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Development and Stability of Forced Degradation Studies Indicating Different Brands of Metformin Drugs

A. J. Giri[1], Anjali D Kingre[2], J. K. Dhumal[3], P. R. Doifode[4], Pratiksha Jaybhaye[5], P. R Tathe[6]
Samarth College of Pharmacy Deulgaon Raja, Buldhana, Maharashtra, India[1,2,3,4,5]
Research Scholar, Shri JJT University, Rajasthan[6]

Abstract: *In present study, Accouring to specification of Indian pharmacopeia the content official limit of not less than (98.5%) and not more than (101.0%) of the lable amount our hypothesis was that when all different brands of metformin were expose to the different degradation parameters. The Forced degradation studies show the chemical behavior of the molecule which in turn helps in the development of formulation and package. A forced degradation study is an essential step in the design of a regulatory compliant stability program for both drug substances and products, and formalized as a regulatory requirement in ICH Guideline Q1A in 1993. Forced degradation is a degradation of new drug substance and drug product at conditions more severe than accelerated conditions.*

Keywords: Drug Degradation, mineral oils, lipogels, Forced, Organic solvent etc.

I. INTRODUCTION

Drug degradation in Semisolid dosage form frequently resembles. The drug degradation is solution, particularly in that dosage form that consists of one liquid phase, such as gels. Gels are semisolid drug dosages that can be as soft as easily or as hard as solid. It mainly consists of liquid, but performs like solid due to a three-dimensional network within the liquids. Thus, form of drug stability point of view gels is single phase liquid state. ex. hydrogen can consist of 99.9% water and only 0.1 % water soluble Polymers that form the network.

Drug degradation in hydrogels follows the same Kinetic and degradation mechanism as in aqueous solution. Organogels (sometimes referred to as oleo gels or lipogels) are gel in which the homogenous liquid phase consists of non-aqueous solvent, search as an organic solvent, Mineral oil or vegetable oil. Ointment consists of single-phase bases in which drug are dispersed. Ointment bases can consist of liquid paraffin or vegetable oils with emulsifying agents (water-emulsifying ointments) or without emulsifying agents (hydrophobic ointments) or with water soluble bases, such as macrogols (hydrophilic ointments). Chemical stability of pharmaceutical molecules is a matter of great concern as it affects the safety and efficacy of the drug product. The FDA and ICH guidance's state the requirement of stability test in data to understand how the quality of adrug substance and drug product changes with time under the influences of various environmental factors. Knowledge of the stability of molecules 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 pathways, and to validate the stability indicating procedures used. But these guidelines are very general in conduct of forced degradation and do not provide details about the practical approach towards stress testing. Although forced degradation studies are a regulatory requirement and scientific necessity during drug development, it is not considered as a requirement for formal stability program.

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It has become mandatory to perform stability studies of new drug moiety before falling in registration dossier. The stability studies include long term studies (12 months) and accelerated stability studies (6 months). But intermediate studies (6 months) can be performed at conditions milder than that used in accelerated studies. So, the study of degradation products like separation, identification and quantitation would take even more time. As compared to stability studies, forced degradation studies help in generating degradants in a much shorter span of time, mostly a few weeks. The samples generated from forced degradation can be used to develop the stability indicating method which can be applied later for the analysis of samples generated from accelerated and long-term stability studies. This review provides a proposal on the practical performance of forced degradation and its application for the development of stability indicating method.

II. OBJECTIVE

Forced degradation studies are carried out to achieve the following purposes:

- To find degradation pathways of drug substances and drug products.
- To differentiate degradation products that are related to drug products from those that are generated from non-drug products in a formulation.
- To clarify the structure of degradation products.
- To determine the intrinsic stability of a drug substance in formulation.
- To expose the degradation mechanisms such as hydrolysis, oxidation, thermolysis or photolysis of the drug substance and drug product.
- To establish stability demonstrating the nature of a developed method.
- To understand the chemical properties of drug molecules.
- To generate more stable formulations.
- To produce a degradation profile similar to that of what would be observed in a formal stability study under ICH conditions.
- To solve stability-related problems.

III. TIME TO PERFORM FORCED DEGRADATION

It is very important to know when to perform forced degradation studies for the development of new drug substances and new drug products. FDA guidance states that stress testing should be performed in phase III of the 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. The results should be summarized and submitted in an annual report. However, starting stress testing early in preclinical phase or phase I of clinical trials is highly encouraged and should be conducted on drug substance to obtain sufficient time for identifying degradation products and structure elucidation as well as optimizing the stress conditions. An early stress study also gives timely recommendations for making improvements in the manufacturing process and proper selection of stability-indicating analytical processes.

IV. LIMITS FOR DEGRADATION

The subject of how much degradation is sufficient has been the matter of many negotiations amongst pharmaceutical scientists. Degradation of drug substances between 5% and 20% has been accepted as practical for validation of chromatographic assays. Some pharmaceutical scientists think 10% degradation is optimal for use in analytical validation for small pharmaceutical molecules for which acceptable stability limits of 90% of label claim is common. Others recommended that drug substances spiked with a mixture of known degradation products can be used to challenge the methods employed for monitoring stability of drug products. No such limits for physiochemical changes, loss of activity or degradation during shelf life have been conventional for individual types or groups of biological products. It is not compulsory that forced degradation would result in a degradation product. The study can be terminated if no degradation is seen after a drug substance or drug product has been exposed to stress conditions than

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those conditions mentioned in an accelerated stability protocol. This is problem-solving of the stability of the molecule under test. Over-stressing a sample may lead to the formation of a secondary degradation product that would not be seen in formal shelf-life stability studies and under-stressing may not generate sufficient degradation products. Protocols for generation of product-related degradation may differ for drug substance and drug product due to differences in matrices and concentrations. It is recommended that a maximum of 14 days for stress testing in solution (a maximum of 24 h for oxidative tests) to provide stressed samples for methods development.

V. Strategy for Selection of Degradation Conditions

Forced degradation is approved to produce representative samples for developing stability-indicating methods for drug substances and drug products. The choice of stress conditions should be constant with the product's decomposition under normal manufacturing, storage, and use conditions which are specific in each case. A general protocol of degradation conditions used for drug substance and drug product is shown in following figure:

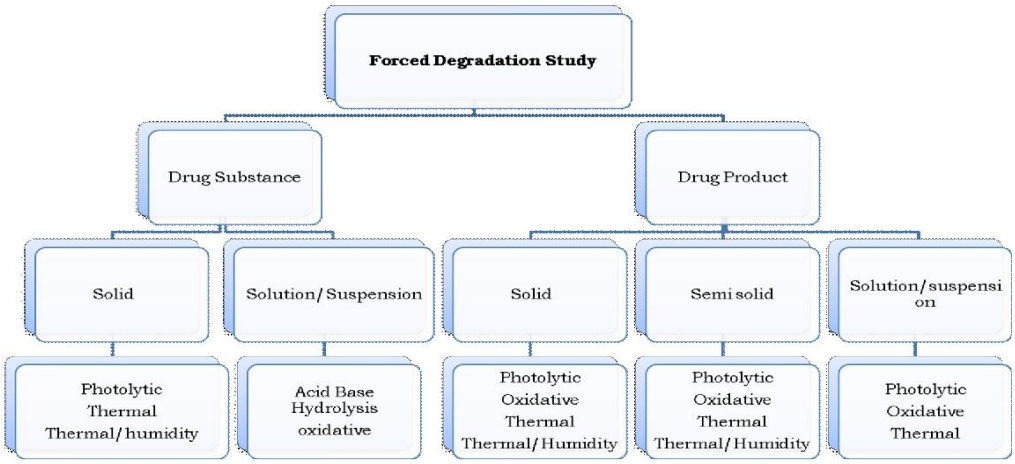

Figure 1: Strategy for selection of degradation conditions

A negligible list of stress factors suggested for forced degradation studies must include acid and base hydrolysis, thermal degradation, photolysis, and oxidation and may include freeze–thaw cycles and shear. There is no specification in regulatory guidelines about the conditions of pH, temperature and specific oxidizing agents to be used. The design of photolysis studies is left to the applicant's diplomacy although Q1B specifies that the light source should produce combined visible and ultraviolet (UV, 320–400 nm) outputs, and that exposure levels should be justified. The initial trial should have the aim to come upon the conditions that degrade the drug by approximately 10%. Some conditions mostly used for forced degradation studies are present in the follows-

Degradation type	Experimental conditions	Storage conditions	Sampling time (days)
Hydrolysis	Control API (no acid or base)	40°C, 60°C	1,3,5
	0.1M HCl	40°C, 60°C	1,3,5
	0.1 M NaOH	40°C, 60°C	1,3,5
	Acid control (no API)	40°C, 60°C	1,3,5
	Base control (no API)	40°C, 60°C	1,3,5
	pH: 2,4,6,8	40°C, 60°C	1,3,5
Oxidation	3%H2O2	25°C, 60°C	1,3,5
	Peroxide control	25°C, 60°C	1,3,5
	Azobisisobutyronitrile (AIBN)	40°C, 60°C	1,3,5
	AIBN control	40°C, 60°C	1,3,5
Photolytic	Light 1 × ICH	NA	1,3,5
	Light 3 × ICH	NA	1,3,5
	Light control	NA	1,3,5
Thermal	Heat chamber	60°C	1,3,5
	Heat chamber	60°C /75% RH	1,3,5
	Heat chamber	80°C	1,3,5
	Heat chamber	80°C /75% RH	1,3,5
	Heat control	Room temp.	1,3,5

Table 1: Degradation Type

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Some scientists have found it practical to begin with extreme conditions such as 80 1C or even higher temperatures and testing at shorter (2, 5, 8, 24 h, etc.) multiple time points, so that the rate of degradation can be evaluated. The primary degradants and their secondary degradations products can be distinguished by testing at early time points and thus help in a better degradation pathway.

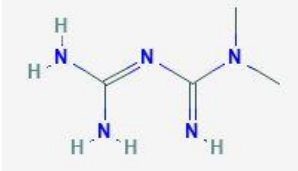
VI. Material and Methods

6.1 Metformin (Metformin HCl)

Metformin hydrochloride extended release tablet is an oral antihyperglycemic. This drug is used in the management of type-II diabetes. Metformin hydrochloride (3-(diamino methylidene)-1,1-dimethylguanidine; hydrochloride) is not chemically or pharmacologically related to any other classes of anti-hyperglycemic agent. The structural formula of Metformin hydrochloride is-

Molecular Formula : $C_4 H_{12} Cl N_5$

Molecular Structure :



Molecular Weight : 165.62 g / mol
Bioavailability : 50-60%
Biological half-life : 4-8.7 hrs.
Solubility : Freely soluble in water and is practically insoluble in acetone and ether.
PKa value : 12.4

6.2 Mechanism of Action

Metformin is an antihyperglycemic agent, which improves glucose tolerance in patients with type II diabetes, lowering both basal and postprandial plasma glucose. It is different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylurea, Metformin does not produce hypoglycemia in either patients with type II diabetes or normal subjects (except in special circumstances see precaution) and does not cause hyperinsulinemia with Metformin therapy. Insulin secretion remains unchanged while fasting insulin level and day long plasma insulin responses may actually decrease. Metformin hcl tablet contains metformin a medicine to treat metformin hydrocholoride. Diabetes belongs to a groups of medicines called as biguanides. Insulin is a hormones produced by the pancreas that makes your body take in glucose (sugar) from the blood. Our body uses the glucose to produced energy or stores it for future uses.

VII. Aim and Objectives of Studies

The aim of the study is to perform forced degradation studies by subjecting to difference brands of metformin under hydrolytic (acidic and basic) photolytic thermal stress conditions, as defined under ICH guidelines Q1A (R2) by using spectrophotometer.

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

VIII. Experimental Work

All the reagents used were of analytical grade including hydrochloric acid, sodium hydroxide deionized water and the material used for the study is the different brands of metformin tablet such as Glycomet 500 mg, Glyciphage 500 mg and Metformin 500 mg.

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Glycomet 500 mg

- Each uncoated tablets contains metformin HCL IP 500 mg excipients …qs
- Batch No. : 28018064
- Manufacturing Industry: USA Pvt. Ltd.
- Expiry date: 12/2021

Glyciphage 500 mg

- Each uncoated tablets contains metformin HCL IP 0.5 g excipients...qs
- Batch No. : GA18020
- Manufacturing Industry: Franco – Indian pharmaceutical Pvt. Ltd.
- Expiry date: 09/2021

Metformin 500 mg

- Each uncoated tablets contains metformin HCL IP 0.5 g excipients...qs
- Batch No. : GA18020
- Manufacturing Industry: Franco – Indian pharmaceutical Pvt. Ltd.
- Expiry date: 09/2021

Glassware

- Volumetric Flask, test tube, Beaker, Measuring cylinder, Pippete, all these glassware are wash properly. Rinsed with deionised water which was freshly prepared in the laboratory.

Instrument used

- Digital weaighing balance
- UV visible Spectrophotometer (UV 1601)

8.1 Methods of Preparing Working Solution

1. Preparation of 0.1 M HCL Acid

9.5 mL of HCL acid of analytical grade (36% , 11 N) was taken in liter volumetric flask and the volume was made up to the mark with deionised water.

2. Preparation of 0.1 N Sodium Hydroxide

4 gm of NaOH was dissolved in small quantity of water taken in a liter volumetric flask and the volume was made up to the mark with deionised water.

3. Preparation of Metformin Solution

Weigh and finally crushed tablet of each tablet and crushed tablets accurately for meking primary solution of metformin, Glycomet, glyciphage. Metformin were weighing accurately of (0.1 gm) and introduced in 100 mL volumetric Flask, add 70 mL of water and shake vigriously for 15 min makeup the volume, filter and discard first 20 mL of filtrate, dilute 10 mL to 100 mL with water, again 10 mL of resulting solution to 100 mL with water, determione the absorbance at max of 232 nm.

IX. Result and Discussion

We have conducted the degradation study on forced degradation parameters of three brands of metformin i.e. Glycomet 500 mg, Glyciphage 500 mg tablets of Franco Indian Pharmaceutical PVT.LTD and metformin 500 mg tablets macleods Pharmaceuticals ltd and their absorbance for degradation parameters before and after treatment (acid, Base, UV and heat).

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Sr. No	Treatment	Glycomet	Glyciphage	Metformin
1	Before	1.709	1.723	1.709
2	After acid	1.541	1.404	1.409
3	After base	1.702	1.732	1.724
4	After heat	1.488	0.999	0.999
5	After UV	1.505	1.517	1.009

- When different brands of metformin were subjected to 0.1 N hcl, Absorbance decreases.
- When brands of metformin wree subjected to 0.1 N NaOH, drugs shows slightly increases in the absorbance.
- When Glycomate, Glyciphage and metformin were exposed to UV light these is decreased in absorption. When Glycomate, Glyciphage and metformin were subjected to heat at 50 degree celcius for 30 min drugs shows great decrease in the absorbance.

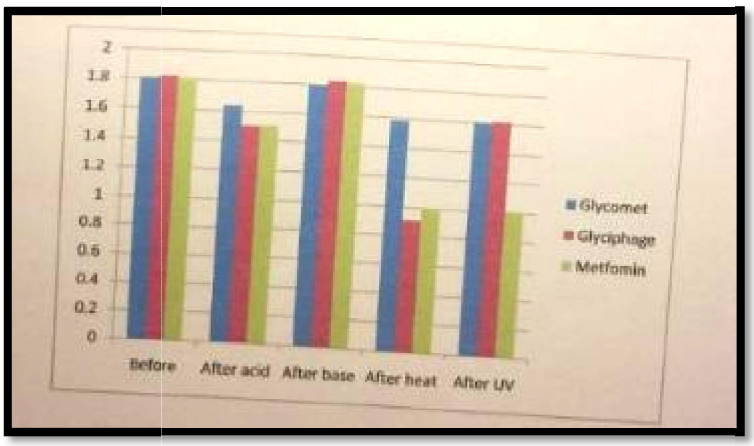

Figure 02: Absorbance degradation of different brands of metformin

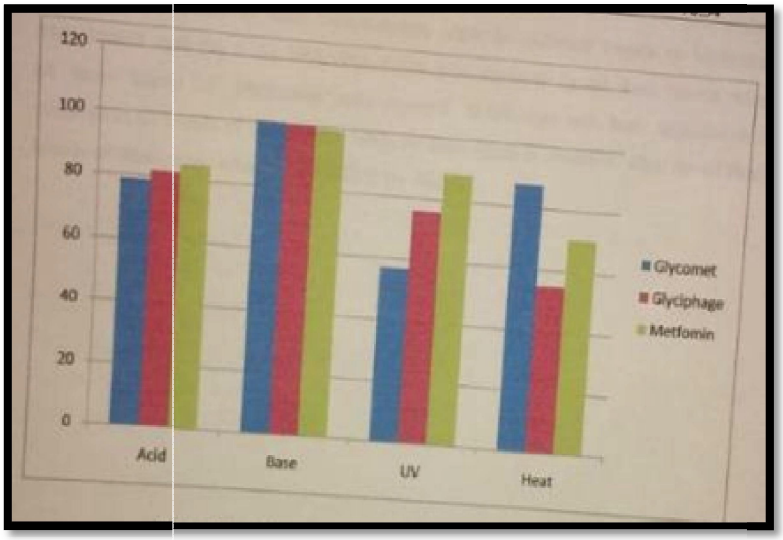

Figure 03: Percentage degradation of different brands of metformin

X. CONCLUSION

Accouring to specification of Indian pharmacopeia the content official limit of not less than (98.5%) and not more than (101.0%) of the lable amount our hypothesis was that when all different brands of metformin were expose to the different degradation parameters. The result of study conclude that when the different brands of metformin were treated

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with the 0.1 N HCL degradation was observed in all three brands, when all three brands of metformin were exposed to UV light and Heat degradation is observed in all brands of metformin while no degradation is observed when the all; three brands of metformin when treated with 0.1 N NaOH.

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