

“Impurity Profile Study of Aspirin in Bulk and Tablet Dosage Forms”

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Abstract

Aspirin is one of the most frequently used and cheapest drugs in medicine. It belongs to the non-steroidal anti-inflammatory drugs with a wide range of pharmacological activities, including analgesic, antipyretic, and antiplatelet properties. Currently, it is accepted to prescribe a low dose of aspirin to pregnant women who are at high risk of preeclampsia (PE) because it reduces the onset of this complication. Drug produce degradation profiles essential to establish to monitor the stable formulation and provide appropriate drug shelf life valuation. Structural description of impurities and degeneracy production in bulk API has become integral part of pharmaceutical product development. The study of these minor leveled unidentified impurities and degradant are very challenging. Various regulatory bodies related International Council for Harmonisation, United States Food and Drug Administration.

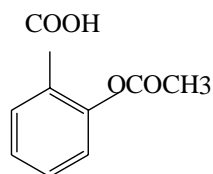
Keywords: Aspirin, Drug, Impurity, Degradation, ASA, Chemical Composition.

INTRODUCTION

Aspirin / acetylsalicylic acid (ASA) is a medicine used to lessen torment, fever, or irritation. Anti-inflammatory medicine was first disconnected Felix Hoffmann, a physicist was the German organization Bayer in 1897. Various medications that are accessible in market today were found from common sources. A significant model is the ibuprofen, which shows pain relieving movement. It is so far the world's most popular and most all around utilized therapeutic operator. Its source is from the plant genera Salix spp. also, Populus spp. what's more, it is identified with salicin.[1]

Chemical Composition

Structural Formula -



Molecular Formula – C₉ H₈ O₄

Molecular Weight -180.00

Impurity Profile

Impurity profiling is the universal term of a class of analytical activities, the purpose of which is the exposure, identification/structure explanation and measurable resolution of organic and inorganic contaminations just as remaining solvents in bulk drugs and pharmaceutical formations.[2]

The highest relevant application in the drug identification is safety related, no more individual of the drug but further impurities also degraded products present in them. Impurities today in the drug may lead to cytotoxicity, carcinogenic or teratogenic effects. For diseases like hypertension or diabetes which are related to change in body physiology, patient for his rest of life is going to be on medication. Though the amount of impurities is very minute still prolong exposure to them may be hazardous. Hence identification and the check on presence of specific amount is must. Drug produce degradation profiles essential to establish to monitor the stable formulation and provide appropriate drug shelf life valuation. [3]Structural description of impurities and degeneracy production in bulk API has become integral part of pharmaceutical product development.

Importance of Impurity Profile Study

Major parts for pharmaceutical industries are product property, safeness and potency of drug. Stability of the drug is a quality attribute, which is associated with drug substance or drug products on account of purity, strength, identity, safety, apparent, chemical, physical, microbiological change, and they affect on the biological performance of drug product. Any variations in quality attributes of drug product with time are mandatory and it is directly proportional to safeness and potency of the drug.

Forced Degradation Study

Stress study is a degeneracy of new medicament substance and medication product at conditions more severe than forward conditions. Constrained debasement considers show the synthetic presentation of the particle which thusly helps in the advancement of formulation and package. As analysis of dosage forms under stability study is an important. [4]Forced degradation studies appearance the chemical performance of the atom which is turn use in the improvement of formulation. In addition, the regulative guidance was very broad and does not explain about the work of stress studies.

Constrained debasement readings gives information to support identification of thinkable degradant; degradation paths and vital stability of the medication molecule and validation of stability representing analytical processes. A draft guidance document recommends results of one-time stress studies should include in Phase III Investigational New Drugs. NDA enrolment needs data of information of stress study concentrates as constrained debasement items, debasement response energy, structure, drug peak purity and mass balance etc. This forced degradation study offer data about stress study pathways of API, alone and in drug item, any conceivable polymorphic or enantiomeric substances and change between drug related debasement and excipient interferences. [5]

MATERIALS AND METHODS-

Chemicals and reagents-

Aspirin Bulk was procured from (Altas Laboratory, Mumbai, Maharashtra), Aspirin Tablet 150 mg was purchased from (USV Ltd., Mumbai, Maharashtra), HPLC grade Acetonitrile was purchased from (Molychem, Mumbai, Maharashtra). HPLC grade Methanol was procured from (Datta Sugar Factory, Shirol, Kolhapur, Maharashtra), Additionally Hydrogen peroxide, Sodium hydroxide and Hydrochloric acid were purchased from (Pallav Chemicals & Solvents

PVT, Boisar, Mumbai, Maharashtra)

Methods-

1. Identification Tests-

A gift sample (Aspirin) was determined by infrared absorption spectrophotometer. The dried compound was triturated with KBr and pellet was prepared using KBr press.[6] The IR was obtained by using the equipment JASCO FTIR-410 at A.B.C.P., Sangli. Compare the spectrum with that obtained with aspirin RS or with the reference spectrum of aspirin.18

Tests for Aspirin

A. Appearance of solution.

To the test solution, 5% solution in ethanol were added and observed whether it gives clarity or not. 18

B. Clarity of solution in alkali.

To the test solution, 5% solution in a warm 5% solution of Na_2CO_3 were added and observed whether it gives clarity or not. 18

C. Limit test for Arsenic.

Disintegrate the given sample in 50 ml water and include 10 ml of stannated hydrochloric acid and move into the arsenic contraction bottle. Include 5 ml of 1 M potassium iodide and 10 g of zinc dust. Promptly amass the mechanical assembly and submerge the container in a water shower at a temperature with the end goal that a uniform advancement of gas is kept up. Following 40 minutes watch the stain made on the mercuric chloride paper.

D. Chlorides Limit test.

Break down the given sample in 20 ml of water and move to a Nessler cylinder. Include 10 ml of weakened nitric corrosive, weaken to 50 ml with water. Include 1 ml of 0.1 M silver nitrate. Blend expeditiously with a glass shaft and permit to represent 5 minutes, protected from light. View temporarily against a dark foundation 18

E. Sulphates Limit test.

To 1.0 ml of a 25.0% w/v solution of barium chloride in a Nessler cylinder include 1.5 ml of ethanolic sulfate standard solution (10 ppm SO_4), blend and permit to represent 1 moment. Break down the given sample in 15 ml of water and include 0.15 ml of 5M acidic corrosive, pour the arrangement in the Nessler cylinder. Add adequate water to deliver 50 ml, mix quickly with a glass pole and permit to represent 5 minutes and saw transitionally against a dark back ground.18

F. Readily carbon stable substances.

Test solution was treated with sulphuric acid to check whether it shows any color produced or not. 18

2. Melting Point-

Capillary strategy was utilized to decide melting point. Drug filled in capillary and capillary dipped in melting point test apparatus. Uniform heating provided to test sample and melting point observed using thermometer. 18

3. UV spectroscopy 19

UV method was used to record absorbance.

Selection of solvent:

Selection of solvent depends on the dissolvability of the Aspirin. From the literature review, it was discovered that drug is soluble in Ethanol and Methanol, dissolvable in chloroform and ether. Here Ethanol is used as solvent

Preparation of stock solutions:

A standard stock solution of Aspirin was set up by dissolving 1 mg of the drug in 10 ml of ethanol in separate volumetric flask to create a concentration of 100 µg/ml

Determination of wavelength (λ max):

A stock solution containing 100 µg/ml of the medication was prepared in ethanol. Taking the absorbance of prepared solution and determine the wavelength having maximum absorbance. The solution was scanned on spectrophotometer into the UV range 200nm – 400nm. In present study the optimal wavelength selected for detection was 276 nm Aspirin respectively.

Calibration curve of Aspirin:

Weighed amount 1 mg of Aspirin dissolved in ethanol to obtain 100ml solution. This standard solution further diluted to obtain concentration of 2, 4, 6, 8, 10 µg/ml. Absorbance checked measured against blank using 276 nm using UV spectrometer. The UV spectrum was performed by using UV spectrophotometer (JASCO V- 730) at A.B.C.P., Sangli.

4. Thin Layer Chromatography Analysis-

TLC was performed on silica gel-G plates with suitable solvent system. Identification of functional group containing Aspirin. To check purity of given sample.

5. OPTIMIZING METHOD FOR FORCED DEGRADATION OF ASPIRIN & ITS TABLET DOSAGE FORM 19,20, 21, 22, 23

Preliminary study:

In the preliminary examination, observations are made about sample stability, including exposure of solid state tests to heat and light and exposure of solutions for various pH and oxidative conditions. Preliminary study can also be used to aid in the improvement of an degradant products or impurity profiling.

Different types of degradation conditions are as follows:

1• Hydrolytic degradation -

Alkali degradation study (NaOH)

2• Oxidative degradation (H₂O₂)

A) HYDROLYTIC DEGRADATION (Alkali degradation NaOH)

The alkaline debasement of medication in fundamental condition can be concentrated by refluxing the medication in 0.1 N NaOH. First into 100ml volumetric flask, accurately weighed 1gm of bulk drug was dissolved with 10 ml of ethanol. It was observed that 30 ml of 0.1N sodium hydroxide at 400c for eight hour time interval was discovered to be critical for getting degradation in the series of 5-20% as per International Conference of Harmonization guidelines [2, 5] (Table 7 and Fig. 5, 6) 20% guideline. (fig.3)

B) OXIDATIVE DEGRADATION (Method First)

Hydrogen peroxide was common oxidant to produce oxidative degradation. In a 100ml RBF, accurately weighed 1gm of bulk drug was dissolved with 10 ml of ethanol. It was observed that 30 ml of 3 % H₂O₂ at 300c for 6 hours time interval was discovered to be critical for getting degradation in that range of 5-20% as stated by ICH guidelines [2, 5] (Fig. 4)

OXIDATIVE DEGRADATION (Method Second)

1. Selection of an oxidizing form, its concentration, and conditions depends upon the drug substance.
2. It was reported that into 100ml volumetric flask accurately weighed 1gm of bulk drug was dissolved with 10 ml of ethanol. It was observed that 30 ml of a 3 % H₂O₂ at RT for 7 days time interval was observed to be critical for getting degradation into the range of 5-20% as stated by ICH guidelines.
3. The oxidative degradation includes an electron transfer system to form reactive anions as well as cations. Sulfides, Amines with phenols also susceptible to electron move oxidation gives- N- oxides, hydroxylamine, sulfones and sulfoxide.

6. Identification of Degradation Products:

For the stress study various chromatographic techniques are used.

Chromatographic Techniques-

A) High Performance Liquid Chromatography (HPLC):18, 24

| Chromatographic mode | Chromatographic condition |
|----------------------|--|
| Instrument used | Thermo scientific-HPLC with Pump 2080 Plus, Detector UV 2000 plus |
| Stationary phase | CHEMSI/OBS - C18 (4.6 mm × 250 mm) 5µm |
| Mobile phase | 0.2v orthophosphoric acid:40v acetonitrile:60 v water. |
| Standard solution | 1000 µg/ml |
| Detection wavelength | 237 nm |
| Flow rate | 1 m/min |
| Sample size | 10 µl |

Selection of Chromatographic Condition

The preliminary steps involving of collect more information about the analyte in regard to the Physicochemical properties (pKa, log P, Solubility) and appropriate wavelength. The chromatographic factors, for example mobile phase, stationary phase, flow rate, solvent ratio were considered. The subsequent chromatogram was recorded. The chromatographic parameters were like retention time, capacity factor, theoretical plates, peak symmetry, tailing factor, etc. for pure drug with tablet dosage form was calculated and the condition that gave best balance and limit factor was decided forestimation.

Optimization of Chromatographic Parameters

Optimizations in HPLC are the method of finding a set of chromatographic conditions that sufficiently enable the quantification of the analyte with satisfactory exactness, accuracy, affectability, explicitness, cost, ease and speed.

Optimization of Mobile Phase Strength

As it was necessary to obtain a good resolution of active drug from its impurity product, various mobile phase combination containing, methanol: water and acetonitrile: water in various proportions was trying to get higher retention time however, the goal was not discovered to be good. At long last, mobile phase containing orthophosphoric acid: Acetonitrile: Water was establish to give satisfactory retention time is 5.825 for further resolution from impurityproducts.

Selection of Detection Wavelength

In case of impurity study a wavelength for UV detection must be chosen so that an accurate mass balance was determined. It was quite difficult to select a wavelength at which adequate response is obtained for active drug within the presence of its impurity, because the impurity have different electron donating and electron withdrawing functional groups joined to the aromatic ring, the absorption spectra shifted to shorter wavelength compare to parent compound. In the current study of drug and its impurity the optimal wavelength selected for detection was 237 nm.

B) Thin layer chromatography:

It is utilized to isolate mixtures of substances into mixtures of substances into individual components. TLC was performed using silica gel G as adsorbent. Silica gel Slurry was prepared in distilled water. silica gel was set up in refined water. The slurry was applied to get a flimsy layer of 0.2 mm thickness over a clean and dry glass plate (7.5X2.5 cm). The plates were air dried and afterward activated at 100C for one hour. The sample was applied by applicator. The slide was kept for development in solvent system. Numbers of solvent systems were used for obtaining better resolution of components. The final solvent system was acquired by experimentation basis and depending upon previous literature. Better resolution of components was observed in solvent system Ethyl acetate: Toluene: Formic acid (8:5:3:1). Total 5 bands were observed. The details of TLC are given below:

Adsorbent: Silica gel G (activated)

Thickness: 0.2 mm

Plate size: 7.5X2.5 cm

Activation temperature: 100C for thirty minutes

Solvent system: Ethyl acetate : Formic acid (8:2)

7) Characterization of major Impurities: 18, 24, 25

IR Study of Degraded Product-

Infrared spectroscopy is remarkable analytical techniques which offer the chance of chemical structural identification. IR helps to identify the functional groups in the structure of compound. The degraded compound from the various degradation methods was scanned.[6] The IR was obtained by using the equipment JASCO FTIR-410 at Rajarambapu college of pharmacy, Kasegaon, Sangli, Maharashtra, India.

RESULT AND DISCUSSION-

IR Study of Degraded Product-

Infrared spectroscopy is remarkable analytical techniques which offer the chance of chemical structural identification. IR helps to identify the functional groups in the structure of compound. The degraded compound from the various degradation methods was scanned. The IR was obtained by using the equipment JASCO FTIR-410 at Raja ram Babu college of pharmacy, Kasegaon.[14]

Table 1. Physical and Chemical Tests for Aspirin

| Test | Observation | Inference |
|----------------------------|--|----------------------------|
| Chemical evaluation | | |
| Appearance of solution | Clear | Confirmed |
| Clarity of solution | Clear | Confirmed |
| Solubility | Freely soluble in Ethanol & Methanol, soluble in chloroform & sparingly soluble in ether, Slightly soluble in water. | Confirmed |
| Limit test for Arsenic | Yellow color | Arsenic might be present |
| Limit test for Chloride | Gives Opalescence | Chloride might be present |
| Limit test for Sulphates | Gives Turbidity | Sulphates might be present |
| Physical evaluation | | |
| Melting Point | 135 ^o c | Confirmed |

Based on physical and chemical evaluation it was confirmed that the given sample is Aspirin.[15-16]

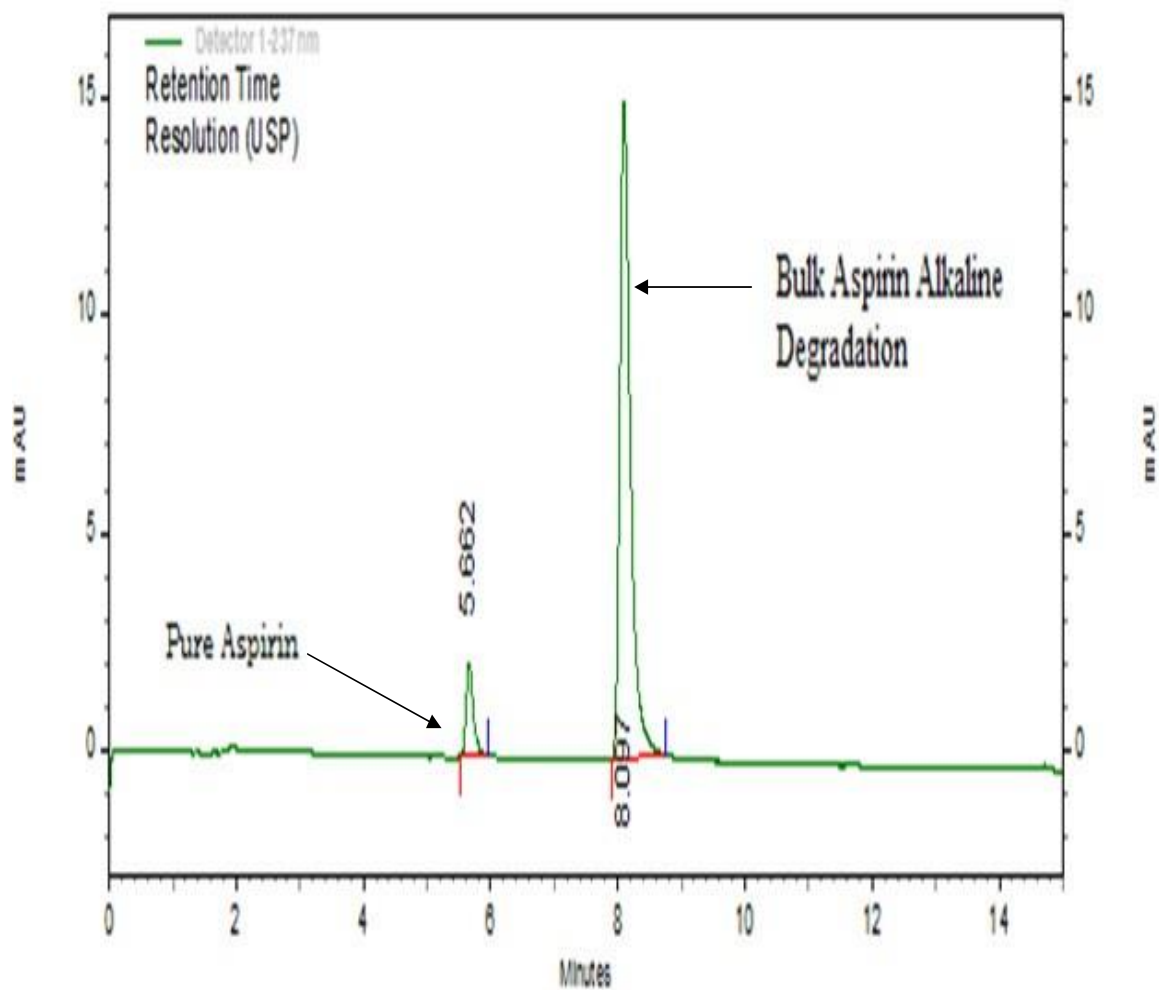


Fig. 2 Chromatogram representing Aspirin and its alkaline degradation products at 0.1 N NaOH.

| Name | Retention Time | Area | %Assay | %Degradation |
|-----------------------------------|----------------|--------|--------|--------------|
| Bulk Aspirin Alkaline degradation | 8.212 | 126654 | 37.49% | 62.51% |

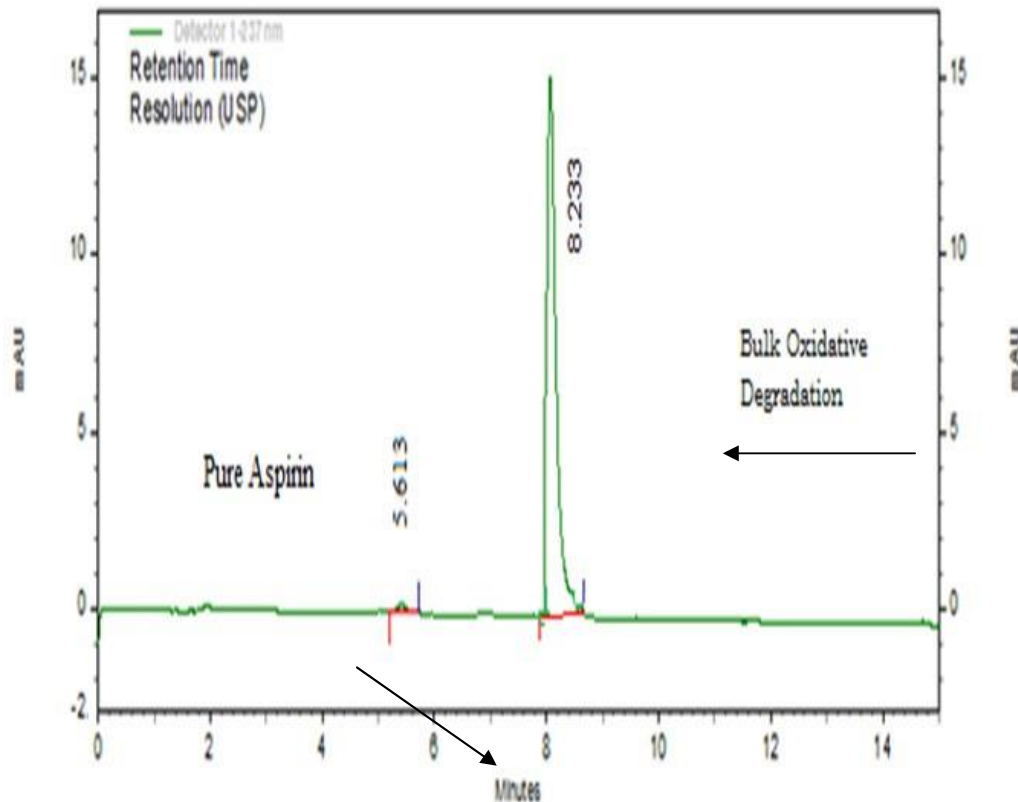


Fig. 3 Chromatogram representing Aspirin and its oxidative degradation products at 3 % H₂O₂.

| Name | Retention Time | Area | %Assay | %Degradation |
|---------------------------------------|----------------|--------|--------|--------------|
| Bulk Aspirin oxidative degradation | 8.097 | 242823 | 71.88% | 28.22% |

CONCLUSION-

Aspirin is Antirheumatic, Antithrombotic and Anti-inflammatory medication. Aspirin's capacity to decrease the production of thromboxanes and prostaglandins is because of its irreversible inhibition of COX enzyme. In present work, for analysis of Aspirin absorbance maxima was discovered to be 276 nm. For stability study conditions were optimized so that degradation between 5-20% of Aspirin can be achieved as per the ICH requirement. In the present work a detailed study and systematic profiling of impurity and degradation behavior of Aspirin have been completed by various techniques like TLC, FT-IR and GCMS is pending. Stress studies were completed to facilitate the advancement of stability indicating assay method (SIAMs) and to gain a better understanding of stability of Finished Pharmaceutical Product & API, to identify and quantify degradation products and to build up degradation pathways of degradation products formed during stress degradation. Significant degradation products were confined based on degradation kinetic study and were characterized.

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CONFLICT OF INTEREST-

The author has no conflicts of interest in the present review.

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