A SYNOPSIS OF THE THESIS ENTITLED

DEVELOPMENT OF STABILITY INDICATING ASSAY METHOD AND STUDY OF DEGRADATION BEHAVIOUR OF SOME DRUGS AND FORMULATION

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INTRODUCTION

The stability indicating method [1] can be defined as validated quantitative analytical method that can detect the change in the chemical, physical or microbiological properties of the drug substance and drug product with respect to time, and that are specific so that the content of active ingredient and degradation product/impurity can be accurately measured without interference. The purpose of stability testing is to provide evidence how the quality of pharmaceutical products varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability indicating method also includes the study of formulation-related factors [2] that influence its quality, for example, interaction of API with excipients, container closure systems and packaging materials.

Ideal characteristics of Stability Indicating Analytical method (SIAM) are :

a. It should be capable of separating major API from any degradation product under¬ defined storage condition.
b. It should be sensitive to detect and quantify one or more degradation products or¬ impurities or related substances.

Degradation study of drug substances and drug products [2] and impurity profiling has attracted global interest because regulatory bodies have become more stringent in maintaining and controlling quality and purity of drugs. Also the regulatory requirements for impurity profiling and forced or stress degradation study have been extended to generic drugs and products in recent years. Due to the stringent environment laid down by regulatory authority, there is steady increase in product recalls from the market. One of the reasons often cited is ―due to the presence of impurities or degradation products (DPs) beyond the prescribed limits. There are two issues in drug therapy are efficacy and safety of drug.

According to ICH guideline Q3A impurity in a drug substance is ―*any component of the drug substance that is not the chemical entity defined as the drug substance* and as per ICH guideline Q3B impurity in a drug product is ―*any component of the drug product that is not the chemical entity defined as the drug substance or an excipient in the drug product.*

Impurity profiling may be defined as ―*the common name of analytical activities with the aim of detecting, identifying and/ or elucidating the structure and quantitatively determining organic, inorganic impurities and residual solvents in bulk drug and pharmaceutical formulations"*. Very broad definition of impurity is given in guideline and it can include DPs as impurity. DPs are defined as ― *molecules resulting from a change in the drug substance brought about over time. For the purpose of stability testing of the products in this guidance, such changes could occur as a result of storage or processing for example oxidation, deamination, proteolysis and aggregation.*

SOURCES OF IMPURITIES

1. The raw materials used.
2. The method of manufacture adopted
3. Due to instability of product.
4. From the atmospheric contaminants

CLASSIFICATION OF IMPURITIES [3]

Organic impurities- These can be formed during the manufacturing process or during storage of new drug substances. They can be identified/unidentified, volatile/nonvolatile. This includes: starting materials, intermediates, by-products, DPs, reagents, ligands and catalysts

Inorganic impurities- These can arise during manufacturing process; normally they are known and identified. This includes: reagents, ligands, catalysts, heavy metals, other residual metals, inorganic salts and other materials like filter aids, charcoal.

Residual Solvents - These are generally inorganic/organic liquids that are used during synthesis of drug substances as a vehicle for preparation of solution or suspension. ICH Q3C (5) guideline provides the limits of residual solvent based on existing safety and toxicity data. These were classified in three categories:

Class 1 (The most toxic and/or environmentally hazardous): These are highly toxic in nature and are limited to 2–8 ppm, for environmentally hazardous chemical like trichloroethane the limit of 1500 ppm is applied.

Class 2 (Considered a lesser risk): These should be limited in their usage. Two different approaches were described in guideline for setting limits of class 2 solvents. The first approach is used when PDE (permitted daily dose) can not be estimated; concentration limits are calculated on the basis of daily intake of theoretical product mass of 10g. The second approach is used when dose is known; the PDE and/or dose value can be used to determine the permissible concentration.

Class 3 (The lowest risk category): These have low toxic potential and are limited to 5000 ppm (0.5% w/w)

SIGNIFICANCE OF IMPURITY PROFILING

1. Analytical procedures – to determine the potential impurities
2. Characterize the structure of actual impurities present in the new drug substance by NMR, IR and MS.
3. To determine the presence of toxic or other pharmacologic effects.

AIMS AND OBJECTIVE

The ICH guideline Q1A(R2) emphasizes that the testing of those features which are likely to influence quality, safety and efficacy must be done by validated stability indicating testing method. The stress testing may also provide information about degradation pathways and selectivity of the applied analytical method.

Regulatory authorities such as US FDA, TGA and MHRA insist on impurity profiling of drugs.

Hence the major objectives of the present project include

1. Development of the simple, sensitive and reliable stability indicating assay methods for the selected drugs .
2. Characterisation of degradation products using LC-MS/MS studies
3. Estabilishing degradation pathways of the selected drugs
4. Isolation and characterization of degradation products/impurities found in API and their formulation
5. Correlation of degradation behavior of drug with found impurities in API and their formulations

Selection of Active Pharmaceutical Ingredients

The API selected for development of stability indicating method are

1. Clevidipine
2. Acotiamide hydrochloride trihydrate
3. Fimasartan potassium
4. Anagliptin
5. Efonidipine hydrochloride ethanolate
6. Riociguat

MATERIALS AND METHODS

(a) Clevidipine

- **Stability indicating method development by HPLC [7,8]**

  Maximum wavelength of Clevidipine was determined by scanning in the range of 200-400nm and maximum wavelength was found to be 239nm.

  Method development of CLEVI was done by HPLC. Various trials were done for optimization. These trials were done and optimised on the following parameters :

  Column – C18, mobile phase - Buffer – phosphate buffer pH (3-6.5) with methanol and acetonitrile in different ratios, flow rate – 1ml/min, max. wavelength – 239 nm

  Retention time and system suitability parameters that is asymmetry factor, theoretical plates were observed.

Stability indicating analytical method of CLEVI has been developed according to the ICH guidelines. Degradation was carried out under following conditions:

- For hydrolytic and oxidative conditions degradation were tried as :
- Acidic – Drug was subjected to 1 M HCl at room temperature and 60ºC for 4 hour. Solution was neutralized by sodium hydroxide and diluted with mobile phase. Slight degradation was observed in 1M HCl at 60˚C for 1 hours.
- Alkaline – Drug was subjected to 0.01M NaOH at room temperature and 50ºC for 1 hr. Solution was neutralized by 0.01 M HCl diluted with mobile phase. Significant degradation was observed.
- Oxidation – Drug was subjected to 3% and 10% hydrogen peroxide at room temperature for 1 hour.
- Thermal – Drug was subjected to thermal degradation at 80ºC for 8 days.
- Photostability condition- Drug was subjected to degradation in photostability chamber for 21 days. Very slight degradation was observed.

RP-HPLC method of Clevidipine Butryate was developed with mobile phase 10mm phosphate buffer pH 3 and acetonitrile (50 : 50), Column C-18 Nucleosil (250 x 4.6mm,5µ) wavelength 239 nm, Flow rate 1ml/min. Retention time of Clevidipine butryate was 10.02 min. Clevidipine butryate was subjected to degradation as per ICH guidelines. Significant degradation was observed in alkaline conditions, slight degradation was observed in acidic and alkaline conditions

(b) Stability indicating method development by HPTLC [10]

Analytical Method Development of CLEVI has been developed by HPTLC. Trials are taken on the following parameters:

Stationary phase is pre-coated silica gel 60 F-254 aluminium plates (10 * 10 cm, 250 mm thickness, solvent front – 8 mm, saturation Time- 20 min

Trials were taken on mobile phase – Methanol: acetonitrile, Methanol: ethyl acetate, Toluene: ethyl acetate.

Method was developed with mobile phase toluene: ethyl acetate (8:2) and was validated with parameters linearity, recovery, Precision, Robustness (Mobile phase composition, saturation time, development distance, wavelength range.

Chromatographic separation was performed on aluminum plate pre coated with Silica Gel 60 F254 using toluene: ethyl acetate (8:2) as mobile phase. Retention factor R_f of clevidipine was found to be 0.49. The method was validated as per ICH guidelines. Calibration curve was in the range of 1000-6000ng/band. The correlation coefficient was found to be 0.999. The precision expressed by RSD was less than 2%. The accuracy of method was confirmed by recovery studies using standard addition method and recovery was found to be 99.03-99.57%. The drug showed significant degradation in alkaline and

acidic condition and slight degradation in oxidative condition. The drug was stable in thermal condition

- **Acotiamide hydrochloride trihydrate**

Method development of Acotiamide hydrochloride trihydrate was done by HPLC. Various trials were done for optimization. These trials were done on the following parameters:
Column – C18, mobile phase - water / buffer – acetate buffer pH (3-5) and 0.1 % formic acid with methanol and acetonitrile in different ratios, flow rate – 1ml/min,Max. wavelength – 282 nm.

Stability indicating analytical method of ACOT has been developed according to the ICH guideline. Degradation was carried out in following conditions:

- Acidic –Drug was subjected to 1 M HCl in a water bath at 100˚C for 3 hrs. Solution was neutralized by sodium hydroxide and diluted with mobile phase. Slight degradation was observed with formation of one degradation product .
- Alkaline –Drug was also subjected to 0.5 M NaOH at 100º C for 3hrs. Solution was neutralized by 0.5 M HCl diluted with mobile phase. Significant degradation was observed with the formation of three degradation products.
- Oxidation – Drug was subjected to 6 % hydrogen peroxide for 48 hrs at room temperature . No degradation was observed.
- Thermal – Drug was subjected to thermal degradation at 80ºC for 8 days.No degradation was observed.
- Photostability condition- Drug was subjected to degradation in photostability chamber for 11 days. No degradation was observed.
- Degradation products were formed in acidic and alkaline conditions. These degradation products were resolved from the drug by changing Column C18 and C8, mobile phase.
- Degradation products in acidic and alkaline conditions were characterised by LC-MS/MS method.
- Two major degradation products in alkaline conditions were isolated and characterized by IR, NMR and Mass.

Method was developed with Hypersil BDS C-8 column (250 X 4.6mm, 5 µ), mobile phase 0.1% TEA adiusted 0.2% formic acid and acetonitrile (70:30). Retention time was 9.23 min, flow rate 1ml/min, wavelength 282 nm. Method was validated with parameters like linearity, accuracy, intraday and interday precision, limits of detection and limits of quantification, robustness (pH, flow rate, wavelength, organic modifier.

An isocratic RP-HPLC method has been developed using C-8 Thermo Hypersil BDS Column (250 x 4.6 mm i.d., 5µparticle size) with the mobile phase composition of

Acetonitrile: 0.1 % Triethylamine in 0.2% formic acid (30: 70) at column oven temperature of 40ºC. The flow rate was 1.0ml min^{-1} and effluent was detected at 282 nm. The method was validated in terms of linearity, accuracy, precision, LOD (Limit of Detection), LOQ (limit of Quantification) and robustness as per ICH guidelines.
Acotiamide was subjected to stress degradation under acid, base, neutral hydrolysis, oxidation, dry heat, photolysis conditions. Significant degradation was observed in acid and base degradation. Degradation products were identified by LC-MS. Two degradation products in alkaline conditions were isolated and characterized by IR, NMR and Mass.

- **Fimasartan potassium**

Method development of FIMA was done by HPLC. Various trials were done for optimization. These trials were done on the following parameters:

Column – C18, mobile Phase - water-methanol, water-acetonitrile, buffer – phosphate buffer pH (3-6.5) with methanol and acetonitrile in different ratios, flow rate – 1ml/min, max. wavelength – 262 nm

Retention time and system suitability parameters that is asymmetry factor, theoretical plates were observed.

Method was developed with Hypersil BDS C-18 column (250 X 4.6mm, 5 µ), mobile phase 10 mm phosphate buffer pH 3 and acetonitrile (50:50). Retention time was 7.35 min, flow rate 1ml/min, wavelength 262 nm. Method was validated with parameters like linearity, accuracy,intraday and interday precision, limits of detection and limits of quantification, robustness (pH, flow rate, wavelength, organic modifier).

Stability indicating analytical method of Fimasartan has been developed according to the ICH guidelines. Degradation was carried out under following conditions:

- For hydrolytic and oxidative conditions degradation were tried as :
- Acidic – Drug was subjected to 1 M HCl at room temperature for 24 hrs. Drug was subjected to 1 M HCl at 60˚C for 12 hours,80˚C and 100˚C for 3 hours, 2 M HCl, 3 M HCl in a water bath at 100˚C for 3 hrs. Solution was neutralized by sodium hydroxide and diluted with mobile phase. Slight degradation was observed in 1M HCl at 100˚C for 3 hours.
- Alkaline – Drug was subjected to 1M NaOH at room temperature for 24 hrs . Drug was also subjected to 1M NaOH at 80ºC for 2 hours, 5 hours and 100º C for 3hrs. Solution was neutralized by 1 M HCl diluted with mobile phase. Five degradation products were observed in 1 M NaOH at 100º C at 4 hrs.
- Oxidation – Drug was subjected to 0.9 % and 3% hydrogen peroxide at at room temperature and at 60 ºC for 30 min. Significant degradation was observed . Kinetics study [11]of degradation was performed at 0.9% and 3% hydrogen peroxide, room

temperature and temperature 60ºc ,time 6 hours. Oxidative degradation followed first order kinetics, degradation rate constant and half life was calculated.

- Thermal – Drug was subjected to thermal degradation at 80ºC for 8 days.
- Photostability condition- Drug was subjected to degradation in photostability chamber for 21 days. Very slight degradation was in solution.
- Degradation product in alkaline ad oxidative conditions were characterised by LC-MS/MS method.

Isolation of degradation product – Major degradation product in oxidative condition was isolated and characterized by IR, NMR and Mass. Fragmentation pathway of degradation product in oxidative condition was postulated.

A simple, specific and sensitive stability-indicating high-performance liquid chromatographic method was developed and validated for the determination of fimasartan in synthetic mixture. Reversed-phase chromatography was performed using Hypersil BDS C18 column (250 mm × 4.6 mm, 5 μm) mobile phase consisting of Phosphate buffer : Acetonitrile (50: 50, v/v) with a flow rate of 1 mL/min. Detection wavelength was 262 nm. Fimasartan was subjected to stress conditions such as acidic, alkaline, oxidation, photolysis and thermal degradations and the proposed method was validated as per ICH guidelines. The peaks of degradation products were well resolved from the standard drug peak and hence this method can be used for quality control assay of fimasartan. The drug is degraded in alkaline and oxidative conditions. Degradation products in oxidative and alkaline conditions were identified by LC-MS. The developed stability indicating method was applied to determine oxidative degradation kinetic. Oxidative degradation follows first order kinetic. Degradation rate constants and half-life were determined. Major degradation product in oxidative condition was isolated and characterized by IR, NMR and Mass.

- **Anagliptin**

Method development of Anagliptin was done by HPLC. Various trials were done for optimization. These trials were done on the following parameters :

Column – C18(hypersil BDS and waters symmetry) , mobile Phase - water :methanol, water : acetonitrile, acetate buffer(pH6) : methanol, acetate buffer(pH6) : methanol: acetonitrile, acetate buffer(pH6) : acetonitrile , flow rate – 1ml/min, max. wavelength – 247 nm.

Method was developed with Waters Symmetry C-18 column (150 X 4.6mm, 3.5 μ), mobile phase 10 mm acetate buffer pH 6 and acetonitrile (80 :20). Retention time was 6.87 min, flow rate 1ml/min, wavelength 247 nm.

Stability indicating analytical method of Anagliptin has been developed according to the ICH guidelines. Degradation was carried out under following conditions:

- For hydrolytic and oxidative conditions degradation were tried as :

- Acidic –Drug was subjected to 1 M HCl at 60˚C for 6 hrs Solution was neutralized by sodium hydroxide and diluted with mobile phase. Slight degradation was observed.
- Alkaline – Drug was subjected to 0.1M NaOH at room temperature for 1 hr . Significant degradation was observed .Two degradation products were formed.
  Kinetics study of degradation in alkaline condition were studies. Factors taken for kinetics study were NaOH (0.05, 0.1, 0.5 N), temperature (RT and 60˚C), time (1-5 hrs). Alkaline degradation followed first order kinetics. Degradation rate constant and half life was calculated.
- Neutral – Drug was subjected to neutral hydrolysis at 80ºC for 5 hrs. Slight degradation was observed.
- Oxidation – Drug was subjected to 0.3 % hydrogen peroxide at room temperature for 2.5 hrs. Significant degradation was observed .Seven degradation products were formed. Kinetics study of degradation was performed at 0.1, 0.3and 0.9% hydrogen peroxide, for 1- 5 hours. Oxidative degradation followed zero order kinetics, degradation rate constant and half life was calculated.
- Thermal – Drug was subjected to thermal degradation at 80ºC for 8 days. Slight degradation was observed.
- Photostability condition- Drug (in dry and solution) was subjected to degradation in photostability chamber for 21 days. Very slight degradation was in solution.
- To resolve the degradation products in alkaline and oxidative condition method was modified to gradient method. The developed method was validated as per ICH guidelines.
- Degradation products in alkaline and oxidative conditions were characterised by LC-MS/MS method.
- Major degradation product in alkaline and oxidative conditions were isolated and characterized by IR, NMR and Mass.

A gradient specific stability indicating high performance liquid chromatographic method was developed and validated for the determination of Anagliptin in synthetic mixture. Reverse phase chromatography was performed on Shimadzu LC-20 AD pump (binary) and Shimadzu PDA M-20A Diode Array Detector using Waters Symmetry C-18 column (150X 4.6 mm, 3.5µm) maintained at column oven temperature of 40ºC with UV detection at 247 nm was used. A gradient programme was run at flow rate of $1 ml min^{-1}$. Mobile phase A consisted of mixture of acetate buffer(10 mm) pH 5: methanol : acetonitrile in the ratio of 90:5:5. Mobile phase B consisted of mixture of acetate buffer (10 mm) pH 5: methanol: acetonitrile in the ratio of 50 :25 :25.The method was validated according ICH guidelines. Anagliptin was subjected to stress conditions such as acidic, alkali, oxidation, photolysis and thermal condition. The drug showed significant degradation in alkaline and oxidative condition. Alkaline degradation followed first order kinetics and oxidative degradation followed zero-order kinetics. Degradation rate constant and half-lives were determined. Degradation products in alkaline and oxidative conditions were identified by LC-MS. One

major degradation products in alkaline and oxidative condition were isolated and characterized by ^{1}H NMR, ^{13}CNMR, DEPT, D_2O exchange, MS/MS, HRMS, IR .

- **Efonidipine**

(a) Method development of Efonidipine was done by HPLC by applying principles of quality by design [12, 13]. Based on the control, noise, and experimental (CNX) approach, initials trials and REM various parameters were selected, which could have a possible impact on CQA and were further screened using 2 Level fractional factorial design. 2 Level Fractional factorial and Box-Behnken design were used for method development and optimization. Fractional factorial design was chosen for screening of parameters as it is suitable for assessment of a large number of factors or factor levels and also evaluates all possible combinations of interactions.

A design layout using fractional factorial design was generated by Design Expert 7.0.0, 6 factors which influence the method parameters were screened for their significance on the analytical method. Variables studied were pH, Flow rate, % organic, Buffer Concentration, Detection wavelength. A Fractional factorial screening design was applied to investigate the significance of these 6 factors. 3 responses were studied, namely Retention time of Efonidipine, Symmetry factor, Theoretical plates of Efonidipine.

On the basis of pareto chart, half normal plot, interaction plots four factors pH, %Organic, Buffer concentration and Flow rate were found to be most significant overall affecting almost all the responses involved. Hence, these 4 factors were selected for the next stage of Optimization in QbD by applying Box-behnken design.

Out of the optimized solutions generated by the software,. One of these solutions was also selected as the final optimized working point for the proposed stability indicating method. Acetate buffer pH 5: acetonitrile in ratio of 35 : 65 was selected as the working point.

Method was Hypersil BDS C-18 column (250 X 4.6mm, 5 µ), flow rate 1ml/min, wavelength 254 nm. Retention time of Efonidipine was found to be 8.3 min, asymmetry 1.035, theoretical plates 8701.

Rapid and simple high performance liquid chromatographic (HPLC) method for the determination of efonidipine. The method was developed applying principles of Quality by Design. Various factors affecting the method were screened using a 2 Level Fractional factorial design. These critical material attributes were further subjected to a Box-Behnken design for Optimization. Point verification of actual versus optimized predicted trials was performed. A Design space in which the method was robust could be generated successfully. Chromatographic separation was performed on a reverse phase Thermo hypersil BDS C18 column. The mobile phase consisted of mixture of acetate buffer (10 mm) pH 6 and acetonitrile in ratio of 35 : 65 respectively at a flow rate of 1.0 mL/min. The wavelength

used for the detection of Efonidipine was 254 nm. The retention times of Efonidipine was found to be 8.3 min.

(b) Stability indicating analytical method of Efonidipine has been developed according to the ICH guidelines. Degradation was carried out under following conditions:

- For hydrolytic and oxidative conditions degradation were tried as :
- Acidic –Drug was subjected to 1 M HCl at 60˚C for 6 hrs Solution was neutralized by sodium hydroxide and diluted with mobile phase. No degradation was observed.
- Alkaline – Drug was subjected to 0.5 M NaOH at room temperature for 18 hr. Significant degradation was observed .Five degradation products were formed.
- Oxidation – Drug was subjected to 10 % hydrogen peroxide at room temperature for 24hrs hrs. No degradation was observed.
- Thermal – Drug was subjected to thermal degradation at 80ºC for 15 days. Slight degradation was observed.
- Photostability condition- Drug (in dry and solution) was subjected to degradation in photostability chamber for 21 days. No degradation was observed in degradation in dry state. Slight degradation was in solution with the formation of three degradation products.
- To resolve the degradation products in alkaline and photolytic condition method was modified to gradient method.
- Degradation products in alkaline and oxidative conditions conditions were characterised by LC-MS/MS method.

A gradient specific stability indicating high performance liquid chromatographic method was developed for the determination of Efonidipine. Reverse phase chromatography was performed on Shimadzu LC-20 AD pump (binary) and Shimadzu PDA M-20A Diode Array Detector using Thermo Hypersil BDS C-18 column (250X 4.6 mm, 5µm) with UV detection at 254 nm was used. A gradient programme was run at flow rate of $1 ml min^{-1}$. Mobile phase A consisted of acetate buffer(10 mm) pH 6:. Mobile phase B consisted of acetonitrile. Efonidipine was subjected to stress conditions such as acidic, alkali, oxidation, photolysis and thermal condition. The drug showed significant degradation in alkaline. The drug showed slight degradation in photolytic and thermal condition.

WORK IN PROGRESS

- Degradation kinetics study of Efonidipine and validation of developed method as per ICH guidelines
- Development of stability indicating method of Riociguat
- Development of stability indicating method by HPTLC
- Evaluation of data and final compilation of results

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