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DEVELOPMENT AND VALIDATION OF STABILITY INDICATING HPLC METHOD FOR SIMULATANEOUS ESTIMATION OF IMIPRAMINE AND DIAZEPAM IN COMBINED DOSAGE FROM

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ABSTRACT

A simple, precise, and stability indicating high performance liquid chromatography (HPLC) method was developed and validated for the simultaneous determination of Imipramine hydrochloride and Diazepam in pharmaceutical dosage form. Materials and Methods: The method involves the use of easily available inexpensive laboratory reagents. The separation was achieved on Phenomenex Prodigy C-18 column (150*4.6 mm, i.d., 5 ?m particle size) with isocratic flow with UV detector. The mobile phase at a flow rate of 1.0 mL/min consisted of methanol and 0.1%v/v ortho phosphoric acid (pH 3) in the ratio of 70:30 v/v. Results: A linear response was observed over the concentration range 5.00-50.00 ?g/mL of diazepam and the concentration range 5.00-50.00 ?g/mL of Imipramine HCl. Limit of detection and limit of quantitation for Imipramine were 2.73 ?g/mL and 1.27 ?g/mL, and for Diazepam were 1.80 ?g/mL and 1.98 ?g/mL, respectively. The method was successfully validated in accordance to ICH guidelines acceptance criteria for linearity, accuracy, precision, specificity, robustness. Conclusion: The analysis concluded that the method was selective for simultaneous estimation of Imipramine HCl and Diazepam can be potentially used for the estimation of these drugs in combined dosage form.

INTRODUCTION

Numerous new medications are released onto the market each day. The time between the date a medication is introduced to the market and the date it is included in pharmacopeias is frequently longer.

This is due to potential flaws in continuous and extensive use of these drugs, disclosure of new side effects, increased patient resistance, and the introduction of superior drugs by competitors. In such circumstances, Pharmacopeias may not contain the usual scientific approaches for these drugs.

In this approach, developing a new explanatory system for such treatments becomes essential. Additionally, since medications contain life, quality is important in every service or product. Investigation that reveals the spatial organization of an ion as a particle and the location or proximity of a particular natural beneficial gathering in a given compound. Additionally, surface analysis plays a crucial role in material studies in order to obtain surface-related physical features, such as geography, profundity profiling, atom introduction, and so on.

Concoction examination involves some key steps, such as system selection, testing, preliminary specimen preparation, partitioning, last estimation, and outcomes evaluation. In the first step, which is choosing a system, care should be taken to select the ideal instrument for a fruitful investigation. Making the wrong decision right now will result in a pointless investigation.

Physical, chemical, and instrumental analysis are the three broad categories that analytical procedures fall under.

Physical observations include compound descriptions, measurements of its dimensions (size, shape), color, and odor, among other things. Titrimetric examination of compounds, such as potentiometry, iodometry, argentometry, permagnometry, etc., is part of chemical analysis. Chemical analysis using instruments has been the foundation of experimental chemistry. Method development is carried out for both new and existing items.

When there are no formal systems available, techniques are developed for new products. For existing (non-pharmacopoeial) products, interchange techniques are developed to save cost and time while improving exactness and roughness. Trial runs are performed, and the approach is validated and optimized. Comparative laboratory data with advantages and demerits are made available when an alternative method is offered to replace an existing approach (Sharma B. K, 2002). The following are some causes for the development of innovative methods of drug analysis: The drug or drug combination may not be listed as official in any pharmacopeias.

Because of patent laws, a suitable expository approach for medication might not be available in writing.

It's possible that excipients in plans for medication won't have access to analytical systems.

Scope of Researh Work

Imipramine and Diazepam are used as antidepressants and muscle relaxants, respectively. Adolescence is currently the worst state for both current and future generations. Measuring methods for such medications in this way will undoubtedly be beneficial to society. For mixes, developed techniques will be useful. Forced debasement data for each of the four drugs will be used to consider the consistency of the medications in measurement units.

Objectives of the Study

Combination dose forms are offered for a variety of commercial formulations. In order to accurately quantify the drug of interest in this mixture, it is important to segregate the drug from contaminants, degradants, and formulation excipients and conduct separate analyses.

- The purpose of the work was to create HPLC and HPTLC techniques for concurrent determination of Diazepam and Imipramine in a combined estimate structure. As a result, an effort has been made to create investigative timelines for determination of Diazepam and Imipramine in mix.
- To acknowledge proposed HPLC & HPTLC designs as shown by ICH regulations.
- To develop a security showing measure system and to implement pressure corruptions in accordance with the unease circumstances specified by ICH.

Review of Literature

For the simultaneous determination of nebivolol and indapamide in combined tablet estimation structure, Bavita G. et al. (2013) examined a different, focal, right & right world-class fluid chromatography framework. Base Deactivated Silica (BDS) Hypersil C18, 250 mm 4.6 mm, 5 (molecular size), Thermo strong from Germany, with isocratic conditions & flexible stage containing potassium dihydrogen orthophosphate invigorate pH 3.5 (0.05M KH2PO4): triethyl amine: acetonitrile (40:0.5:60) at stream rate of 1 ml/min using UV presentation at Inexplicably, the upkeep times for nebivolol and indapamide were 3.587 minutes and 5.730 minutes. Structure for Nebivolol 25-75 g/ml and Indapamide 7.5-22.5 g/ml was straight over the focal degree. Nebivolol and indapamide recovered to levels of 98.70–101.32% and 98.72–100.04%, respectively. Using ICH gages, the strategy was ensured. For

the assessment of pharmaceutical delicate parts with unified estimates structure, the depicted HPLC structure was sufficient. The methodology outlined in the current study interacts with the estimation of Nebivolol and Indopamide in combined tablet structures. Every support test's data and results, including those for specificity, linearity and compass, LOD and LOQ, exactness and accuracy, power and recuperation, and structure appropriateness, fall within the requirements of the ICH major. As a result, all of the results fall under the cutoff, making the investigation framework eligible for usage.

Two innovative, dynamic, thoughtful, unmistakable, and unique chromatographic structures were developed by Delhiraj N. (2012) for the simultaneous measurement of telmisartan, amlodipine besylate, and hydrochlorothiazide in predetermined pharmaceutical estimate plots. Qualisil BDS C18 segment (250 mm X 4.6 i.d., 5 m) is a key component used as a piece of solicitation to start started in reverse-phase liquid chromatography. With orthophosphoric acid and acetonitrile (60:40) being injected at a flow rate of 1 ml per minute and an affirmation wavelength of 281 nm, the pH of the adaptable stage, which contains 1.0 ml of triethylamine in a liter of water, was brought to a normal 2.5. The second framework used a reduced stage of chloroform, methanol, and formic acid (85:15:5) together with silica gel 60F254 top delicate layer chromatography and densitometric unambiguous confirmation at 281 nm. The Agilent movements 1220 system, which used a 20-l circular manual injector and an isocratic pump type G4286B, was used for the analysis. The Agilent Qualisil BDS C18 zone (250 mm X 4.6 i.d., 5 m iota estimates, produced in USA) was used to pull out the samples. The Agilent 1200 technique vacuum degasser with stream rate of 1 ml min. - 1 with isocratic elution and UV-Variable wave length locator consolidates 1.0 ml of triethylamine in one liter of water and changes the pH by adding orthophosphoric acid and acetonitrile in a 60:40 ratio. Utilizing the information management system EZChrom Elite Compact 3.3.2 SP2 software, the Model G1314 was calibrated at 281 nm. Methyl acetate was used as a diluent for HPLC analysis. Every determination was made with a blend volume of 20 l at a wrapping temperature of 25 5 °C. For the purpose of determining tablets that are clear, lively, time-tested, practicable, and important, structure was created. Results show that plot structure can be used for quantitative compound analysis.

The synchronous determination of amlodipine besylate (AML), valsartan (Vals), and hydrochlorothiazide (HCT) by top-notch fluid chromatography without prior identification was contributed to by Samya M. et al. (2012). RP-C18 chromatographic piece,

PhenomenexKinetex (150 mm 4.6 mm i.d), and conventional stage with acetonitrile-phosphate cushion (0.05 M) with pH 2.8 in proportion to (40/60, v/v) at stream rate 0.8 mL/min and wavelength declaration of 227 nm were used to fit the tasteful determination. Sponsorship times for HCT, AML, and Vals were 2.26, 3.16, and 11.19 minutes, respectively. Delineated systems were clearly above levels of 4-28 g/ml, 5–40 g/ml, and 1–12 g/ml for AML, Vals, and HCT. The average percent recoveries for AML, Vals, and HCT were 99.94%, 99.96%, and 99.78%, respectively. F-test and t-tests with a 95% confidence level were used to examine the focus accuracy of data stored in clear test sets. Structure could be used to examine the definition of a united estimates tablet that contains AML, Vals, and HCT in addition to spiked human plasma. Agilent 1200 technique HPLC, with quaternary pump, auto injector, thermostated segment compartment G1316A/G1316B, and vacuum degasser included (Germany). Degree of chromatography; PhenomenexKinetex (150 4.6 mm i.d) P.N. 00F-4462-E0 Chromatographic tops were linked and recorded electronically using the chemstation programming (Agilent Chemstation V. B.03.01, Germany). Chromatographic analysis was performed between 22°C and 25°C, the temperature of solidification. Separate isocratic analyses of the mixtures were performed using a flexible stage, a master tonetrile-phosphate support (0.05 M), a level of (40/60, v/v), a stream rate of 0.8 mL/min, and a blend volume of 20 L. Using a 0.45 m film channel (Millipore, Bradford, MA), the Mo.-bile stage was detached, and the transmitting was seen spectrophotometrically at a wavelength of 227 nm. Thereafter, the stage was ultrasonically sonicated for 15 minutes. The suggested HPLC approach was specific and easy to use, allowing for the intelligent simultaneous detection of AML, Vals, and HCT in tablets and human plasma. Circulating air was used to validate the suggested methodology in accordance with ICH [35, 36] and USP standards.

Chandana. M. et al. (2012) created an RP-HPLC apparatus with a UV identifier for the purpose of examining bendroflumethiazide and nadolol in planned and bulk dosages. This method was financially deplorable. Due to the short runtime, we can complete this examination and wrap everything up quickly. Our method is amazing in its precision and parade. For bendroflumethiazide and naproxen, linearity of the drug was detected in the range of 40 to 100 g/ml. Nadolol's linearity coefficient and rate turn fitting slant were determined to be 0.996 and 99.6%, whereas bendroflumethiazide's were 0.999 and 99.9%. Bendroflumethiazide was seen to be 1.5 g/ml and Nadolol was seen to be suppressed at 0.5 g/ml for obvious reasons. The most remote reason for the evaluation of naproxen was 1.5 g/ml, and bendroflumethiazide was 5 g/ml. The accuracy of the process was clarified through

drug recovery examinations. Recovery of the arrangement is well within the thresholds for confirmation. Precision of framework was coordinated by using standard arrangement, and accuracy of approach was managed by examinations of arrangement courses of action by duplicate implantation. The %RSD of the tests is observed to be within 2% of the sites of confinement. As a result, the created framework is discovered to provide odd conditions of exactness and reproducibility. Violence was controlled by conducting the same inspection on predetermined days, with measure being handled by unmistakable authority. Results of the tests were within reason. Results appear to be repeatable. Despite combinations of circumstances that an expert or investigator may generally expect. Soundness was controlled by modifying the way you look at stream rate and trademark arrangement on a flexible stage. The energy's aftereffects on the framework were contained within the boundaries. It is possible to implement a system for Nadolol and Bentoflumethiazide with only minor variations in stream rate and flexible stage thanks to results obtained with stream rate modification and flexible stage creation. This reveals that operational and regular variables for the made-system have no impact on test results. By repeatedly performing have strong resemblance, the framework's suitability was coordinated. It was determined that the dimensions of hypothetical plates were 37966 for nadolol and 5440 for bendroflumethiazide. With all of that highly detailed illustration, the tailing variable, which was observed to be 1.2 for nadolol and 0.1 for bendroflumethiazide, is demonstrating a tremendous and full division of two segments from one another. Because there are no salt cushions in our structure, production is not threatened by our system. Our design is suitable for mechanical use for the qualitative and quantitative analysis of bendroflumethiazide and nadolol.

Nageswara R. et al. (2011) improved the careful, very delicate, exact, and reproducible isocratic RP-HPLC method and developed a method that was used for the simultaneous analysis of hydrochlorthiazide and eprosartan in mass spectra and tablet estimation traces. Agilent Eclipse XBD-C18 (5 m, 150 mm, 4.6 mm I.D.) region system progress was performed. The supportive stage was an 80:20 v/v mixture of methanol and support (20 mM KH2PO4) according to ICH Q2 R1 regulations. In a linearity focus, numerical explanations for Hydrochlorthiazide and Eprosartan were found to be y=0.0123x + 0.0019 & y=0.0034x - 0.0163. Relationship coefficients for Hydrochlorthiazide and Eprosartan were 0.9984 and 0.9989, respectively. The proposed system was useful for estimating the mass and medicinal component present in tablet dose form.

Utilizing a JASCO HPLC 2080 model chromatograph (Japan) with a PU-2080 isocratic transport structure (pump), UV-2075 identifier (JASCO), and Rheodyne 7725 blend valve with a 20-L circle volume, chromatography was carried out. Agilent xbd-reverse stage C18 component (150 x 4.6 mm I.D., 5 m) was the expressive fragment.

JASCO BORWIN programming was used to secure and organize the information (Japan). Chromatographic distribution was adjusted at room temperature on a flexible stage using a mixture of buffer solution (20 mM potassium dihydrogen orthophosphate): methanol at a ratio of 80:20. The pH of the reinforcement, which was used as part of that cutoff with no change, was 4.85 0.05.

For the simultaneous determination of hydrochlorothiazide and eprosartan in a robust estimation framework, a reasonable, rapid, delicate, precise, and definite approach has been developed. This method is the greatest option for routine analysis of HCTZ & EPRO in the pharmaceutical business because to its simplicity in reduced stage construction and suitably low cost of parts of adaptable stage combined with its accuracy.

Mahesh K. (2011) used clear isocratic instrumentation to create important, specific, fragile, and reverse stage pervasive fluid chromatographic (HPLC), which was then attested for the simultaneous detection of hydrochlorothiazide and ramipril in combination. Partitioning was performed using a flexible stage with 0.1 mM sodium dihydrogen phosphate cushion, acetonitrile, and a pH 3.0 ortho phosphoric ruinous solution. The stream rate was set to 1.0 ml/min. UV confirmation at 215 nm was used on the C18 traded organized (4.6250mm, 5.0m) fragment. Hydrochlorothiazide and Ramipril independently revealed maintenance times of 3.0371 and 3.553 minutes. The strategy was supported by the use of the informational components. Assessments of linearity, accuracy, precision, assay, LOD, LOQ, and specificity were made, and they all fell within acceptable cutoff ranges. Structure and outline examination of strong dose definitions have been appropriately integrated. All solvents underwent HPLC assessment, and all of the reagents underwent trial evaluation. We purchased sodium dihydrogen phosphate from SD Fine Chemicals (India). From Rankem, acetonitrile, orthophosphoric ruinous, and methanol were obtained (India). Using the Millipore System and MilliQ Plus, water was purified (USA). Before use, all solvents and techniques were degassed and sifted through layer channels (Nylon Millipore Millex-HV channel units, 0.45 m pore size). Prior to blending into the HPLC framework, each technique was tested using a Millipore Milex hydrophilic PTFE unit channel with a 0.45 m pore size.

As required, consider that a prompt, temperamental system has been established for the synchronized determination of ramipril and hydrochlorothiazide's combined estimations. When compared to the prior piece, the structure moreover in this method exhibits excellent gainfulness & unprecedented illustration portion. The system's linearity, accuracy, and precision show that it is particularly replicable under quality-control settings if the above-mentioned steps are carefully followed.

Angiotensin II Receptor Type 1 Inhibitors have been extensively employed in the treatment of conditions like hypertension, heart failure, myocardial necrosis, and diabetic nephropathy, according to research by Nadeem S. et al. (2011). Their beneficial effects are connected to the inhibition of Angiotensin II caused by blocking the AT1 receptor. Valsartan is an orally active antagonist of Angiotensin II receptor type 1 that lowers blood pressure and is used to treat hypertension. It was initially manufactured by Novartis and enjoys a sizable market in manufacturing nations. It is often offered in combination with other antihypertensive medications. It is a lipophilic medicine and acts more gradually than other medications in the same class. Drug is a typical location for tasteless business endeavors. This overview assesses the pharmacological characteristics of valsartan, as well as its sufficiency and tolerability in the treatment of hypertension patients. Similar examinations of the existing and future roles of medicine in business have been made. In individuals with sensitive to direct hypertension, valsartan is effective & persistent once consistently antihypertensive administration. Additionally, when taken as a monotherapy or as an additional treatment for people with true hypertension, prescription drugs may lower blood pressure. Imperatively, Valsartan has all the resources to always be as strong & persistent as other commonly utilized antihypertensive medications. Thus, medicine positions itself as a successful treatment option for individuals with hypertension. It will be especially helpful for patients who do not respond to, or who are tolerant to, hypertensive experts from other drug classes. Valsartan is an appropriate option for patients with mild to moderate hypertension and its anticipated estimation response feasibility provides the justification for titration in clinical practice.

Enalapril Maleate, Hydrochlorothiazide, and Paracetamol were estimated using a direct, reproducible, and financially successful speak stage top liquid chromatography (RP-HPLC) system by Pratap P. et al. (2011) in their tablet measurements of these medications. The mechanical setup used was the JASCO HPLC-2000 dissolveable movement system with a general circle injector (Rheodyne 7725i) with a 20 L imbuement point of confinement, a

JASCO UV-2075 Plus smart Visible discoverer, and a JASCO PU-2080 isocratic HPLC pump. Division was performed on HiQsilC18HS (250 X 4.6 mm I.D., 5 m particle size) using a different stage designation for chromatography. Rigging was managed by a PC that had been correctly programmed for chromatography. In general, all chemicals used were of the cleanest grade possible and were utilized directly out of the package. We used water, HPLC-grade (99.8%) acetonitrile, and orthophosphoric destructive. Adaptive fixes As reference standards, hydrochlorothiazide, enalapril maleate, and paracetamol were purchased from USP and BP. We used HPLC grade water. Business tablet obtained from a nearby commercial area. Acetonitrile:water (25:75 V/V) is the game plan for the adaptable stage, and orthophosphoric destructive was used to modify the pH to 4.7. Adaptable stage was degassed using a sonicator for around 15 minutes while continuously channel employing 0.45 m layer channel. Additionally, 0.45 m layer channels were used in the example plans. It flowed at 1.2mL/min. 220 nm was utilized as the wavelength. The hard and quick run lasted 10 minutes. The produced approach is appropriate for verifying and evaluating the ternary combination of enalapril maleate, hydrochlorothiazide, and paracetamol.

A high rate of recovery shows that the technology can be used successfully for everyday purposes. The suggested process is crucial, delicate, rapid, specific, and could be related to quality and soundness when considering combinations of enalapril maleate, hydrochlorthiazide, and paracetamol.

Reseach methodology

Experimental work

- Selection of common solvent for Imipramine Hydrochloride (IMI) & Diazepam (DIA)
- Preparation of Mobile Phase
- Preparation of standard Stock solutions
- Selection of analytical wavelength
- Selection of chromatographic condition
- Validation of method
- Analysis of marketed formulation
- Force degradation study

Selection of Solvent For Imipramine Hydrochloride (Imi) & Diazepam

Imipramine Hydrochloride (IMI) and Diazepam (DIA) are more soluble in ethanol and methanol than in water, which was initially employed to test the solubility of both medicines. Methanol has been chosen as a typical analytical solvent as a result.

Solubility DataofImipramine Hydrochloride & Diazepam

Solvent	Imipramine Hydrochloride (IMI)	Diazepam(DIA)
Water	Freelysoluble	Soluble
Methanol,Ethanol	Freelysoluble	Slightlysoluble
Ether	Insoluble	Slightlysoluble
Acetone	Freelysoluble	Freelysoluble

Validation of the HPLC Method

When a framework has been properly passed on, it is essential to support it and ask that it be appropriate for its intended purpose. The level of insistence reveals how impressive timelines are, particularly if they are suitable for the suggested use. Structure Validation is currently the main source of anxiety in the transition to enlightening science research workplaces. In the pharmaceutical industry, everything is extremely quickly performed. US Food & Drug Administration (FDA) revised draft regulations with a straightforward recommendation for strategic authentication of bio-informative systems in the pharmaceutical industry [Shah V.P., 2001]. For the disciplines of bio-intelligent theory, pharmaceutical & biotechnological frameworks, the International Conference on Harmonization (ICH) has produced results of supporting issues linked into "symptomatic methodology" [ICH, Q2A, Q2B, Q6B, 2002]. As a result, US Pharmacopeia (USP) has established guidelines for the approach statement of appropriate schedules for pharmaceutical items [USP, 1995]. However, ICH & USP criteria are not as precise as those from the FDA, and there are no stated essential certification regulations in the predicted biotechnology zone. Standard Q2 was used for endorsing (R1). The most frequently used support parameters are briefly illustrated here. In terms of factors like linearity, precision, accuracy, specificity, quality, soundness, and solution stability, made RP-HPLC frameworks were approved.

Expected Outcome

Numerous new medications are released onto the market each day. The time between the date a medication is introduced to the market and the date it is included in pharmacopeias is frequently longer. Combination dose forms are offered for a variety of commercial formulations. In order to accurately quantify the drug of interest in this mixture, it is

important to segregate the drug from contaminants, degradants, and formulation excipients and conduct separate analyses. Therefore, an effort has been made to create investigative schedules for figuring out how much diltiazem and imipramine is in the mixture. The purpose of the work was to develop HPLC and HPTLC strategies for the simultaneous determination of benzodiazepines and imipramine in a combined estimation structure, to identify proposed HPLC and HPTLC plans as demonstrated by ICH regulations to prevent pressure corruptions under the ICH-specified unease conditions, and to develop a security showing measure system. Imipramine hydrochloride (IMI) and diazepam (DIA) were estimated using two specific chromatographic frameworks, for example, HPTLC and RP-HPLC, in their solidified pharmaceutical estimation structures. Clear, doubtful, and Stability exhibiting The C18 range was used as the stationary stage for the RP-HPLC structure, and Methanol and Water (Phosphate support) (75:25 v/v), pH 6.6 adjusted with Potassium Hydroxide, were used as the versatile stage. Stream rate was maintained at 1 ml/min, and ID was performed at 251 nm, where diazepam (DIA) and imipramine hydrochloride (IMI) had focal absorbance. Imipramine hydrochloride (IMI) and diazepam (DIA) had respective upkeep times of 2.85 and 5.25 minutes. Compelled debasement studies were completed, and prescription tops were examined while looking over corruption object tops.

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