ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

ANALYTICAL METHODS FOR THE QUANTITATIVE DETERMINATION OF CARDIOTONIC DRUGS

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Article Info

Key words:
Cardiotonic Drugs, Analytical Method, Spectrophotometer, Chromatography

Access this article online
Website: https://www.jgtps.com/
Quick Response Code:

ABSTRACT

Cardiotonic medications are drugs used to enhance effectiveness and boost heart muscle contraction, which leads to increased blood flow to all body tissues. According to US-FDA SIAM, validated quantitative analytical methods are used to detect changes in the chemical, physical or microbiological properties of the drug material and drug products over time, identified as validated quantitative analytical techniques, and that are precise enough that the active pharmaceutical ingredient content can be reliably determined with interference. In this article we have compiled few analytical methods used for the quantitative determination of cardiotonic drugs explained briefly along with the recent filing of procedures followed for the same.

INTRODUCTION

Medications that increase the myocardium's contractile strength and thereby improve its potential and efficacy are considered cardiotonic agents. Cardiac inadequacy can be characterized as the heart's inability to pump a sufficient amount of blood to supply organs and tissues with oxygen and nutrients, leading to exhaustion, shortness of breath, and Edema. Arterial hypertension and ischemic heart disease most frequently cause cardiac insufficiency. Cardiotonic medications are intended for the treatment of heart failure. Cardiotonic medications are drugs used to enhance effectiveness and boost heart muscle contraction, which leads to increased blood flow to all body tissues.[1] Even according to US-FDA SIAM, validated quantitative analytical methods are used to detect changes in the chemical, physical or microbiological properties of the drug material and drug products over time, identified as validated quantitative analytical techniques, and that are precise enough that the active pharmaceutical ingredient content can be reliably determined with interference. It's expensive and time consuming to create and test modern Analytical approaches. A literature review should be performed for current methodologies of the expected analytes or related compounds before beginning the arduous operation. [2-5] among current analytical methods, DART (Direct Analysis in Real Time) is a promising method for rapid detection. The total analysis time is substantially decreased, the chromatographic separation stage is omitted, and the use of solvent is reduced. DART performs effectively for rapid qualitative research in the fields of pharmaceutical industry, forensic science, and hygiene, materials analysis, as an ionization method consistent with different mass spectrometers. Previous uses of DART for quantitative analysis of TDM are, however, very limited. Two barriers could, to the best of our understanding, influence its use in quantitative analysis. One being the loss of the capacity to replicate. DART is likely to be influenced by variations in temperature, humidity, and sample loading location, like other atmospheric ionization strategies. The low throughput sample loading method is the other barrier. Because most DART samples are loaded into a 10 or 12

sample loading device, vast numbers of clinical TDM samples are inadequate.[6-7]

Analytical Methods:

For the quantitative estimate of Pravastatin in bulk and in its pharmaceutical formulation three simple, sensitive, effective, precise, reliable and economical methods have been developed. Method-1 was an HPLC method and on a column of Hypersil ODS,3µm,10cm * 4.6mm, chromatographic separation was carried out. The mobile process consisted of a 23:20:57 v/v/v ratio of acetonitrile, methanol and 0.08M ortho phosphoric acid. TEA (Tri Ethyl Amine) changed the mobile phase pH to 2.8, pumped at a flow rate of 1 ml/min and tracked the eluent at 234 nm. Techniques 2 and 3 were colorimetric predictions based on the condensation between Pravastatin and vanillin in the presence of concentrated sulphuric acid leading to the formation of blue-colored chromogen with a linearity range of 2-12 µg/mL at λmax 610nm and an oxidative coupling reaction between Pravastatin and the chromogenic agent MBTH (3-Methyl-2- benzothiazolinone hydrazone hydrochloride) in the presence of cerricammonium sulphate which obeyed Beer's law in the concentration range of 2-10 µg/mL at absorption maxima of 616nm respectively. The three approaches were scientifically tested in compliance with ICH guidelines.[2] An oral anti-hyperlipidemic agent Simvastatin is generally used to decrease the risk of cardiovascular disease. There is no pharmacopoeic way of evaluating this treatment in capsules. A system for measuring the concentration of simvastatin in capsules by UV/visible spectrophotometry (l = 237 nm), a more affordable compounding pharmacy method, was proposed and validated. The system has been validated for linearity, specificity, range, precision, accuracy, efficiency, reproducibility, identification and quantifying limits.[3]

For the estimate of Carvedilol, a ß-blocker, in bulk and pharmaceutical dosage type, the current study indicates a simple, precise and reliable HPLC process. For mobile phase 1.77g of potassium dihydrogen phosphate was immersed in purified water and reduced with the same solvent to 650 ml; the phosphoric acid pH was changed to 2.0. Further 350 ml of acetonitrile was added and blended. It was then filtered through a 0.2µ membrane filter. Chromatographic system specification, 4.6 mm * 25 cm * 5-micron (c8) column, 240 nm wave duration, 1 ml/min flow rate and 55 ° c oven temperature conditions. A linear response with a regression coefficient of 0.994 was observed between the 806-1202µg/ml concentration levels. The procedure was then tested according to the standards of the ICH (International Conference for Harmonization) for various criteria. This approach can be used without intervention from the excipients for the assessment of Carvedilol in the quality management of the formulation.[4] A simple, sensitive, reliable and rapid method of LC-MS/MS for the quantitative determination of the antihypertensive drug Riociguat was developed in positive mode using electrospray ionization in its formulation. A zorbax (50mm x 4.6mm x 5µm) column with a 0.1% mobile phase of formic acid: acetonitrile (15:85, v/v) was used in this process at a flow rate of 0.5mL/min. With a correlation coefficient of 0.9994, the linearity spectrum of Riociguat varied from 10 to 110ng/mL. As per the ICH rules, the procedure was validated. 3.5ng/mL and 10ng/mL, respectively, were considered to be the limit of quantitative determination. Riociguat's recoveries at varying concentration ranges were found to be in the 97.34 percent to 99.76 percent range. The developed method was found to be simple, quick, accurate and precise and can be used in routine formulations for the quality control analysis of Riociguat. The approach has been shown to be selective, precise, reasonably sensitive, highly reproducible and durable for Riociguat's formulation research.[5]. For the simultaneous determination of Propranolol (PRO) and Prazosin hydrochloride (PZH) in a synthetic mixture using the simultaneous equation method, a simple, fast, reliable, precise and economical, reproducible and cost-effective UV spectroscopy method has been developed and validated. The procedure is based on the simultaneous calculations for the study of both drugs using 0.1 percent W/V HCl in methanol as a solvent, and the maximal absorption was observed to be 289 nm and 329 nm respectively for Propranolol and Prazosin. With a correlation coefficient of 0.λλ8 and 0.999 for PRO and PZH respectively, a linear response was observed in the 12-72µg/mL and 12-72µg/mL range. With a correlation coefficient of 0.λλ8 and 0.999 for

PRO and PZH respectively, a linear response was observed in the 12-72µg/mL and 12-72µg/mL range. The percentage of RSD for precision was found to be less than 2 per cent for these two developed and validated methods. The precision was calculated by recovery experiments and the mean recovery for PRO and PZH was 102.31 ± 0.001 and 102.5 ± 0.00574, respectively. In compliance with ICH Q2 (R1) (International Conference on Harmonization) guidelines, the defined method was then validated for various parameters such as accuracy, precision, sensitivity and linearity. LOD and LOQ were observed to be 0.162µg/ml and 0.4λ1µg/ml for PRO at 28λnm and 0.204µg/ml, and 0.618µg/ml for PZH at 329nm and 0.4λ1µg/ml for PRO at 28λnm and 0.204µg/ml respectively.[8]

The goal of the research was to verify the analytical approach for the quantitative determination of amlodipine in tablets and to determine the medicinal equivalence between amlodipine-containing pharmaceutical reference, generic and related drugs. With a detection wavelength of 366 nm, an ultraviolet spectrophotometric method was developed; ethanol:HCl 0.01M (50:50 v/v) was used as a solvent. To determine their equivalence, quality control checks of weight uniformity, hardness, friability, disintegration, test and dissolution profile and leaflet analysis were conducted for commercially available reference (R), generic (G1 and G2) and related amlodipine-containing drugs (S1 and S2). The overall recovery was 99.86% and the identification and quantification limits were respectively 0.2 and 1.0 µg/mL. The findings of the quality control study have shown that G2 and S2 samples can be found to be pharmaceutically similar, while G1 and S1 samples have been refused in the hardness test. The G1, S1 and S2 samples displayed statistically distinct dissolution profiles. With these findings, there is a need for a more active and comprehensive mechanism to track the efficacy and equivalence of medications to minimize potential damage to the population's health.[9] The current work was carried out in order to establish and verify a fast and accurate UPLC system in which, in compliance with the ICH Guidelines, the peaks would occur within a limited period of time. The approach proposed was a simple, quick, accurate and precise method for quantifying the medication in the dosage form, the bulk drug, and for routine quality control analysis. For the simultaneous measurement of Sitagliptin and Simvastatin in bulk medication and mixed dosage types, the UPLC approach was developed and validated. On a Symmetry C18 (2.1 × 100mm, 1.7mm, Make: BEH) or similar under an Isocratic Mode, UPLC separation was achieved. 0.4 ml per min, the flow rate was tracked. For identification, the wavelength chosen was 213 nm. The time for the run was 3min. The survival period observed was 0.509 min. & 1.623 min. for the medications Sitagliptin and Simvastatin. For the drug Sitagliptin and 200 to360ppm for the drug Simvastatin, the linearity was defined in the range of 500 to 900ppm. The LOD was determined to be 0.18µg/ml & 0.17µg/ml for the medications Sitagliptin & Simvastatin. The LOQ was determined to be 0.61µg/ml & 0.56µg/ml for the medications Sitagliptin & Simvastatin. The proposed method was sufficiently sensitive, reproducible and specific for the bulk determination of Sitagliptin and Simvastatin as a reproducible bulk method. For the study of pharmaceutical formulations containing a combined dosage type, the mentioned UPLC approach has been successfully used.[10]

Overall, it was found that the suggested procedure was acceptable and effective for the quantitative determination of the medication in the form of a tablet dose. The approach was straightforward, reliable, precise and receptive and was applicable to the simultaneous determination of Sitagliptin and Simvastatin in bulk medication and hybrid dosage types.[10] The combination drug used to treat heart failure is Sacubitril/Valsartan (SAC/VAL). In the present work, in the presence of their seven related impurities and degradation materials, novel and rapid, sensitive, precise and robust ultra-high-performance liquid chromatography methods were developed and validated for the simultaneous estimation of SAC/VAL. On Accucore XL C8, (100 × 4.6) mm, chromatographic separation was achieved; the 3 µm reverse phase column was held at 30 °C. Tetrahydrofuran (THF) and 0.1% perchloric acid is used to elute the peaks in water (8:92, percent v/v) as mobile phase A and THF:water: acetonitrile (5:15:80, percent v/v/v) as mobile phase B in gradient mode. Flow rate was set to

0,6 ml/minute, and analytes with Photo Diode Array (PDA) detector were tracked for 21 minutes within the range of 200-400 nm. As per the ICH Q2 (R1) guideline, the procedure was validated, and all the validity parameters were considered within the approval requirements. The SAC/VAL forced degradation analysis found that the drugs were vulnerable to conditions of acidic, alkaline, and neutral hydrolytic and oxidative stress. Both degradation materials, SAC/VAL and their impurities, were isolated from each other, showing the stability suggesting the method's strength. The recently developed approach can be used to predict bulk or its finished good efficiency measure and related goods.[11]

For the evaluation of Cilnidipine and Valsartan in bulk medication and synthetic mixture, the process for the reverse phase high performance liquid chromatography (RP-HPLC) has been developed and validated. The system that has been developed is fast, reliable, accurate and simple. The distribution was conducted with a gradient column with a mobile phase of acetone-based acetonitrile: water (85:15, v/v) of 5 µm reverse phase (phenomenex, luna®). This separation was achieved in gradient mode. Flow concentrations are 1.0 ml/min, with effluent control at 240 nm. At a time of retention for Cilnidipine of 2,083 min and for Valsartan of 5,458 min. Chromatogram showed peak. The device suitability, linearity, precision, precision, precision, robustness, LOD and LOQ is validated. Recovery is 100,36% and 100,14%, respectively with Cilnidipine and Valsartan. LOD and LOQ of 0.037µg/ml, 0.31µg/ml and 0.206µg/ml and 0,62µg/ml are found for estimations of Cilnidipine and Valsartan. For the quantifying of cilnidipine and Valsartan in bulk medicine and the synthetic combination, the proposed approach is used successfully.[12] For the detection of metolazone and losartan potassium in bulk or pharmaceutical dosages, a reverse phase liquid chromatography (RP-HPLC) process has been developed and subsequently validated. Metolazone is diuretic and Losartan Potassium is an anti-hypertensive treatment. The isolation of the moving phosphate buffer (0.02M) and methanol (35:65) v/v at a flow rate of 1.0 mL/min was accomplished with the Agilent TC-C18 4.6 x250 mm 5µm Column. This was achieved in the HPLC. With a 10 min run-time, eluents were detected at 230 nm. A linear approach of 1µg/mL to 5µg/mL and 10µg/mL to 50µg/mL respectively with the correlation coefficient of 0.996 and 0.995 is represented for metolazones and losartan potassium. The less than 2% RSD value indicates that the methods have been established. The system allows for precise, accurate and fast study of bulk, prescription dosage of metolazone and losartan potassium. These methods have been developed easily, quick, selectively and can be used in bulk and prescription dose to routine analysis of metolazone and losartan potassium. Main words: Metolazone, RP-HPLC, RP-HPLC, Losartan Potassium.[13]

Azilsartan, a receptor antagonist of angiotensin II used in hypertension therapy. The DoE approach was developed and validated according to the ICH guideline in the reverse-phase high-performance chromatography process. Materials and Methods: Isolation of Azilesartan in low-pressure gradient mode with 249 nm photodiode array detector, by means of the BDS C18 column (250 x 4,6 mm, particle sickness 5 µ). For improvement of Azilsartan's chromatographic conditions with fewer experiments using box-Behnken-styles from its formulation. A statistical model was developed to analyze the impact of these independent variables on retention time, tailing factor, and theoretical plates using the critical consistency attributes such as mobile acetonitrile concentrators, aqueous phases pH, and flow rate parameters. Variances research (ANOVA) reported that the p-value was less than 0.05 for three reasons. For proposed work the improved conditions of experimentation obtained from the DoE method consists of water and acetonitrile (75:25% v/v), pH 5.00 was estimated to be 3.516min modified with the mobile phase orthophosphoric acid at a flow rate of 1ml/min. The method developed was tested in compliance with ICH directives. A three-tier precision analysis was conducted and found in the 98.94 - 100.46 percent range. With strong precision and robustness, the approach was considered simple and rapid.[14] Calcium channel blocker Felodipine, is used for the treatment of hypertension along with metoprolol succinate. For simultaneous felodipine (FEL) and sucinate metoprolol (MET), their principal metabolites, dehydrafelodipine, and metoprolol acid, two

chromatographic methods were created. respectively. The first approach was the HPLC-RP separation of the components tested through gradient elution using the Phenomenex column C8 and motive water step (adjusted to pH 3.5 with phosphorous acid)–acetonitrile – methanol (45:40:15, volume) for the first 6 minutes and (30:60:10, by volume) next 4 minutes at a flow rate of 1 mL / min and the eluted peaks were determined at 225 nm. Second approach is the HPTLC separation system, where toluene–ethyl acetate–methanol–ammonia– formic acid (10:5:2.5:0.3:0.1 by volume) was used as part of a mobile step and the different bands were screened at 225 nm.[15]

Olmesartan medoxomil is a receptor antagonist category of angiotensin II, and Hydrochlorothiazide is a diuretic selective mostly added to elevated blood pressure, although it is much more efficacious for mixture of both. The mix has been released recently. The ultimate purpose of this study is to design and validate an isocratic HPLC process for testing Olmesartan medoxomil and Hydrochlorothiazide at the same time, which is a clear, fast and exact reverse step. The procedure was conducted by means of WATERS pomp no. 510, 248 sensors, c:18-agilent (zorabax) and T2100P columns (Japan). Acidonitrile and phosphate buffer (60:40v/v) of pH 3 is the buffered solution and solvent used. For Olmesartan medoxomil and for Hydrochlorothiazide, the calibration curves were linear with a coefficient association of 5–25 μg/ml and were 0.998 and 0.999.[16] For an effective administration of antiarrhythmic medications in heart arrhythmia, therapeutic medicines surveillance (TDM) is important. The purpose of the study was to establish and confirm a direct examination of 5 anti-arrhythmic medicines (metoprolol, diltiazem, amiodérone, propafenone and verapamil) and one metabolite (5-hydroxy (OH)propafenone) in human serum in real-time tandem mass spectrometry (DART–MS/MS) for the rapid and simultaneous determination. Following addition of internal isotope labelling criteria and acetonitrile protein precipitation, anti-arrhythmias is ionized in positive modes with DART and accompanied by multiple monitoring reaction (MRM) monitoring. The use of DART–MS/MS prevents chromatographic separation and permits quick, ultra-high-performance analyses of anti-arrhythmic medicines for 30s per sample. Reasonable linearity (R2 to 0.9906), precision (86.1-109.9 per cent) and precision (CT 14.3 percent) is obtained with reduced effects of biological matrices by the DART/MS/MS process. The process was used to evaluate 30 clinical TDM samples successfully. In DART–MS/MS and fluid chromatography tandem mass spectrometry (LC–MS/MS) the relative mistake (RE) was +/- 13 percent. This thesis highlights DART's potential utility for fast quantitative analysis of antiarrhythmics in human serum.[17]

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