μm filter and then injected.

2.2.7 Preparation of standard drug plasma solutions

Blood samples were collected from healthy volunteers and then centrifuged at 3000 rpm for 10 minutes and supernatant was stored at −20°C. After thawing, serum was deprotinated by acetonitrile and spiked daily with working solutions to produce desired concentrations of enalapril and interacting drugs. 10 μL volume of each sample was injected and chromatographed under above conditions.

2.3 Method development and optimization

HPLC methods were developed and optimized for certain parameters before method validation. The optimization of the analytical procedure has been carried out by varying the mobile phase composition, flow rate, pH of the mobile phase, diluents of solutions and wavelength of analytes in order to achieve symmetrical peaks with good resolution at reasonable retention time.

2.3.1 Method validation

All validation steps were carried out according to the ICH guidelines such as system suitability, selectivity, specificity, linearity (concentration–detector response relationship), accuracy, precision and sensitivity i.e. detection and quantification limit.

2.3.2 System suitability

System suitability of the method was evaluated by analyzing five replicate analyses of the drug at a specific concentration for repeatability, peaks symmetry

(symmetry factor), theoretical plates of the column, resolution between the peaks of enalapril and other drugs, mass distribution ratio (capacity factor) and relative retention.

2.3.3 Specificity and linearity

The drugs were spiked with pharmaceutical formulations containing different excepients. The linearity of the method was evaluated at different concentrations with different groups. Linear correlation coefficient, intercept and slope values were calculated for statistical analysis.

2.3.4 Accuracy and precision

The accuracy of the method was calculated at three concentration levels (80, 100 and 120%) by spiking known quantities of the drug analytes. Three injections of each solution were injected to HPLC system and % recovery was calculated in each case.

For the precision of the method, six replicates of each level were injected to system on two different non-consecutive days in each case and %RSD was calculated.

2.3.5 Limit of detection and quantification

Detection limit (LOD) of the method was calculated by the formula LOD = 3.3 SD/slope. The quantitation limit (LOQ) is the lowest level of analyte that is accurately measured and it was evaluated as ten times the noise level LOQ =10σ/S; where σ is the standard deviation of the lowest standard concentration and S is the slope of the standard curve.

2.3.6 Robustness

Robustness was performed by making minor changes in the percentage of mobile phase (methanol, water and acetonitrile) wave length, pH and flow rate. Therefore, five repeated samples were injected under small variations of each parameter. When a parameter was changed ±0.2% (in flow rate), ± 0.2% pH and ± 5% wave length from its optimum condition.

2.3.7 Ruggedness

Ruggedness of our method was determined in two different labs. Lab 1 was the Research Institute of Pharmaceutical Sciences, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Karachi while other lab was lab 9, Department of Chemistry, Faculty of Science, University of Karachi. Two different instruments one was LC 10 and LC 20. Two different columns Purospher STAR C_{18} and Hypersil ODS were used.

2.3.8 Interaction studies by HPLC

Enalapril solution was mixed with each solution of interacting drug separately that gave the final concentration of 100μgmL^{-1} for each constituent. These were kept in water bath maintained at 37°C for 3 hours. An aliquot of 5 mL was withdrawn after every 30 minutes intervals, after making appropriate dilutions was filtered through 0.45 μ filter paper and three replicates were injected to HPLC system. The concentration of each drug was determined and % recovery was calculated and the same procedure was applied for captopril and lisinopril.

3. Result and discussion

3.1 Simultaneous quantitation of enalapril and antidiabetic drugs (metformin, glibenclamide and glimepiride)

There are number of HPLC methods reported for the quantitation of metformin using UV detector [108, 109] liquid chromatography–tandem mass spectrometry [110] and from human plasma [111]. Moreover, there are many methods reported for the simultaneous analysis of metformin with other anti-diabetics [112, 113]. Likewise, there are methods reported for the analysis of glibenclamide from pharmaceutical formulations [114], human plasma [115, 116] using HPLC. Similarly, there are methods reported for the simultaneous analysis of glibenclamide with other anti-diabetics. However, no method reported in the literature for the simultaneous quantitation of enalapril, metformin, glibenclamide and glimepride.

3.1.1 Method optimization and chromatographic conditions

In the present investigation the best separation of enalapril and antidiabetic drugs was achieved using a Hypersil, ODS, C18 (150 × 4.6 mm, 5micron) column which provides efficient and reproducible separation of the components. Using other type of column under similar experimental condition, the separation lasted about 11 minutes. A mobile phase of methanol: water (70:30 v/v) having pH adjusted with phosphoric acid to 2.8 provided a reproducible, baseline resolved peak. Small changes in pH of the mobile phase had a great influence to the chromatographic behavior of these drugs, higher pH of the mobile phase also results in peak tailing and at a lower pH retention time of antidiabetic drugs and enalapril was delayed. It is obvious from the chromatogram (**Figure 1**) that antidiabetic drugs and enalapril eluted out forming symmetrical peaks and were well separated from each other. The method was found to be rapid as the drugs separated in a very short time i.e. enalapril 3.6 min and metformin, glibenclamide and glimepiride elution time was 2.4, 8.5 and 10.9 min respectively, which is important for routine analysis. The advantages of this method are ease of operation, short analysis time (total run time < 12 minutes), utilization of readily available cost-effective solvents, no matrix interferences, and satisfactory limit of quantification to enable pharmacokinetic studies of enalapril and NIDDMs.

3.1.2 Method validation

The developed method was validated by ICH guidelines [117]. It includes various parameters for example system suitability, selectivity, specificity, linearity, accuracy test, precision, robustness, ruggedness, sensitivity, limit of detection and quantification.

3.1.2.1 System suitability

The HPLC system was equilibrated with the initial mobile phase composition, followed by 6 injections of the same standard to evaluate the system suitability on each day of method validation. Parameters of system suitability are peaks symmetry (symmetry factor), theoretical plates of the column, resolution, mass distribution ratio (capacity factor) and relative retention as summarized in **Table 6**.

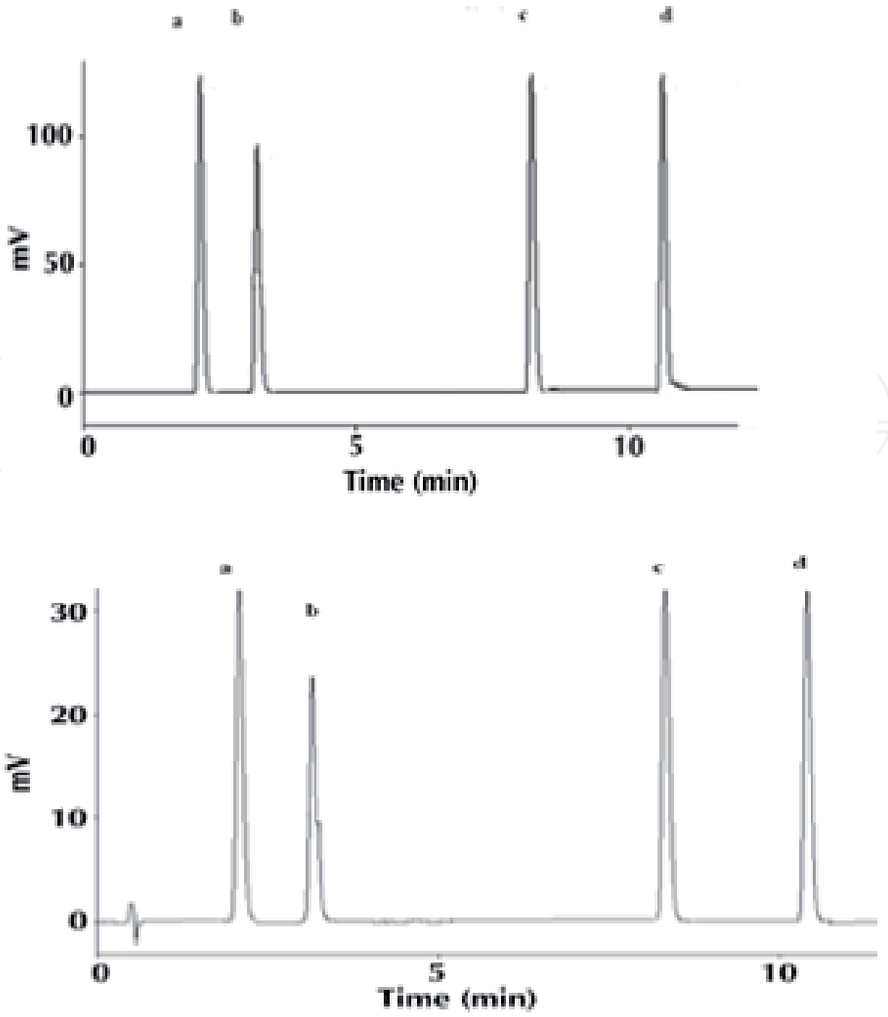


Figure 1.
A representative chromatogram of, and (a) MET (b) ENP (c) GLB (d) GMP in formulation and serum.

Analytes	Retention time (T_R) (mm)	Capacity factors (K′)	Theoretical plates (N)	Tailing factor (T)	Resolut ion (R)	Separation factor
ENP	3.6	2.6	3200	1.23	3.3	2.48
MET	2.4	2.9	3250	1.25	3.5	2.56
GLB	8.5	2.89	3256	1.26	3.6	2.59
GMP	10.9	2.69	3246	1.28	3.9	2.69

Table 6.
System suitability parameters.

3.1.2.2 Linearity

Linearity is generally reported as the variance of the slope of the regression line. Linearity was tested with known concentrations of ENP, MET, GLB and GMP i.e. 2.5, 5, 10, 25, 50 and 100 μgmL^{-1} respectively. Injected concentrations versus area were plotted and the correlation coefficients were calculated which are shown in **Table 7**.

Drugs	Conc. μgmL^{-1}	Regression Equation	r^2	LOD	LOQ
				μgmL^{-1}	
ENP	2.5–100	y = 2489.4x + 255.5	0.9996	1.53	4.6
MET	2.5–100	y = 10406x + 24139	0.9993	0.317	0.96
GLB	2.5–100	y = 14651x + 33832	0.9998	0.19	0.58
GMP	2.5–100	y = 15438x + 39969	0.9996	0.1	0.32

Table 7.
Regresssion statistics LOD and LOQ.

3.1.2.3 Accuracy

Method accuracy was evaluated as the percentage of recovery by estimation of all investigated analytes in presence of various commonly used tablets' excepients at three levels of concentrations that were 80, 100 and 120%. Each sample was injected five times and accuracy was determined in range of 98.6–102.3% (**Table 8**). No significant difference observed between amounts added and recovered without serum and with serum. Thus, used excepients did not interfere with active present in tablets.

3.1.2.4 Precision

Precision was evaluated by carrying out six independent sample preparation of a single lot of formulation. The sample solution was prepared in the same manner as described in sample preparation. Percentage relative standard deviation (%RSD) was found to be less than 2% for within a day and day to day variations, which proves that method is precise. Results are shown in **Table 9**.

3.1.2.5 Sensitivity

The limit of quantitation (LOQ) of the method as signal/noise of ENP, MET, GLB and GMP were found to be 4.6, 0.96, 0.58 and 0.32 μgmL^{-1} respectively.

Analytes	Assay (spiking method)			Assay in serum	
	Conc. μgmL-1	%RSD	% Rec	%RSD	%Rec
ENP	8	0.011	101	0.9	100.3
	10	0.326	100.3	0.23	101.23
	12	0.001	100	0.8	102
MET	8	0.007	100.6	0.96	101
	10	0.002	100.9	0.56	99.98
	12	0.001	100.5	0.89	101.3
GLB	8	0.008	99.7	0.69	99.69
	10	0.002	99.9	0.69	101.6
	12	0.001	100	1.03	102.3
GMP	8	0.008	99.7	0.89	101.3
	10	0.002	100.2	0.36	98.36
	12	0.001	100.1	1.02	99.89

Table 8.
Accuracy of ENP and NIDDM drugs.

Drugs	Conc. injected μgmL^{-1}	Inter-day		Intra-day	
		%RSD	%Rec	%RSD	%Rec
ENP	2.5	0.4	97.44	0.96	100.9
	5	0.3	100.5	0.63	101.1
	10	0.2	99.87	0.65	99.49
	25	0.11	99.2	0.63	101.2
	50	0.56	100.8	0.62	98.94
	100	0.36	99.92	0.62	101.1
MET	2.5	0.35	97.4	0.63	100.9
	5	0.36	102	0.89	101.1
	10	0.9	99.5	0.5	100.9
	25	0.56	101	0.63	100.5
	50	0.25	101	0.36	99.45
	100	1	100	0.63	100.6
GLB	2.5	1.2	97.6	0.07	100
	5	1.3	100.8	1.56	101
	10	1.02	100	0.56	101
	25	1.03	102	0.57	101
	50	1.03	100.2	0.63	99.1
	100	1.05	101.8	0.69	99.6
GMP	2.5	0.69	99.2	0.36	98.85
	5	0.65	102	1.02	99.5
	10	0.68	100	0.9	100.55
	25	1.65	102	0.9	101.19
	50	0.07	100.1	1.2	98.14
	100	0.36	101.6	0.65	99.58

Table 9.
Inter day and intraday precision of ENP and NIDDM drugs.

Similarly a signal/noise of 3, a LOD of ENP, MET, GLB and GMP were determined to be 1.53, 0.317, 0.19, and 0.1 μgmL^{-1} respectively.

3.1.2.6 Ruggedness

The ruggedness of this method was calculated in two different labs with two different instruments. The method did not show any notable deviations in results from acceptable limits.

3.1.2.7 Robustness of method

To evaluate the robustness of the developed RP-HPLC method, small deliberate variations in the optimized method parameters were done. The effect of change in flow rate, pH and mobile phase ratio on the retention time and tailing factor were studied. The method was found to be unaffected by small changes like ±0.1 change in pH, ± 0.1 change in flow rate and ± 1 change in mobile phase.

3.2 Simultaneous determination of captopril and antidiabetic drugs (metformin, pioglitazone and glibenclamide)

The aim of the present study was to establish an efficient, reliable, accurate, precise and sensitive method for the separation and quantitative determination of both drugs simultaneously. These drugs belonged to different classes that could be co-administrated in a number of cases. Simultaneous determination of these drugs is desirable as this would allow more efficient generation of clinical data and could be performed at more modest cost than separate assays. We have developed the method for the simultaneous determination of captopril, metformin, pioglitazone and glibenclamide. The method has been validated according to ICH guidelines and was found to be reproducible. Further, this validated method was used to study the possible *in vitro* interactions of captopril with (metformin, pioglitazone and glibenclamide). Several problems were resolved in the simultaneous determination of compounds investigated.

3.2.1 Method optimization and chromatographic conditions

To optimize the operating conditions for isocratic RP-LC detection of all analytes, a number of parameters such as the mobile phase composition, pH and the flow rate were varied. Various ratios (50:50, 60:40, 70:30 v/v) of methanol: water were tested as starting solvent for system suitability study. The variation in the mobile phase leads to considerable changes in the chromatographic parameters, like peak symmetry, capacity factor and retention time. The pH effect showed that optimized conditions are reached when the pH value is 2.8, producing well resolved and sharp peaks for all drugs assayed. However, the ratio of (70:30 v/v) methanol: water pH adjusted to 2.8 with phosphoric acid as mobile phase (filtered through a 0.45 micron filter), a flow rate of 1.0 $mLmin^{-1}$ using wavelength 230 nm was chosen as optimal condition. Retention time for captopril was found to be 3.3 minute, metformin, pioglitazone and glibenclamide 2.4, 2.8, 7.2 minutes respectively (**Figure 2**).

3.2.2 Method validation

The developed method was validated by ICH guidelines [5]. It includes various parameters for example system suitability, selectivity, specificity, linearity, accuracy test, precision, robustness, ruggedness, sensitivity, limit of detection and quantification (**Table 10**).

3.2.2.1 Linearity

Linearity was studied by preparing standard solutions at different concentration levels. The linearity range for CAP and antidiabetics was found to be 2.5–100 μgmL^{-1} and 0.625–25 μgmL^{-1}, respectively, regression equations for CAP and antidiabetics are given in **Table 11**.

3.2.2.2 Accuracy

Method accuracy was evaluated as the percentage of recovery by estimation of all investigated analytes in presence of various commonly used tablets' excepients at three levels of concentrations that were 80, 100 and 120%. Each sample was injected five times and accuracy was determined in range of 98.45–102.2%. No significant difference was observed between amounts added and recovered without serum and with serum (**Table 12**).

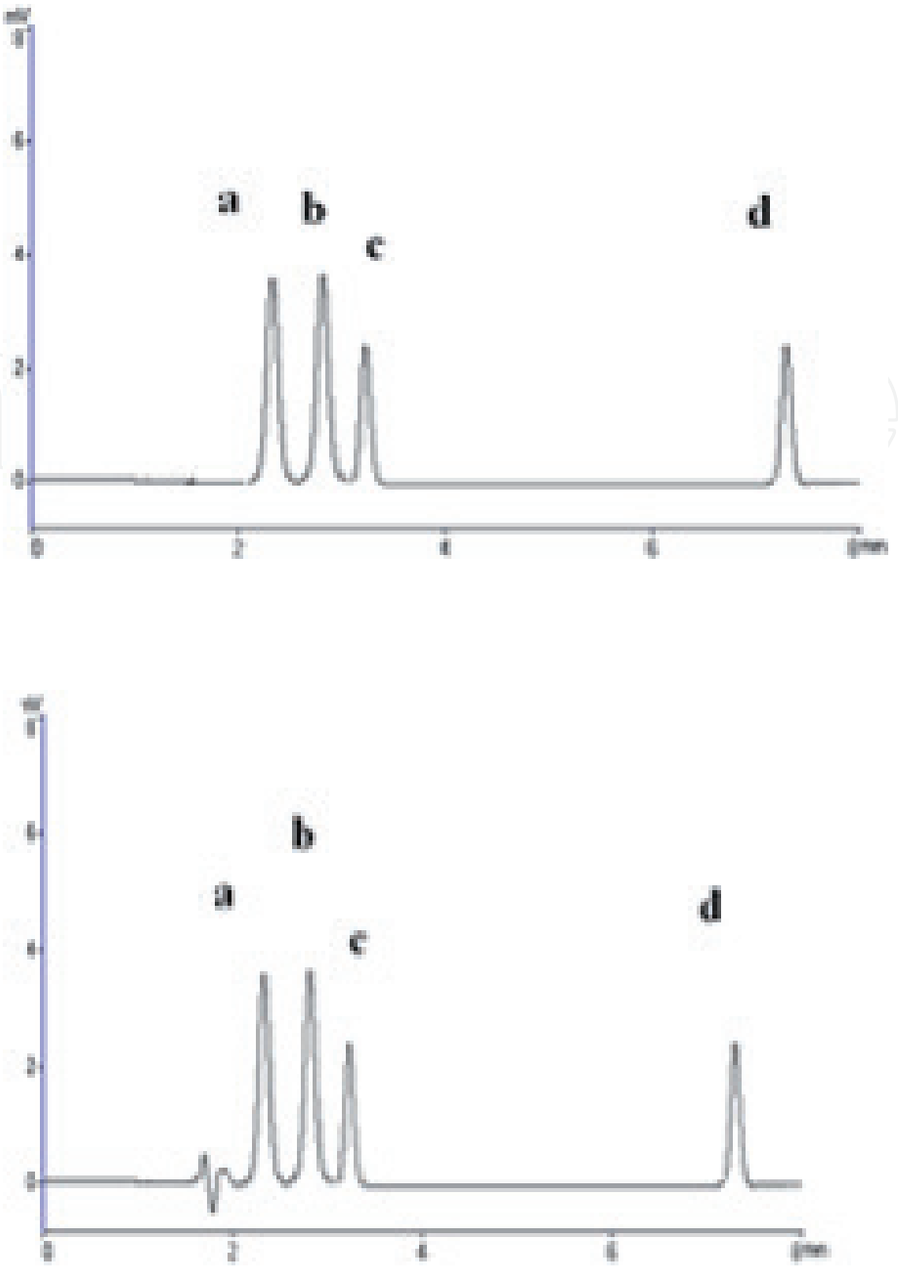


Figure 2.
A representative chromatogram of (a) metformin (b) pioglitazone (c) captopril and (d) glibenclamide in formulation.

3.2.2.3 Precision

Precision was evaluated by carrying out six independent sample preparations of a single lot of formulation. The sample solution was prepared in the same manner as described in sample preparation. Percentage relative standard deviation (%RSD) was found to be less than 2% for within a day and day to day variations, which proves that method is precise (**Table 13**).

3.2.2.4 Sensitivity

The limit of quantitation (LOQ) of the method as signal/noise of CAP, MET, PGL and GLB were found to be 2.3, 1.5, 2.3and 2.3 μgmL^{-1} respectively. Similarly a signal/noise of 3, a LOD of CAP, MET, PGL and GLB were determined to be 0.7, 0.4, 0.7, and 0.7 μgmL^{-1}, respectively.

Analytes	Retention time (T_R) (min)	Capacity factors (K′)	Theoretical plates (N)	Tailing factor (T)	Resolution (R)	Separation factor
CAP	3.3	2.13	3200	1.23	3.4	2.48
MET	2.4	2.25	3250	1.25	3.5	2.36
PGL	2.8	2.36	3250	1.36	3.6	2.59
GLB	7.2	2.36	3246	1.69	3.3	2.56

Table 10.
System suitability parameters.

Drugs	Conc. μgmL^{-1}	Regression equation	r^2	LOD	LOQ
				μgmL^{-1}	
CAP	2.5–100	A = 2501.7x + 3073.7	0.9995	0.7	2.3
MET	2.5–100	A = 3841.3x + 4744.2	0.9998	0.4	1.5
PIO	2.5–100	A = 2419.8x + 2988.8	0.9995	0.7	2.3
GLB	2.5–100	A = 2419.8x + 2988.8	0.9995	0.7	2.3

Table 11.
Regression characteristics.

Analyte	Assay (spiking method)			Assay in serum	
	Conc. μgmL^{-1}	%RSD	% Rec	%RSD	%Rec
CAP	8	0.01	99.98	0.002	102
	10	0.33	100.04	0.02	101
	12	0.36	99.97	0.03	101
MET	8	0.01	100	0.002	101
	10	0	100.02	0.002	101.3
	12	0.3	99.98	0.02	100.3
PGL	8	0.22	99.3	0.03	100.2
	10	0.4	99.98	0.036	100.6
	12	99.73	79.79	0.3	101.3
GLB	8	0.01	99.73	0.06	101.3
	10	0.3	100.24	0.05	101.6
	12	0.5	100.06	0.06	102.0

Table 12.
Accuracy of captopril and antidiabetic drugs.

3.2.2.5 Ruggedness

Ruggedness of this method was evaluated in two different labs with two different instruments. The method did not show any notable deviations in results from acceptable limits.

Drugs	Conc. injected μgmL^{-1}	Inter-day		Intra-day	
		%RSD	%Rec	%RSD	%Rec
CAP	2.5	0.0073	101.11	0.073	101.11
	5	0.0109	102.36	0.009	102.36
	10	0.3261	100	0.361	100.02
	25	0.0009	100	0.09	100.03
	50	0.0005	99.826	0.005	99.26
	100	0.0002	99.998	0.002	99.98
MET	1.25	0.0047	99.997	0.047	99.9
	2.5	0.0071	99.988	0.071	99.88
	5	0.0024	100.12	0.024	100.1
	10	0.0006	99.983	0.006	99.93
	25	0.0006	99.968	0.006	99.98
	50	0.0003	99.991	0	99.91
PGL	1.25	0.0075	98.72	0.007	98.72
	2.5	0.0075	99.98	0.075	99.98
	5	0.0019	99.73	0.019	99.73
	10	0.0012	99.97	0.012	99.87
	25	0.0005	99.97	0.005	99.87
	50	0.0003	100.02	0.003	100.1
GLB	1.25	0.008	100.02	0.08	100.2
	2.5	0.008	99.783	0.008	99.7
	5	0.002	99.983	0.002	99.9
	10	0.001	99.972	0.001	99.9
	25	5.00E-04	99.996	5.00E-04	99.9
	50	3.00E-04	99.997	3.00E-04	99.9

Table 13.
Inter day and intraday precision of captopril and NIDDM drugs.

3.2.2.6 Robustness of method

To evaluate the robustness of the developed RP-HPLC method, small deliberate variations in the optimized method parameters were done. The effect of change in flow rate, pH and mobile phase ratio on the retention time and tailing factor were studied. The method was found to be unaffected by small changes like ±0.1 change in pH, ± 0.1 change in flow rate and ± 1 change in mobile phase.

3.3 Simultaneous determinations of lisinopril, pioglitazone, glibenclamide and glimepiride

There is no method reported for the simultaneous determination of LSP and antidiabetic drugs using HPLC however there are methods for the determination of lisinopril [118, 119], similarly, there are methods reported for the simultaneous analysis of anti-diabetics. An isocratic reversed phase high-performance liquid

chromatographic (RP-HPLC) method has been developed for the simultaneous determination of lisinopril and antidiabetic drugs pioglitazone, glibenclamide and glimepride in bulk, dosage formulations and human serum and used for interaction studies.

3.3.1 Method optimization and chromatographic conditions

To develop a precise, accurate and suitable RP- HPLC method for the simultaneous estimation of LSP with antidiabetic drugs, different mobile phases were tried and the proposed chromatographic conditions were found to be appropriate for the quantitative determination. The short analysis time (<8 min) also enables its application in routine and quality-control analysis of finished products. pH of mobile phase containing methanol: water (80:20),was adjusted to 2.9 with phosphoric acid.The mobile phase was filtered on a 0.45 micron filter and then sonicated for 10 min. The flow rate was set to 1.0 $mLmin^{-1}$. The retention time for LSP was found to be 2.0 minute pioglitazone 2.6 minute, for glibenclamide was 5.3 minute and glimepride 6.1 minute.

3.3.2 Method validation

The developed method was validated by ICH guidelines, it includes system suitability, selectivity, specificity, linearity, accuracy test, precision, robustness, ruggedness, sensitivity, limit of detection and quantification.

3.3.2.1 System suitability

The HPLC system was equilibrated initially with the mobile phase, followed by 6 injections of the same standard to evaluate the system suitability on each day of method validation. Parameters of system suitability are peaks symmetry (symmetry factor), theoretical plates of The column, resolution, mass distribution ratio (capacity factor) and relative retention as summarized in **Table 14**.

3.3.2.2 Linearity

Linearity was studied by preparing standard solutions at different concentration levels. The linearity range for LSP, PGL, GLB and GMP was found to be 2.5–100 μgmL^{-1}. The regression equation for LSP and antidiabetic drugs were given in **Table 15**.

3.3.2.3 Accuracy

The accuracy of the method was evaluated as the percent recovery by estimation of all investigated analytes in presence of various commonly used tablets' excepients at three levels of concentrations that were 80, 100 and 120%. Each sample was injected five times and accuracy was determined in range of 98.45–102.2%. No significant difference observed between amounts added and recovered without serum and with serum (**Table 16**). Thus, used excepients did not interfere with active present in tablets (**Figure 3**).

3.3.2.4 Ruggedness

Ruggedness of the method was calculated in two different labs with two different instruments. The method did not show any notable deviations from acceptable limits.

Analytes	Retention time (T_R) (min)	Capacity factors (K)	Theoretical plates (N)	Tailing factor (T)	Resolution (R)	Separation factor
LSP	2	2.13	3200	1.23	3.4	2.3
PGL	2.6	2.25	3250	1.25	3.2	2
GLB	5.3	2.36	3250	1.23	3.6	2.59
GMP	6.1	2.5	3246	1.25	3.3	2.1

Table 14.
System suitability parameters.

Drugs	Conc. μgmL^{-1}	Regression equations	r^2	LOD	LOQ
				μgmL^{-1}	
LSP	2.5–100	y = 1788.4x + 2214	0.9995	0.53	1.6
PGL	2.5–100	y = 2419.8x + 2988.8	0.9995	0.07	0.23
GLB	2.5–100	y = 17605x + 14118	0.9992	0.09	0.29
GMP	2.5–100	y = 15254x + 21932	0.9992	0.04	0.12

Table 15.
Regression statistics LOD and LOQ.

Analyte	Assay (spiking method)			Assay in serum	
	Conc. μgmL^{-1}	%RSD	% Rec	%RSD	%Rec
LSP	8	0.23	100	36	102
	10	0.326	100.23	54	100.36
	12	0.23	99.9	0.96	100.69
PGL	8	0.28	100	1.2	99.98
	10	0.36	100	1.3	101.3
	12	0.001	100	1.02	101.3
GLB	8	0.96	99.7	1.03	100.2
	10	0.96	99.9	1.05	102.02
	12	0.26	101	1.06	101.3
GMP	8	0.56	99.7	1.02	101.3
	10	0.32	100.2	0.69	100.69
	12	0.69	100.2	0.96	102.03

Table 16.
Accuracy of LSP and NIDDM drugs.

3.3.2.5 Precision

Precision was evaluated by carrying out six independent sample preparation of a single lot of formulation. The sample solution was prepared in the same manner as described earlier. Relative standard deviation was found to be less than 2% for within a day and day to day variations, which proves that method is precise (**Table 17**).

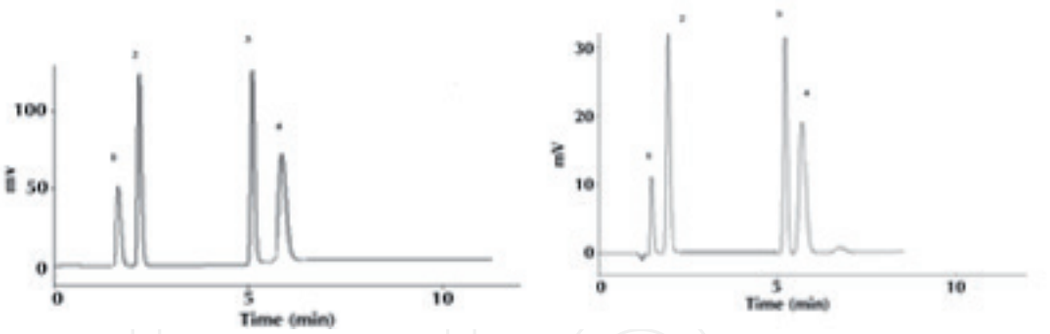


Figure 3.
A representative chromatogram of (1) lisinopril (2) pioglitazone (3) glibenclamide and (4) glimepride in formulation and serum.

Drugs	Conc. injected	Inter-day		Intra-day	
	μgmL^{-1}	%RSD	%Rec	%RSD	%Rec
LSP	2.5	0.3	100.9	1.3	100.8
	5	0.36	101.1	1.3	101
	10	0.6	99.49	1.6	100.4
	25	0.9	101.2	0.6	101.2
	50	0.6	99.32	1.5	100
	100	0.26	100.2	1.08	100
PGL	2.5	1.3	100.9	1.03	99.9
	5	1.3	101.1	1.02	100.2
	10	1.2	100.9	1.32	100.2
	25	0.3	100.5	1.02	101.2
	50	0.65	99.45	0.3	98.9
	100	0.36	100.6	0.96	101.2
GLB	2.5	1.3	100.0	1.02	100
	5	1.2	101.0	0.63	100
	10	1.0.	101.0	1.03	100
	25	1.02	100.0	1.02	100
	50	1.23	99.1	1.023	100
	100	1.23	99.6	1.03	99.6
GMP	2.5	1.6	98.85	1.02	100.2
	5	0.3	99.5	1.03	100.02
	10	1.0	100.5	0.36	100.55
	25	0.02	101.1	0.36	100.23
	50	10.2	98.1	0.23	100.3
	100	1.02	99.5	0.65	99.89

Table 17.
Inter day and intraday precision of LSP and N1DDMdrugs.

3.3.2.6 Sensitivity

Limits of quantitation of the method as signal/noise of 10, for lisinopril, pioglitazone, glibenclamide and glimepride were found to be 1.6, 0.23, 0.29 and 0.12 μgmL^{-1}respectively. Similarly a signal/noise of 3, LOD of lisinopril, pioglitazone glibenclamide and glimepiride were determined to be 0.53, 0.07, 0.09 and 0.04 μgmL^{-1}.

3.3.2.7 Robustness of method

To evaluate the robustness of the developed RP-HPLC method, small deliberate variations in the optimized method parameters were done. The effect of change in flow rate, pH and mobile phase ratio on the retention time and tailing factor were studied. The method was found to be unaffected by small changes like ±0.1 change in pH, ± 0.1 change in flow rate and ± 1 change in mobile phase.

3.4 Interaction of ACE inhibitors with antidiabetic drugs

Hypertension in diabetics represents an important health problem as the combination of these diseases is common, carries significant morbidity and mortality and is frequently difficult to treat. The prevalence of hypertension in diabetic people is probably 1.5–2 times higher than in the general population [118]. Reduction of cardiovascular risk is therefore a high priority in the management of diabetes. Micro albuminuria is an important predictor of cardiovascular events and forms one of the components of insulin resistance/metabolic syndrome, which confers a particularly high risk of cardiovascular death [119]. Diverse classes of antihypertensive prescription may be used for blood pressure manage in diabetes among these angiotensin-II type 1 receptor blockers (ARBs), calcium channel blockers, thiazide diuretics and ACE inhibitors are common [120]. Cheung demonstrated that the calcium antagonists have been extensively used in hypertensive patients with diabetes [121]. Use of Verapamil a calcium channel blocker significantly reduced the risk of developing diabetes [122]. Similarly diabetic patients often take anti-hypertensive medications and coadministered with antidiabetic drugs [123]. Treatment of patients with hypertension and diabetes with ARBs improved both macrovascular and microvascular alterations [124].

Diverse classes of antihypertensive prescription may be used for blood pressure manage in diabetes among these calcium channel blockers, angiotensin-II type 1 receptor blockers (ARBs), thiazide diuretics and ACE inhibitors are common. Cheung demonstrated that calcium antagonists have been extensively used in hypertensive patients with diabetes. Collective pharmacological treatment generally entails in management of type 2 diabetes mellitus to attain satisfactory glucose manage and dealing of concomitant pathologies, drug–drug interactions must be cautiously considered with antihyperglycaemic drugs [125]. Mitra [126] conducted a study to examine the interaction of diabecon (D-400), a herbomineral anti-diabetic the most important purpose of this cram was to assess the "*in vitro*" drug interaction of enalapril, captopril and lisinopril with commonly prescribed antidiabetic drugs (metformin, pioglitazone glimepride and glibenclamide) by utilizing HPLC.

3.4.1 Interaction of enalapril with antidiabetic drugs by HPLC

In vitro interactions of enalapril in the presence of antidiabetic drugs (metformin, glibenclamide and glimepride) were carried out in 1:1 at 37°C and method for simultaneous determination of both interacting drugs was also developed as described in former sections. Results of these interactions are summarized in **Table 18** and plotted in **Figure 4**. The % availability of enalapril and metformin was found to be between 98 and 106% indicating no reaction between drugs. These results clearly indicated that enalapril could be safely co administered with metformin. The two drugs did not inhibit or disturb the absorption of each other. Similar behavior was observed with glibenclamide and glimepride, the availability of enalapril was found to be between 102 and 103% with glibenclamide and

Time	ENP	MET	ENP	GLB	ENP	GMP
0	99.89	100.01	100.34	100.34	102	99.99
30	99.65	99.02	99.54	99.54	101.3	100
60	100.23	95.31	98.12	98.99	102.3	101
90	101.61	105.56	99.69	99.69	102.3	102.3
120	100.2	98.3	98.46	98.46	101.2	102
150	101.98	98.88	100.3	100.63	102.3	103
180	106.46	99.99	100.36	100.36	102.3	104.3

Table 18.
% availability of enalapril and antidiabetic drugs by HPLC.

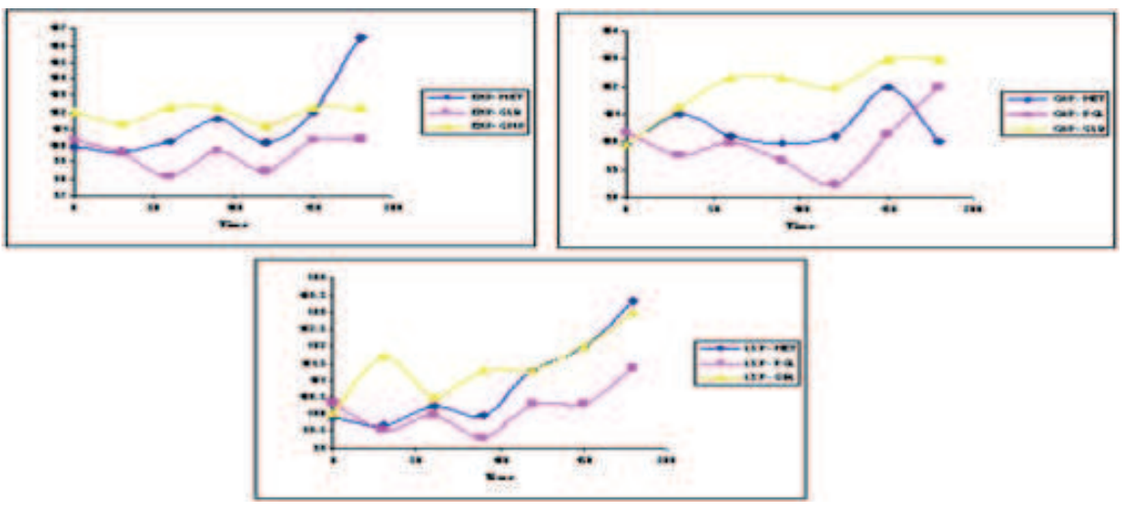


Figure 4.
% Availability of a inhibitors and antidiabetic drugs by HPLC.

glimepride and the availability of glibenclamide and glimepride remained almost unchanged. No remarkable change in area under curve and drift in retention time were observed. However, the results showed that no interaction occurred as there % recovery remained almost unchanged.

3.4.2 Interaction of captopril with antidiabetic drugs by HPLC

In this study drugs were analyzed by measuring the area under curve (AUC), % recovery and considerable drift in retention time. Captopril and metformin did not affect the availabilities of each other i.e. 101% and 103% was observed respectively up to 30 minutes and at the end of experiment both were available up to 100% and 105% respectively. Similar effect was observed in presence of pioglitazone i.e. 102% of captopril, while 104% of pioglitazone was available at the end. In presence of glibenclamide, the %availability of captopril and glibenclamide were 102 and 101% at 30 minutes, which gradually increased and after 180 min were found to be103 and 106% respectively. Interacting results shows that no remarkable drifts in the availabilities and no drift in retention time were observed (**Table 19**). However the results showed that no interaction occurred as there was no significant change in % availabilities of both drugs were observed by HPLC.

(mins)	CAP	MET	CAP	PGL	CAP	GLB
0	99.89	100.01	100.34	100.34	99.9	99
30	101	103	99.54	99.54	101.3	101
60	100.23	103.3	99.98	99.6	102.3	102.3
90	99.98	103.2	99.3	99.69	102.3	102.6
120	100.2	104	98.46	99.96	102	102
150	101.98	104.3	100.3	100.3	103.02	104.02
180	100.03	105.3	102	104	103	106.03

Table 19.
% availability of captopril and antidiabetic drugs by HPLC.

mins	LSP	MET	LSP	PGL	LSP	GLB
0	99.89	100.01	100.34	100.34	100	99.2
30	99.65	100.3	99.54	100.3	101.7	101.3
60	100.23	100.8	99.98	100.6	100.5	101.3
90	99.98	101.3	99.3	100.9	101.3	101.02
120	101.3	102.5	100.3	101.3	101.3	101
150	101.98	103.6	100.3	102.3	102.01	102.5
180	103.33	104.0	101.36	102.3	103	103.2

Table 20.
% Availability of lisinopril and antidiabetic drugs by HPLC.

3.4.3 Interaction of lisinopril with antidiabetic drugs by HPLC

In this study drugs were analyzed by measuring the area under curve (AUC), % recovery and considerable drift in retention time. Presence of metformin, pioglitazone and glibenclamide could also not assert any significant change in availability of lisinopril at 37°C. Availability of lisinopril with metformin was 103.33 at the end of experiment and that of metformin was 104.33%. In presence of pioglitazone and glibenclamide 100.3 and 102% of drug was available at the end of experiment and the availability of pioglitazone and glibenclamide were also not affected in presence of lisinopril. The obtained results showed that the NIDDMs and lisinopril do not affect *in-vitro* availability of each other at 37°C (**Table 20**).

4. Conclusions

The method described is simple, universal, convenient and reproducible simultaneous method that can be used to determine and quantify ACE inhibitors and antidiabetic drugs. Reliability, rapidness, simplicity, sensitivity, economical nature, good recovery and precision of this method give it an advantage over the other reported HPLC methods for the determination of ACE inhibitors and antidiabetic drugs. In summary, the proposed method can be used for drug analysis in routine quality control. In addition, this method has wide application in clinical research and pharmacokinetics drug interactions.

Conflict of interest

The authors declare no conflict of interest.

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Author details

Safila Naveed* and Halima Sadia
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan

*Address all correspondence to: safila117@gmail.com

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