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Review Article

ASSESSMENT OF CHROMATOGRAPHIC SEPARATIONS FOR ANTIHYPERTENSIVE AND ANTIDIABETIC DRUGS

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ABSTRACT

Context: The focus of this review is to compile the different chromatographic methods that were reported earlier for the analysis of different antihypertensive and antidiabetic drugs.

Objective: The magnitude of chemical entities investigated and entering into the medicinal field for various health-related ailments is escalating year after year. The drugs are either innovative entities or fractional structural variation of the preexisting chemical molecule. These drugs may exhibit unexpected toxicities after Phase IV of clinical trials, resulting in their withdrawal from the market. Under these circumstances, analytical measures for these drugs may not be accessible in the pharmacopeias. The main aim of this work is to compile the different analytical techniques for the quantification of various antihypertensive drugs and antidiabetic drugs.

Methods: The present work is to thoroughly study the literature for the application of different analytical techniques such as high-performance liquid chromatography (HPLC) and liquid chromatography-mass spectroscopy/tandem mass spectroscopy (LC-MS/MS) for the quantification of antihypertensive drugs and anti-diabetic drugs.

Results: The present study attempts to collate various analytical techniques that were developed and validated for the estimation of few important antidiabetic and antihypertensive drugs either in pure, individually or combined with other pharmaceutical dosage form by HPLC, LC-MS/MS, and high-performance thin-layer chromatography techniques.

Conclusion: Different chromatographic methods are considered to be rapid tools for qualitative and quantitative analysis of newer chemical entities in pharmaceuticals. The amount of these newer chemical entities which are reaching the pharmaceutical market is increasing day by day nevertheless there exists a lag in establishing the standard protocols for the identification, impurity profiling, related substance and assay method. Hence, the present review compiles the different analytical methods that were reported in the literature and thus helps the researchers and chemists to make use of the analytical techniques for the quantification and validation of various antidiabetic and antihypertensive drugs.

Keywords: Liquid chromatography, High-performance liquid chromatography, Antihypertensive, Antidiabetic, Oral hypoglycemics, Liquid chromatography-mass spectroscopy/tandem mass spectroscopy.

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INTRODUCTION

Nowadays, hypertension is prevalently seen among individuals across the world and is an important modifiable risk factor for various cardiovascular ailments. It ultimately affects the functioning of the heart, kidney, and brain. Antihypertensive drugs comprise vasodilators, diuretics, angiotensin receptor blockers, and sympathoplegic agents [1]. Vasodilators reduce the tension in the vascular muscle; a diuretic depletes the levels of sodium and lessens the volume of blood; angiotensin receptor blockers hinder the angiotensin-converting enzyme; and sympathoplegic agents taper off the cardiac output [2].

Elevated levels of glucose in blood and fluctuations in the levels of insulin production by the pancreas provoke the disease called diabetes mellitus. Other than insulins, oral hypoglycemics such as antidiabetic drugs comprise thiazolidinediones, biguanides, incretin-based drugs, sulfonylureas, alpha-glucosidase inhibitors, glitinides and amylin analog. All these drugs help to regulate the amount of insulin in the blood [3].

The important objective of this study is to collate the different bioanalytical techniques that are available for various drugs in the class of antihypertensives and antidiabetics. Accordingly, a thorough literature search from the PUBMED (NCBI) database using appropriate keywords was performed. Table 1 summarizes the salient features of different antihypertensive and antidiabetic drugs. The present review compiles the reported bioanalytical methods with more emphasis for approved drugs such as pioglitazone, metformin, glipizide, amlodipine, nifedipine, valsartan, and captopril.

Hence, the present manuscript is based on the various analytical method developments and validation carried out for antihypertensive and antidiabetic drugs. In this review, a detailed study on the assay, impurity profiling, and stability indication assay, bio-analytical methods that were carried out by various chromatographic methods are discussed for hypertension and diabetes drugs in their pure form, individually or in combined pharmaceutical dosage form.

Analysis involving liquid chromatography-mass spectroscopy/tandem mass spectroscopy (LC-MS/MS)

Pioglitazone and its metabolic products (III and IV) were analyzed in the plasma using LC–MS/MS involving electrospray tandem mass spectrometer system. The drug was extracted from plasma using liquid-liquid extraction (LLE) with methyl t-butyl ether:n-butyl chloride

Table 1: Salient features of some antihypertensive and antidiabetic drugs

Parameters	Antidiabetic drugs				Antihypertensive drugs			
	Pioglitazone	Glipizide	Metformin	Tolbutamide	Nifedipine	Amlodipine	Valsartan	Captopril
Molecular formula	$C_{19}H_{20}N_2O_3S$	$C_{21}H_{27}N_5O_4S$	$C_4H_{11}N_5$	$C_{12}H_{18}N_2O_3S$	$C_{17}H_{18}N_2O_6$	$C_{20}H_{25}ClN_2O_5$	$C_{24}H_{29}N_5O_3$	$C_9H_{15}NO_3S$
Molecular weight	356.439	445.535	129.1636	270.347	346.335	408.879	435.5188	217.285
CAS number	111025-46-8	29094-61-9	657-24-9	64-77-7	21829-25-4	88150-42-9	137862-53-4	62571-86-2
pKa	5.19	5.9	12.4	5.16	2.60	19.12	3.9	3.7, 9.8
LogP	2.3	1.91	-0.5	2.34	2.2	3	1.499	0.34
Trade name	Actos	Glucotrol	Fortamet	Orinase	Procardia	Norvasc	Olmesartan	CAPOTEN
Therapeutic dose	15–30 mg PO	5 mg orally	2500 mg daily	1–2 g daily	30–60 mg	10 mg/day	80–320 mg/day	25 mg t.i.d
Route of drug administration	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral
Time to peak concentration	2 h	1–3 h	4 and 8 h	≤3–5 h	1.2±0.1 h	6 and 12 h	2–4 weeks	60–90 min
Half-life	3–7	2–5 h	6.2 h	7 h	2 h	30–50 h	2.1 h	2 h
Protein binding	>99%	98–99%	Negligible	95%	92–98%	98%	94–97%	25–30%
Majorly metabolized by	CYP1A1	CYP2C9	Not metabolized	CYP2C9	CYP3A4	Cytochrome P450 3A4	CYP2C9	-
Route of elimination	Feces	Urine	Urine	Urine and feces	Urine	Urine	Feces and urine	Urine
Oral bioavailability	83%	100%	50–60%	100%	100%	64–90%	23%	70–75%

1:1 (v/v). The calibration range was found to be 0.5–2000 ng/mL [4]. Pioglitazone and candesartan were extracted from 0.1 mL human plasma by SP extraction with reversed phase column (C_{18} column), and organic phase consists of 20:80 (v/v) formic acid (0.1%) and acetonitrile [5]. Tolbutamide and its related substances were studied in rat plasma by sim in positive mode using C_{18} (Zorbax) column using 0.1% formic acid along with acetonitrile used as eluant. Extraction was achieved by liquid-liquid scheme using ethyl acetate [6]. The separation of drugs such as sitagliptin and metformin in human plasma was studied using SCX column involving biochemical partition using acetonitrile (ACN) (50):50% of ammonium acetate buffer (20 mM) as mobile phase, and pH was maintained at acidic condition during the course of analysis [7].

LC-MS study was carried out using human plasma for the determination of metformin, atorvastatin, and glimepiride [8]. The extraction was done with protein precipitation with acetonitrile. Pharmacokinetic parameters were investigated in nifedipine, montelukast, and gliclazide, and they were analyzed using SB-C_{18} with formic acid (0.1%) 84:16 acetonitrile as mobile phase [9]. Analysis of sacubitril and valsartan in rat plasma was carried out using liquid chromatography, and further, the eluent was subjected for ionization by ESI in positive mode. The study was carried out using Hypersil GOLD C_{18} column, with acetonitrile and formic acid (0.1%) as mobile phase. Before the analysis, the drugs were extracted using deproteinization [10]. Extraction of metformin, ramipril, and glimepiride from the plasma was performed by LLE using 50% butanol and 50% n-hexane, and further, separation was achieved by organic phase containing 90% of methanol and 10% of formic acid (0.1%) in aqueous medium by ultra-performance liquid chromatography (UPLC) partition using C_{18} column. The eluent was further studied with multireaction monitoring tandem quadrupole mass spectrometer [11]. Hypersil GOLD C_{18} (50 mm 3.0 mm, 5 µm) column using 15% of ammonium formate (5.0 mM) and 85% of acetonitrile as eluent in acidic conditions (pH 4.5) was employed for the resolution of hydrochlorothiazide and lisinopril [12].

Antihypertensive (β-blockers) and broncho agonist in plasma and urine were extracted using determined using solid phase microextraction method, and later, they were analyzed using pentafluorophenyl stationary phase and the mobile phase comprised of acetonitrile and water [13]. Telmisartan and pioglitazone were estimated using C_{18} (50 mm 4.6 mm 5 µm) column with methanol-ammonium formate (10 mM) mixture (9:1, v/v) as eluent [14]. Healthy Chinese subjects were used for the estimation of amlodipine in human plasma [15]. Glimepiride and atorvastatin are estimated in human plasma by LCMS/MS. Extraction was performed by liquid-liquid method. The US FDA guidelines were followed for the method development and validation [16].

Analysis using high-performance liquid chromatography (HPLC)

Telmisartan and pioglitazone were simultaneously separated using ODS-3v column with 65% of ammonium dihydrogen phosphate buffer (pH 4.5) and 35% of acetonitrile as mobile phase and the retention times were found to be 2.38 min (telmisartan) and 3.16 min (pioglitazone), respectively [17]. Glimepiride, vildagliptin, and pioglitazone hydrochloride were estimated using HPLC coupled to UV detector, where the separation was achieved using Hypersil GOLD C_{18} reverse phase column with 45% of acetonitrile and 55% of 0.05 M potassium dihydrogen phosphate buffer as eluent, and the retention times were found to be vildagliptin (1.27 min), pioglitazone hydrochloride (2.71 min), and glimepiride (8.87 min) respectively [18]. In another study, the separation of pioglitazone hydrochloride and glimepiride analytes was done by HPLC using reversed phase C_{18} (ODS) column with mobile phase potassium dihydrogen phosphate buffer (pH 3.4) and acetonitrile (40:60 v/v) and the retention times were found to be 4.5±0.1 min (pioglitazone) and 10.0±0.1 min (glimepiride) [19]. In binary combination of carvedilol, glimepiride, or glibenclamide, the separation was achieved chromatographically using XDB-C_{18} reversed phased column using 30% of 0.2 M phosphate buffer (pH 3.5) and 70% of methanol as eluent using RRHT method [20].

Chromatographic separation and validation of the combined tablet containing atorvastatin, metformin, and glimepiride reported using BEH C_{18} column, and eluent consists of 600 mL of acetonitrile (60%) and phosphate buffer (pH 3) 400 mL (40%) [21]. UPLC with PDA detector was used for the development of method and validation for metformin and telmisartan in pure solid dosage form using column C_{18} (150 × 4.6 ID) 5 µm, with sodium dihydrogen phosphate buffer (NaH_2PO_4):acetonitrile (60:40v/v) as mobile phase [22]. In another study, metformin hydrochloride, ramipril, and glimepiride were separated using mobile phase of 0.02 M KH_2PO_4 buffer and methanol (150:850) using Hypersil BDS C_{18} column [23].

The estimation of nifedipine, nateglinide, and lovastatin was achieved simultaneously by Millennium C_{18} column and 40% of 10 mM phosphate buffer (pH 3.5) and 60% acetonitrile as eluent [24]. Estimation of antihypertensive and antidiabetic drugs using RP-HPLC separation was achieved by organic and aqueous phase (60:40, v/v) [25]. Degradation studies of valsartan were performed using isocratic HPLC method with C_{18} reverse stationary phase, with 70% methanol and 30% water (pH 7.2) as mobile phase was used in acid hydrolysis stability-indicating assay [26]. Analysis of glibenclamide, metformin, captopril, and pioglitazone in API was reported with 70% methanol and 30% water using Hypersil ODS C_{18} column [27]. Glibenclamide, amlodipine, atorvastatin, and metformin in human plasma were separated and validated by HPLC-UV method [28]. Antidiabetic and antihypertensive drugs were studied for stability indicating assay using RP HPLC method; the separation was achieved isocratically on a C_{18} column [29]. In a similar study, the combination of metformin and telmisartan was analyzed and validated by RP-HPLC method in bulk and in formulations [30].

The estimation of metformin hydrochloride, glimepiride, and atorvastatin calcium was carried out simultaneously in bulk and combined dosage form by stability indicating RP-HPLC technique [31]. Telmisartan and metformin hydrochloride were estimated by RP-HPLC method in bulk and synthetic mixture [32]. The interaction of nifedipine and metformin in hypertension with type II diabetic patients was studied using ODS Hypersil column C_{18}, using acetonitrile, 25 mM KH_2PO_4, and methanol as eluents [33].

Pioglitazone and telmisartan in a formulation were estimated by RP-HPLC technique using 35% of 0.5% triethylamine and 65% of acetonitrile [34]. High-performance thin-layer chromatography (HPTLC) technique was used for the estimation of metformin, glimepiride, and atorvastatin in fixed dosage combination using water:methanol:ammonium sulfate as mobile phase [35]. In a similar study, the determination of antidiabetic and antihypertensive drugs in pharmaceutical formulations was analyzed by RP-LC with Lichrocart C_{18} as a stationary phase and methanol:water:orthophosphoric acid (75:25:0.2) as mobile phase [36]. Simultaneous estimation of atorvastatin, metformin, and glimepride in the formulation was carried out by RP HPLC technique, and the separation was achieved by Hibar C_{18} as stationary phase using 40% of ACN and 60% ammonium acetate (10 mM, pH 3.0, adjusted using acetic acid) as eluent, respectively [37].

CONCLUSION

Chromatographic methods are considered to be rapid tools for qualitative and quantitative analysis of newer chemical entities in pharmaceuticals. In recent times, there were several new drug molecules that were introduced in to the market, but always there exists a lag in establishing a defined protocol for the analysis of impurities, their identification and the development of assay methods. Hence, this review attempts to collate various analytical techniques that were developed and validated for the estimation of few important antidiabetic and antihypertensive drugs either in pure, individually or combined with other pharmaceutical dosage form by HPLC, LC-MS/MS, and HPTLC techniques.

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AUTHORS' CONTRIBUTIONS

The authors SV and HG had contributed equally towards the collection of literature and preparation of the manuscript.

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