CHAPTER 2

REVIEW OF LITERATURE

2.1 AMLODIPINE BESYLATE

Calcium ions are required to generate electrical activity for the contraction of cardiac and smooth muscle and conduction of nerve cell. Calcium antagonist is a drug that inhibits the entry of excess calcium into cells and prevents the mobilization of calcium from intracellular stores, resulting in relaxation of blood vessel walls and cardiac muscle for blood to flow more freely. This causes lowering of blood pressure thereby reducing oxygen demand in the heart and relieving angina pain.

Amlodipine besylate, 3-ethyl 5-methyl (4RS)-2-(2-aminoethoxy) methyl)-4-(2-chlorophenyl)-6-methyl-1, 4-dihydropyridine- 3, 5-dicarboxylate benzene sulphonate is a relatively new potent long-acting calcium channel blocking agent [54–56]. Amlodipine is a third-generation dihydropyridine calcium antagonist which is used alone or in combination with other medications for treating high blood pressure, certain types of vasospastic angina, hypertension, cardiac arrhythmias, and coronary heart failure [57–59]. It is more effective than β-blockers for the variant angina because it selectively inhibits the arterial vascular smooth muscle cell proliferation resulting in prevention of the progressive narrowing of the arteries and prevents the coronary spasms resulting in increased blood flow with myocardial oxygen supply [60–62].

Amlodipine besylate is available in the market as bulk material, tablets, capsules and compounded capsules, hence, owing to its therapeutic importance it is important to have a rapid and simple analytical technique for the determination of Amlodipine in pharmaceutical preparations and human body fluids. Various methods including HPLC [63, 64], liquid chromatography (LC) [65], high-performance thin layer chromatography [66],
gas chromatography (GC) [67], capillary electrophoresis [68], flow injection analysis [69], enzyme-linked immunosorbent assay [70], spectrofluorometric [71] and spectrophotometric methods [72, 73] have been used for the determination of Amlodipine Besylate in biofluids and pharmaceutical preparations. Recently, in order to obtain an effective separation and sensitive detection some coupled methods such as liquid chromatography coupled with tandem mass spectrometry [74, 75] and solid-phase extraction with cation-exchange column [76] have also been used to monitor the Amlodipine Besylate concentration. Voltammetric determination of Amlodipine on electrodes such as carbon paste [77], glassy carbon electrode [78–80] and multi walled carbon nanotubes [81] have also been reported in pharmaceuticals and human urine.

### 2.2 HYDROCHLOROTHIAZIDE

Hydrochlorothiazide (6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine- 7-sulfonamide 1,1-dioxide) is a diuretic, representative of the benzothiadiazine class sulfonamide derivatives, commonly known as thiazide [82]. Its action is to deplete the body’s sodium stores. It also reduces the levels of chloride, bicarbonate, phosphate and magnesium. The drug also reduces the loss of calcium. The drug inhibits cell’s reabsorption of NaCl. Thiazides are organic anions and bind to the site of the Cl⁻ on the sodium chloride transporter molecule preventing it from picking up NaCl. The depletion of NaCl stores in the body reduces blood pressure and cardiac output. After a few weeks, cardiac output returns to a normal level. Distal calcium reabsorption is also increased [83, 84]. It was often used in combination with other antihypertensive drugs such as beta blockers, Angiotensin-Converting Enzyme (ACE) inhibitors, or more recently, Angiotensin II Receptor Blockers (ARBs) [85–90].

Numerous publications described the determination of hydrochlorothiazide concentration in plasma or urine by HPLC with ultraviolet or electrochemical detection [91–99]. Several chromatographic methods have been reported for the analysis of Hydrochlorothiazide in human
plasma individually or in combination, such methods have included: HPLC coupled with UV [100–102] or diode array [103, 104], electrochemical detection [105], LC–MS [106, 107] or with tandem LC–MS/MS [108–112].

2.3 IRBESARTAN

Irbesartan, an ARB and is widely used for the treatment of hypertension and heart failure in clinical patients. Angiotensin II is an octapeptide regarded as the main effector of AT1 receptor in renin–angiotensin system. It causes vasoconstriction, tachycardia and an increase of aldosterone secretion from the adrenal cortex and retention of sodium and body fluid [113]. These compounds are the key factors in raising blood pressure. Irbesartan is a selective non-peptidic angiotensin AT1 receptor antagonist associated with a lower incidence of side effects than other classes of antihypertensive drugs. Irbesartan also demonstrated superior antihypertensive efficacy versus Losartan and Valsartan [114]. ARBs have been the choice of drugs in diabetic nephropathy by World Health Organization (WHO)/International Society of Hypertension (ISH) guidelines [115].

Several analytical methods have been developed for the determination of Irbesartan including LC [116–128], capillary electrophoresis (CE) [129–132] and spectrophotometry [133–135]. LC is the major method for measurement of Irbesartan in human plasma and urine. It is combined with ultraviolet (UV) detector [116, 117], diode array detector (DAD) [118–120], fluorescence (Flu) detector [121–125], electrospray ionization mass spectrometric detection [126], tandem quadruple mass spectrometer [127] and with time of flight analyzer [128]. In the CE technique, all the relative references apply in pharmaceutical formulation, except Zhang et al. used polymer monolith microextraction as a clean-up procedure and capillary zone electrophoresis to analyze Irbesartan and three other sartans in urine [129]. The reported spectrophotometric methods were using pharmaceutical preparations.
2.4 LOSARTAN

Losartan, 2-butyl-4-chloro-1-[[2’-(1H-tetrazol-5-yl)[1,1’biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol, is the first orally available angiotensin II-receptor used as an antihypertensive agent. Losartan and its active metabolite block the vasoconstrictor and aldosterone secreting effects of angiotensin II by type AT1 receptor blockage. Following oral administration, Losartan is rapidly absorbed, reaching maximum concentrations 1–2 h post administration. The active metabolite, Losartan acid, is 10–40 times more potent by weight than Losartan [136–138].

Numerous analytical methods for determination of Losartan in human plasma based on ultraviolet or fluorescence detection are reported for extraction and determination of Losartan in biological matrices [139–142]. The estimation of Losartan along with active metabolite in human plasma was quantified using LC-MS was also reported [143].

2.5 MANIDIPINE DIHYDROCHLORIDE

Manidipine, 1,4-dihydro-2,6-(dimethyl-4-(3-nitrophenyl)-3,5-pyridine dicarboxylic acid 2-[4-(diphenylmethyl)-1-piperazinyl] ethyl methyl ester, is a second generation calcium antagonist with peculiar and favourable characteristics like the ability in increasing hematic renal flow and giving rise to a remarkable sodium excretion without modifying glomerular filtrate [144-146]. On the other hand, its depressive effect on heart is less marked compared to analogous drugs [147]. Manidipine in human plasma was reported to have been quantitatively determined by chromatographic techniques [148-150]. Manidipine was quantitatively analysed from the API by visible spectrophotometric methods [151]. The simultaneous quantitative estimation of Manidipine and its main photo degradation by-product have been optimized by using multivariate calibration on UV spectra based on a classical least squares regression [152].
2.6 RAMIPRIL

Ramipril, 2-[N-((S)-1-ethoxy carbonyl-3-phenyl propyl)-lalanyl]-(1S, 3S, 5S)-2-azabicyclo [3,3,0]-octane-3-carboxylic acid is a prodrug [153] which is rapidly hydrolyzed with the cleavage of an ester group through hepatic metabolism in human body forming an active metabolite, i.e., Ramiprilat. The spectrophotometric methods have been reported for the assessment of drug content in commercial dosage forms, which are based on the formation of ternary complex of the drug with Cu (II)–eosin [154] and Fe (III)–ammonium thiocyanate [155].

More recently a spectrofluorimetric assessment of Ramipril was made with optical sensor doped in sol-gel matrix [156]. The drug content in pharmaceutical formulations has been determined spectrophotometrically in visible region based on the charge transfer reaction of Ramipril with π acceptors such as 7,7,8,8–tetra cyano quinodimethane and p-chloranilic acid then subsequently measuring the absorbance at 840 and 520 nm, respectively [157]. The quantitation of Ramipril has been done by spectrophotometric and fluorimetric techniques using the reaction of the drug with 7-fluoro-4-nitrobenzo-2-oxo-1,3-diazole which exhibits maximum absorbance at 460 nm, and maximum fluorescence intensity at 530nm after excitation at 465nm [158].

A spectrophotometric kinetic method based on the reaction of the carboxylic acid group of the drug with a mixture of potassium iodate (KIO₃) and potassium iodide (KI) in aqueous medium has been reported [159]. A spectrophotometric and spectrofluorimetric method for determination of Ramipril based on the oxidation of the drug with 1-chlorobenzotriazole reagent (CBT) in strong alkaline medium is followed by measuring the absorbance at 350nm has been reported [160]. The concentration of Ramipril in human plasma and pharmaceutical formulations were measured by Gas Chromatography–Mass Spectrometric (GC–MS) [161, 162], HPLC [163, 164], voltammetric [165], radioimmunoassy [166], potentiometry [167, 168] and flow-injection analysis [169].
2.7 TELMISARTAN

Telmisartan, 4 - [(2-n-propyl-4-methyl-6- (1-methyl benz imidazole-2-yl)-benz imidazole-1-yl) methyl] –biphenyl -2-carboxylic acid, is a selective angiotensin II type 1 receptor (AT1R) blocker, which belongs to the group of angiotensin II receptor antagonists [170]. It inhibits the angiotensin II receptor in a way that the effect of angiotensin II is blocked resulting in a decrease of blood pressure [171]. There are different mechanisms: increasing the activity of the sympathetic nervous system, causing a boosted sodium revertive resorption in the kidneys and promotion of the secretion of aldosterone in the adrenal glands [172–175].

The most recent clinical trials [176] demonstrated that Telmisartan also has preventive roles against ischemic heart diseases in diabetic patients with a similar potency to angiotensin converting enzyme inhibitor. Several studies recently suggest that the effects of Telmisartan are mediated via not only blockade of AT1R but also activation of peroxisome proliferators-activated receptor [177, 178]. A variety of methods have been developed for determination of Telmisartan in biological samples including immunoassay [179], linear sweep polarography [180], HPLC with fluorimetric detection [181–187] and HPLC coupled with mass spectrometric detection (HPLC–MS/MS) [188–191].

2.8 TRANDOLAPRIL

Trandolapril is a long acting, highly lipophilic non-peptide, angiotensin converting enzyme inhibitor with a carboxyl group but without sulphhydryl group [192]. It is used for the management of hypertension and for the stable patients who have evidence of left ventricular systolic dysfunction or symptoms of heart failure within the first 2 days after acute myocardial infarction [193,194].

In the literature there are limited reported methods referring to the determination of Trandolapril in biological fluid, restricted in pharmaceutical preparation [192], comparative lipophilicity studies of Trandolapril and other angiotensin converting enzyme inhibitors [193], a study [195] in investigation
on the stereochemical purity of Trandolapril and octahydro-lH-indole-2-carboxylic acid by HPLC method [196] and in studies including pharmacokinetic and pharmacodynamic investigations [197–201]. A reversed-phase HPLC method with UV detection has been reported for the determination of Trandolapril in capsules [202]. A liquid chromatographic tandem mass spectrophotometric determination of Trandolapril in human plasma has also been reported [203].

2.9 VALSARTAN

The chemical formula of Valsartan is N-(1-oxopentyl)-N-[[2-(1H-tetrazol-5-yl) [1,1-biphenyl]-4-yl]methyl]-l-valine. Valsartan is a potent, highly selective, and orally active antagonist at the angiotensin II AT1-receptor that is used for the treatment of hypertension. Very few methods appeared in the literature for the determination of Valsartan individually based on HPLC [204–206].

Sampath et al. [207] described identification and characterization of potential impurities of Valsartan AT1 receptor antagonist. There has been some estimation of assays of analyte in human plasma including the use of liquid chromatography [208–212] and some combination with other drugs using high pressure liquid chromatography and derivative spectroscopy [213–218].

2.10 VERAPAMIL

Verapamil is a calcium blocker with a widespread use in management of supraventricular tachyarrhythmias, angina pectoris, hypertrophic cardio myopathy and hypertension [219]. Verapamil is metabolized mainly in human liver to six metabolites, which are excreted through the kidneys. Only norverapamil, the N-demethylated metabolite, is pharmacologically active [220]. Many investigations have been performed for determination of Verapamil in human plasma using HPLC with various detection systems. Some of them employ fluorescence detection [221–228], very few employ spectrophotometric detection in the UV range [229, 230], whereas mass spectrometric detection is used in the recent developed methods [231–235].