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DRUG DEGRADATION: BY USING DIFFERENT BRANDS OF PARACETAMOL

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***Abstract*— The objective of this study is to analysed force degradation studies by treating the different brands of Paracetamol under hydrolytic (acidic and basic), photolytic nd thermal stress condition by using spectrophotometer, as define under International Conference on Harmonisation guidelineQ1A(R2).**

According to specification of United state of pharmacopoeia, the content official limit of not less than (98%) and not more than (110%) the label amount. Our hypothesis was that when all the brands of paracetamol (pacimol, febrex and pyrigesic) where exposed to different degradation parameters. The result of study conclude that when different brand of paracetamol where treated with 0.1N HCl and 0.1N NaOH degradation was observe in all the three brands. Whereas when the three brands were expose to ultraviolet light slight degradation where observed while no degradation is observe when expose to heat.

Index Terms— **DRUG DEGRADATION, Pacimol, Febrex, Pyrigesic, spectrophotometer.**

I. INTRODUCTION

Chemical stability of pharmaceutical molecules is a matter of great concern as it .The FDA and ICH guidances state there requirement of stability testing data to understand and how the quality of a drug substance and drug product changes with time under the influence of various environmental factors. Knowledge of the stability of molecule helps in selecting proper formulation and package as well as providing proper storage conditions and shelf life,which is essential for regulatory documentation. Forced degradation is a process that involves degradation of drug products and drug substances at conditions more severe than accelerated conditions and thus generates degradation products that can be studied to determine the stability of the molecule. The ICH guideline states that stress testing is intended to identify the likely degradation products which further helps in determination of the intrinsic stability of the molecule and establishing degradation path ways, and to validate the stability indicating procedures used.

II. TIME TO PERFORM FORCED DEGRADATION

It is very important to know when to perform forced degradation studies for the development of new drug substance and new drug product. FDA guidance states that stress testing should be performed in phase III of regulatory submission process. Stress studies should be done in different pH solutions, in the presence of oxygen and light, and at elevated temperatures and humidity levels to determine the stability of the drug substance. These stress studies are conducted on a single batch.

One of the most common symptoms is pain and this is one of the most frequent reasons why people seek medical care. Therefore, it is not surprising that the analgesics are among the most widely used categories of drug. Hence, for the treatment of inflammation and pain, paracetamol is used, and chemically paracetamol (4-hydroxyacetanilide) is used. Paracetamol is a weak peripheral cycloxygenase inhibitor and from the inhibition of prostanoid synthesis in the central nervous system, analgesic effect of paracetamol may arise. Antipyretic effect of paracetamol is reported to inhibit prostaglandin synthesis at the level of the hypothalamus causing alteration in body temperature.

In many laboratories spectrophotometric method was used due to less equipment cost and economical maintenance advantages. By the help of this technique, the UV absorbance spectra are measured at 200–380 nm.

Table 1: Condition mostly used for forced degradation studies

Degradation type	Experimental condition	Storage condition	Sampling time(days)
Hydrolysis	Control API(no acid or base) 0.1 M HCI 0.1 M NaOH Acid control(no API) Base control(no API) pH:2,4,6,8	40°C, 60°C 40°C, 60°C 40°C, 60°C 40°C, 60°C 40°C, 60°C 40°C, 60°C	1.3.5 1,3,5 1,3,5 1.3.5 1.3.5 1.3.5

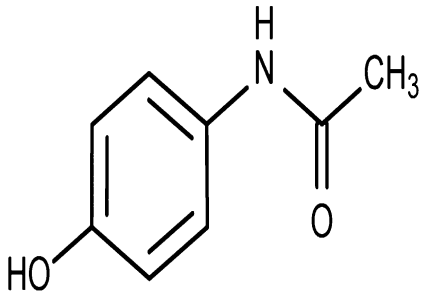
Oxidation	3% H_2O Peroxide control Azobisisobutyronitrile(AIBN) AIBN control	25°C, 60°C 25°C, 60°C 40°C, 60°C 40°C, 60°C	1,3,5 1,3,5 1,3,5 1,3,5
Photolytic	Light 1 × ICH Light 3 × ICH Light control	NA NA NA	1,3,5 1,3,5 1,3,5
Thermal	Heat chamber Heat chamber Heat chamber Heat chamber Heat control		1,3,5 1,3,5 1,3,5 1,3,5 1,3,5

In accordance with the International Conference on Harmonization guideline, the force degradation state of active pharmaceutical substance includes acidic, basic and photolytic conditions. For the estimation of forced degradation of a pharmaceutical ingredient, acid/base stress testing is performed. By exposure to acidic or basic medium over time to its chief degradation products, this test involves degradation of a drug substance.

III. DRUG PROFILE

Paracetamol, also known as acetaminophen, is a medicine used to treat pain and fever. It is typically used for mild to moderate pain relief. Paracetamol is also used for severe pain such as cancer pain and pain after surgery. It is typically used for either by mouth or rectally but is also available intravenously. Effects last between two and four hours.

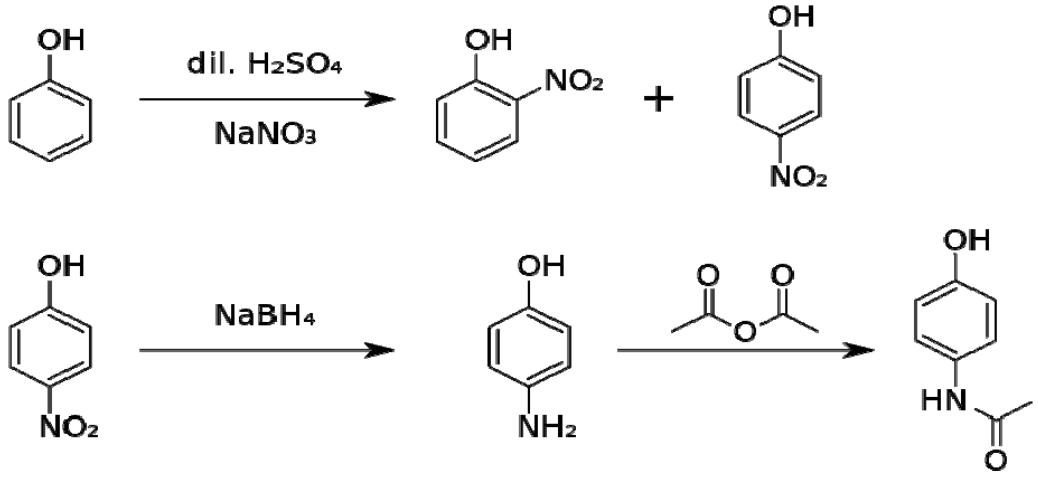
The molecular formula is C8H9NO2 and molecular weight 151.163 g/mol. It has an absolute bioavailability of 63-89% and metabolism predominantly takes place in liver. After being taken by mouth it is rapidly absorbed by the gastrointestinal (GI) track (although absorption through the stomach is negligible); its volume of distribution is roughly 50 L.



The concentration in serum after a typical dose of paracetamol usually usually peaks below 30 µg/ml(200 µmol/l).After four hours the concentration is usually less than 10 µg/ml(66 µmol/l).

Paracetamol consist of a benzene ring core, substituted by one hydroxyl group and the nitrogen atom of an amide group in the para pattern. The original process for production involves the nitration of phenol with sodium nitrate give a mixture of two isomers, from which the wanted 4-nitrophenol (BP 279 °C) can easily be separated by steam distillation.

In this electrophilic aromatic substitution reaction, phenol's oxygen is strongly activating thus the reaction required only mild conditions as compared to nitration of benzene itself. The nitro group is then reduced to an amine, giving 4-amineo phenol. Finally, the amine is acetylated with acetic anhydride.



IV. PRODUCT

A. Pacimol

Each uncoated tablet contains Paracetamol IP 500 mg
Batch no.- GR267193AZ
MFD- 11/2017
Exp. Date -10/2020
Manufacturing company- Ipac laboratories limited

B. Febrex

Each uncoated tablet contains paracetamol IP 500mg
Batch no.-FAL2F64
MFD-06/2016
Exp.Date-05/2019
Manufacturing company- INDOCO REMEDIES LTD.

C. Pyrigesic

Each uncoated tablet contain paracetamol IP 500mg
Batch no.-DF7044
MFD-03/2017
Exp.Date-02/2020
Manufacturing company- EAST INDIA PHARMACEUTICAL WORKS LIMATED.

AIM: To investigate the forced degradation study of different brands of paracetamol for the determination of the degradation of the drug substance.

V. OBJECTIVES

[1] To establish degradation pathways of Paracetamol and its drug product.
[2] To determine the intrinsic stability of Paracetamol in formulation.
[3] To reveal the degradation mechanism such as hydrolysis, oxidation, thermolysis or photolysis of paracetamol and its product.

VI. MATERIAL AND REAGENTS

The reagents use were 0.1N Hydrochloric acid, 0.1 N Sodium hydroxide de-ionized water or distilled water, all the reagents were of analytical grade and the active use was in the form of different brands of Paracetamol (pacimol-500mg Ipca Laboratories Ltd.,febrex-500mg INDOCO REMEDIES LTD., Pyrigesic-500mg EAST INDIA PHARMACEUTICAL WORKS LIMITED).

A. Glasswares:

Volumetric flask, test-tubes, beakers, measuring cylinders, pipette.

All these glasswares are washed properly (rinsed with deionized water which was freshly prepared in the laboratory)

B. Instruments used:

Digital Weighing balance, UV visible spectrophotometer: (UV-1601), Electric Water bath

VII. PREPARATION OF WORKING SOLUTIONS:

A. Preparation of NaOH

In 100 ml volumetric flask, accurately 40 g NaOH was dissolved and to make up the volume up to 100 ml, de-ionized water was added.

B. Preparation of HCl

A total of 8.36ml hydrochloric acid (37% 12 mol/L) was took accurately analytical grade in 100 ml volumetric flask to make up the volume up to 100 ml by adding de-ionized water.

C. Preparation of paracetamol solution

The tablets of each of the brands were weighed individually. Each brand of tablets was triturated in mortar pestle individually. Powder was equal to 20 mg of paracetamol. Pacimol (11.0 mg), febrex (11.6 mg), pyrigesic (11.0 mg) were accurately weighed. In the 100 ml volumetric flask, all of 3 brands powders transferred individually. These powder samples were dissolved and shaked with water and finally more water was added to make up the volume up to 100 ml respectively for each sample. A total of 20 mg/100 ml concentration solution was preferably obtained. By using spectrophotometer at 294 nm wavelength individually all brands absorbance were determined.

VIII. PROCEDURE FOR FORCE DEGRADATION STUDIES

A. For acid

Forced degradation of drug substance in acidic media was performed by taking 5 ml of 20 mg/100 ml of pacimol, febrex and pyrigesic in 3 separated test tubes, then 5 ml of 1 mol/L HCl was added in each test tube. The sample was left for 30 min. Solution was transferred to a separated cuvette after the time period completion and UV absorbance of the solution was measured at the 256 nm wavelength.

B. For base

Forced degradation of drug substance in basic media was performed by taking 5 ml of 20 mg/100 ml solution of pacimol, febrex and pyrigesic in 3 separated test tubes, then 5 ml of NaOH was added in each test tube and the sample was left for 30 min, and then UV absorbance of solution was measured at 256 nm wavelength.

C. For UV light

Forced degradation of drug substance in UV light was performed by taking the 5 ml of 20 mg/100 ml solution of pacimol, febrex and pyrigesic, then 5 ml of water was added in each test tube and these test tubes were exposed to UV light for 30 min, and then UV absorbance of solution was measured at 256 nm wavelength.

D. For heat

Forced degradation of drug substance in thermal/humidity environment was performed by taking 5ml of 20 mg/100 ml solution of pacimol, febrex and pyrigesic, then in each test tube, 5 ml of water was added and kept in water bath at 50°c for 30 minutes and UV absorbance of solution was measured at 256 nm wavelength.

IX. RESULT

We have conducted the degradation study on three brands of paracetamol using pacimol 500mg tablets of Ipca laboratories LTD., febrex 500mg tablets of INDOCO REMEDIES LTD., pyrigesic 500mg tablets of EAST INDIA PHARMACEUTICAL WORKS LTD. Table 2 represent absorbance of different brand of paracetamol under different condition. When brand of paracetamol (pacimol, febrex and pyrigesic) were subjected to 0.1N HCl, absorbance decreases.

When brands of paracetamol(pacimol, febrex and pyrigesic) were treated with 0.1N NaOH, absorbance increases greatly. When pacimol, febrex and pyrigesic were expose to UV-light there is slight decrease in absorbance. When pacimol, febrex and pyrigesic were subjected to heat at for 30 minutes, it show negligible changes in absorbance.

Table 2: Absorbance of different brands of paracetamol

Treatment	Pacimol	Febrex	Pyrigesic
Before	2.95	2.95	2.834
After Acid	2.515	2.68	2.408
After base	3.311	3.67	3.61
After heat	2.887	2.883	2.757
After UV	2.834	2.68 2	2.737

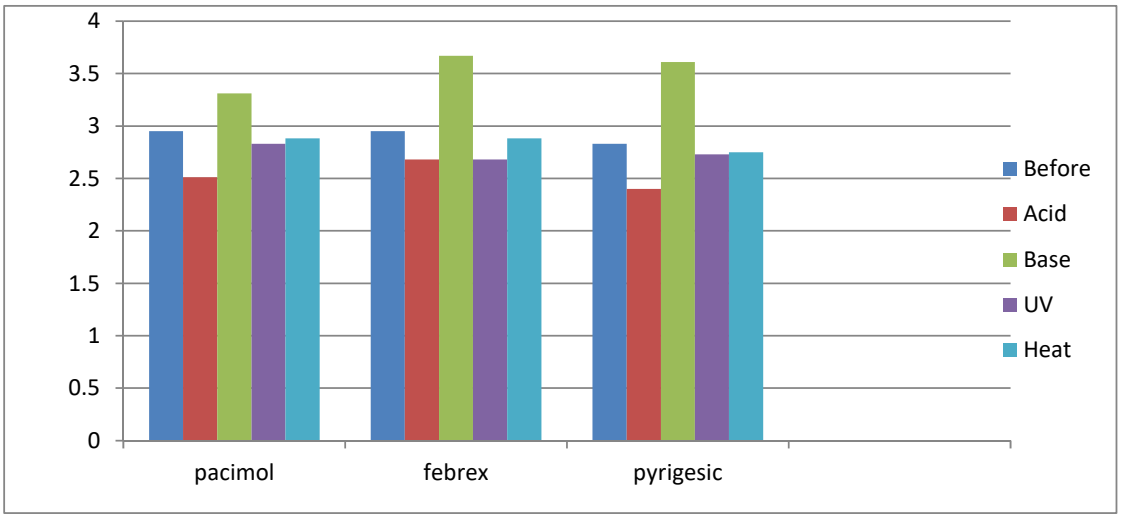


Figure 1: Degradation pattern of different brands of paracetamol

Table 3 Percentage degredation of different brands of paracetamol

PARAMETER	Pacimol	Febrex	Pyrigesic
Acid	85.25	90.84	84.96
Base	112.23	124.40	127.38
UV	96.06	90.91	92.77
Heat	97.86	97.72	97.28

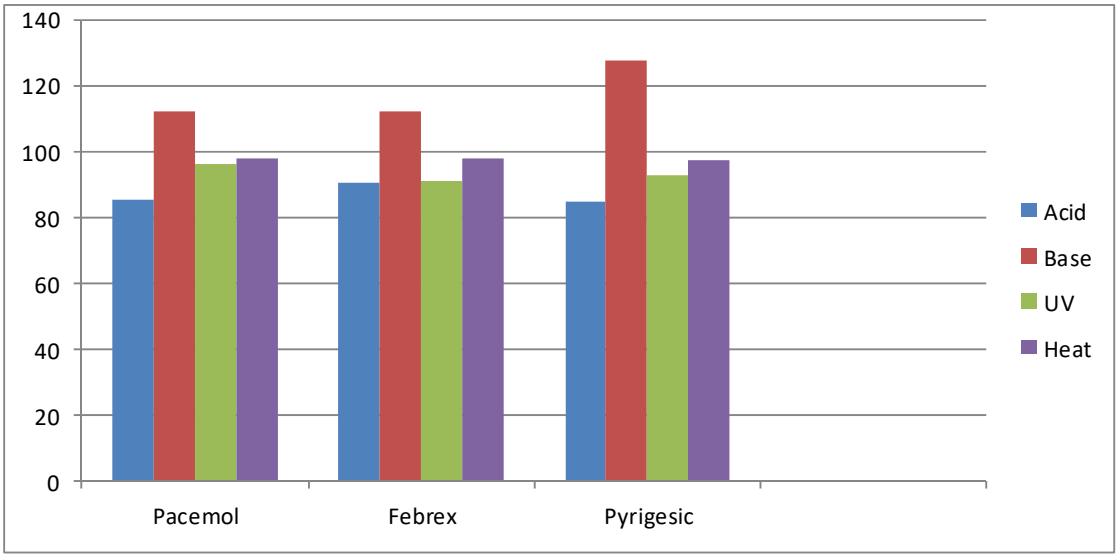


Figure 2 : Percent degredation pattern of different brands of paracetamol

X. CONCLUSION:

According to specification of United State Pharmacopoeia, the content official limit of not less than (98%) and not more than (101%) the label amount. Our hypothesis was that when all the brands of paracetamol were expose to different degradation parameters. The result of study concludes that when different brand of paracetamol were treated with 0.1N HCLand 0.1N NaOH, degredation was observe in all the three brands, Whereas when the different brands(pacimol, febrex and pyrigesic) were expose to ultraviolet light slight degradation were observed while no degradation is observe when expose to heat.

XI. REFERENCE :

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