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Effect of Acid, Base and Time on Different Brands of Glimepiride

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Abstract

The objective of this study is to develop the degradation studies of different brands of glimepiride available in market. Forced degradation is a powerful tool used routinely in pharmaceutical development in order to develop stability-indicating methods that lead to quality stability data and to understand the degradation pathways of the drug substances and drugs. Glimepiride is a medium- to long-acting sulfonylurea antidiabetic drug as it is the most prescribed oral antihyper glycaemic agent indicated to treat type 2 diabetes mellitus. Its mode of action is to increase insulin production by the pancreas. This is not used for type 1 diabetes because in type 1 diabetes the pancreas is not able to produce insulin. Glimepiride was subjected to different stress conditions as per (ICH) International Conference on Harmonization guidelines. Distilled water was used as solvents and the amount of drug was calculated after degradation by taking absorbance at 200 nm. According to the assay limit of USP specified that the content should not be less than 95% and not more than 105% of labelled amount. On basic pH brand A, and E showed degradation after the addition of 0.1 N base while other brands degraded as base has no impact on glimepiride concentration. On addition of 0.1 N HCl only brand E showed heavy degradation. After 48 hours the absorbance of all brands are different compared with initial absorbance which shows degradation of all brands.

Keywords

Glimepiride, Degradation Studies, Assay, USP

Subject Areas: **Analytical Chemistry, Geometry, Medicinal Chemistry**

1. Introduction

Forced degradation (FD) study is a process in which the natural degradation rate of a pharmaceutical product is increased by the application of an additional stress. FD studies 1) help to identify reactions that cause degrada-

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tion of pharmaceutical product; 2) are part of the development strategy and an integral component of validating analytical methods that indicate stability and detect impurities which are formed during manufacture, their proper storage and their properties are different from the desired product with respect to activity, efficacy and safety; and 3) are designed to generate product-related variants and develop analytical methods to determine the degradation products formed during accelerated and long term stability studies [1] [2]. This article describes the mechanism of formation and characterization of generated impurities during force degradation studies in pharmaceuticals [3]. Force degradation studies ensure appropriate stability of final pharmaceutical products in very early stages of pharmaceutical development. Any significant degradation product should be evaluated for characterization and quantization for its potential hazard. While performing the forced degradation studies question may arise that how much amount for degradation is enough in stress testing. We classified the forced degradation into the following types.

1) Deceptive: Degradation level is good (<15%) but no relevant degradants are observed.

2) Predictive: Degradation level is good (<15%) but one or more relevant degradants are observed.

3) Useless: Between 15 to 100% degradation but no relevant degradants are observed [4].

Typical stress tests include four main degradation mechanisms: hydrolytic, heat, photolytic, and oxidative degradation. By selecting suitable reagents such as the concentration of acid, base, and varying the conditions (e.g., temperature), length of exposure can achieve the preferred level of degradation [3]. Over-stressing a sample may lead to the formation of secondary degradants that would not be seen in formal shelf-life stability studies and under-stressing may not serve the purpose of stress testing.

Glimepiride is an oral sulfonylurea. Glimepiride (**Figure 1**) is identified as 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1carboxamido)ethyl] phenyl] sulfonyl]-3-(trans-4-methylcyclohexyl) urea (C24H34N4O5S) with a molecular weight of 490.62 [5]. Glimepiride is a white to yellowish-white, odorless to practically odorless powder and is practically insoluble in water. Glimepiride acts as an insulin secretagogue and it lowers blood sugar by stimulating the release of insulin by pancreatic beta cells and by inducing increased activity of intracellular insulin receptors.

As a result of the importance of this oral hypoglycaemic agent in the treatment of noninsulin-dependent diabetes mellitus DM, this work aims to compile the published analytical methods reported so far in the literature for determination of degraded products of glimepiride in biologic samples and pharmaceutical formulations [6]-[10]. Techniques like high-performance liquid chromatography with ultraviolet, mass spectroscopy, array-diode, evaporative light scattering and liquid chromatography-atmospheric pressure chemical ionization-mass spectrometry, ionization-tandem mass spectrometry, high-performance liquid chromatography with column-switching, micelle electro kinetic chromatography, high-performance thin layer chromatography, and spectrophotometry have been used for analysis, from which we have seen that high-performance liquid chromatography methods have been used most extensively [11] [12]. The aim of present work is to develop and validate a simple UV spectrophotometric method to be applied for analysis of glimepiride degradation in tablets, which serves as a tool for the quality control of pharmaceutical dosage forms. Spectrophotometry technique is generally preferred especially by small-scale industries as the cost of the equipment is less and the maintenance problems are cheap. UV spectrophotometric technique can be used for degradation studies of glimepiride. The active pharmaceutical ingredient is subjected to a number of forced degradation conditions to include acidic and basic conditions as per ICH guidelines.

1.1. Parameters in Forced Degradation

The forced degradation studies for drug substance include Temperature and or with humidity, Acid/base Stress testing, Time, Photo degradation and pH variation (high and low).

1.2. Acid/Base Stress Testing

Acid/Base stress testing is performed to force the degradation of a drug substance to its primary degradation

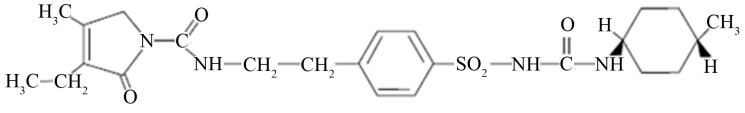

Figure 1. Glimepiride structure.

products by exposure to acidic or basic conditions. The functional groups likely to introduce acid/base hydrolysis are compounds that have labile carbonyl functionality such as amides (lactam), esters (lactones), carbamates, imides, imines, alcohols and aryl amines [13].

2. Experimental

The glimepiride brands used were GLORY 4 mg; MEGAPRIDE 4 mg; GLIOPTIM 4 mg; DIABOLD 4 mg; GLYSET 4 mg and AMARYL 4 mg of sandoz, Mega pharmaceuticals, merck, barret hodgson Pakistan, Wilshire laboratories, sanofi Aventis respectively.

2.1. Reagents

The reagents were used all of analytical grade including hydrochloric acid, sodium hydroxide, Deionized water used was double distilled, deionized and filtered.

2.2. Glassware's

Volumetricflask, pipette, beakers, measuring cylinder, funnel, stirrer all the glassware's were of Pyrex type and were washed with chromic acid followed by thorough washing with water and finally rinsed with double distilled or de-ionized water which was freshly prepared in the laboratory.

2.3. Equipments Used

pH meter: Starter 2000 OHAUS, Spectrometer: T80 UV/VIS spectrometer PG Instrument ,Weighing Balance: Item PA214C ,Pioneer OHAIUS, Water Bath used is Digital constant temperature tank HH-4, the lamp which is used is Serial N 045571, LF-204.LS, 4W-254 nm, 4W-365 nm, Power: 8 N, used.

2.4. Preparation of 0.1 M Hydrochloric Acid

9.1 ml hydrochloric acid of analytical grade (36%, 11 N) was taken in a liter volumetric flask and the volume was made up to the mark with de-ionized water.

2.5. Preparation of 0.1 N Sodium Hydroxide

40 gm sodium hydroxide was dissolve in very small quantity of water taken in a liter volumetric flask and the volume was made up to the mark with de-ionized water.

2.6. Preparation of Glimepiride Solution

Weigh and finally crushed tablets and weigh crushed tablets accurately for making primary solutions of Glimiperide, Megapride (0.1284 gm), Amaryl (0.170 gm), Glioptim (0.1381 gm), Diabold (0.1662 gm), Glory (0.1804 gm), Glyset (0.1837 gm) were weighed accurately and introduced in 100 ml volumetric flasks. Then add 70 ml of water and shake well for 15 min and makeup the volume, after that filter and discard first 20 ml of filtrate. Dilute the solution 10 ml to 100 ml with water then again dilute 10ml of resulting solution to 100 ml with water. Determine the absorbance at max of 200 nm.

2.7. Procedure for Degradation Studies

1) For time

We placed the solution for 5 days and measure the absorbance after 2 days at the same wavelength 200 nm.

2) For acidic pH

Place the final solution of glimepiride in a beaker and add 0.1 N hydrochloric acid HCL drop wise to the final solution and keep adding 0.1 N HCLuntil the pH reaches to 3. Then determine the absorbance at 200 nm.

3) For basic pH

Place the final solution of glimepiride in a beaker and add 0.1 N sodium hydroxide. Check the absorbance of this solution at maximum of 200 nm.

Table 1. Effect of acid base and time on glimepiride brands.

S.NO	BRANDS	% ASSAY AFTER ACID	% ASSAY AFTER BASE	% ASSAY AFTER 48 HOURS
A	GLORY	91.6%	117.43%	97.96%
B	MEGAPRIDE	95.83%	92.03%	99.3%
C	GLIOPTIM	96.8%	90.63%	81.9%
D	DIABOLD	96.7%	91.03%	80.3%
E	GLYSET	174.22%	179.83%	154%
F	AMARYL	94.04%	88.52%	78.9%

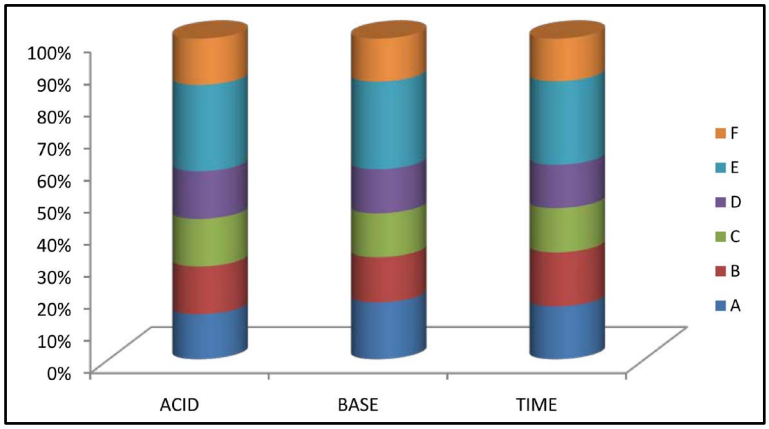

Figure 2. Effect of acid base and time on glimepiride.

3. Results and Discussion

Degradation Studies

The limit of assay by USP specified that the content should not be less than 95% and not more than 105% of labelled amount. All brands of glimepiride results were within the stated limit for assay before any degradation. Brand E degraded after the addition of 0.1 normal HCL into it showing acid has the least degradation impact on the product. Brand A and E showed degradation after the addition of 0.1 N NaOH while other brands does not degraded as base has little impact on glimepiride concentration. Only brand E shows degradation after 2 days that was the effect of time on glimepiride (**Table 1** and **Figure 2**). Our research group has performed these types of studies for different drugs and these are very helpful for pharmacy profession [14]-[16].

4. Conclusion

It was used to study the stress degradation studies as per ICH guidelines. Glimepiride was found to be degraded not in all types of stress conditions and was found to be stable. The proposed method is accurate and precise as well as reproducible and economical and can be successfully used degradation studies of different dosage form. It was concluded that only brand E showed unexpected results and most unstable among other brands for all the stresses applied for degradation studies, whereas only brand A showed degradation in stress of base.

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