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Relative Degradation Study of Local Vs Multinational Brand of Diltiazem by Means of UV Spectrophotometer

Safila Naveed* and Hina qamar

Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan

*Corresponding author e-mail: safila117@gmail.com

ABSTRACT

Forced degradation is a extensively employed method carried out in pharmaceutical development in order to develop stability, demonstrating methods that provides quality and steadiness information to comprehend the degradation pathways of the drug substance and its impurities. There are various distinctive brands accessible in market for diltiazem. It will be a calcium opponent profitable in the medicine about secure, variant and unstable (flimsy angina pectoris). Concomitant perusing parallel β-adrenoceptor opponent therapy, happen infrequently as an adverse impact about diltiazem medication. The reason for this examine create the investigations from claiming two diverse brands for diltiazem 60mg. It might have been subjected under different stress condition concerning illustration for every (ICH) worldwide meeting with respect to harmonization rules. Sresses like Acid/base, variability in temperature, photo degradation and with time (7days). Also with occasion when under capacity temperature. Ultraviolet-visible spectroscopic headway might have been produced should ascertain. Furthermore examine the measure about medication. Refined water might have been taken as solvents. The measure about stress effect of medication might have been computed by taking absorbance at 237 nm. As stated by those test farthest point for USP characterized that those content ought not make under 95% not more than 105% for claimed amount. Local brand demonstrated degradation after the addition of 0.1 N NaOH, 0.1 N HCL and with the passage of time (7 days) on storage conditions. The method was found to be uncomplicated and less time strong and cost effective. Henceforth this system might make effectively used to consider stress degradation for diltiazem to little business the place secondary limit instruments are not accessible.

Keywords: Diltiazem, Degradation studies, ICH, Assay, USP.

INTRODUCTION

Diltiazem hydrochloride (DLZ), d-cis diltiazem, d-cis-3-acetyloxy-5-[2-(dimethylamino) ethyl]-2, 3-dihydro-2-(4-methoxyphenyl)-1, 5-benzothiazepin-4(5H) one) hydrochloride (Figure 1) are one of the widely used benzodiazepine calcium channel-blocking drugs. Therapeutically it is used to treat cardiovascular diseases such as angina pectoris, hypertension, and cardiac arrhythmias[1,2]. (See figure 1.)

Diltiazem is an orally and intravenously active calcium channel blocking agent revealed to be an effective and well- tolerated treatment for stable angina and angina owing to coronary artery paroxysm. Its efficacy has by and large been similar to that of nifedipine or verapamil-substitute calcium channel blockers in above mentioned diseases with which diltiazem has many electrophysiological, anti-arrhythmic and haemodynamic, similarities. The mechanism of antiangina diltiazem cannot be accurately described; conversely, it appears to increase myocardial oxygen supply and diminish myocardial oxygen demand, mainly by coronary artery dilatation and/or via both indirect and direct hemodynamic alterations. Diltiazem has also exposed considerable effectiveness in the treatment of unstable angina, supraventricular tachyarrhythmia's, and hypertension, but auxiliary study is necessary prior to its position in the treatment of these diseases may be clearly recognized[2].

Literature survey discovered that a number of assay methods have been used for analysis of diltiazem, pharmaceutical preparations, and serum via different techniques including LC-MS/MS[3-6], gas chromatography[7-10], and electron capture gas chromatography[11] Many research papers have described the spectrophotometric methods for the detection of diltiazem in raw materials and different pharmaceutical formulations .Recently Ayad *et al*.[12] established a method by kinetic spectrophotometric and spectrofluorimetric technique using NBD-Cl (4-Chloro-7-nitrobenzene-2-oxa-1, 3-diazole). The reported technique has much recompense in contrast with other methods in terms of sensitivity and selectivity by way of high-quality precision and accuracy. Hosny[13] reported an ion-pair complex formation method for the assaying of diltiazem in its formulation by using chromotrope 2R and Bengal rose reagents. One more spectrophotometric determination of diltiazem by ternary complex formation reaction with cobalt thiocyanate at acidic pH (3-5). After extraction complex was deliberated at 627 nm[14]. Pietraś *et al*.[15] compare the classical and derivative spectrophotometric method for the quantitations of diltiazem in bulk and formulation. At present, HPLC is the most widely used technique for the analysis of bulk drugs and their formulations[16]. Derivatization of the drugs prior to analysis is normally not essential. The sample preparation is tremendously straightforward, easy and the errors associated with it are generally kept to a minimum by using HPLC[17] several investigations performed[18-20] on development of HPLC methods for determination of drugs in biological fluids. Li *et al*.[21] presented an HPLC method and applied in pharmacokinetic studies. Drug has been extracted in mixture of chloroform, hexane and isopropanol (40: 60: 5 v/v/v) and separated with isocratic mode. Method was linear above the clinical range of 0-300 ng mL-1 with 3 ng mL-1 of LOD. Spiked extraction recoveries of diltiazem were found to be 91.4-104.0. High-performance liquid chromatographic analysis of diltiazem and its metabolite in plasma[22] Further Analysis of diltiazem and its related substances by HPLC and HPLC/MS[23] Validation of manufacturing process

of Diltiazem HCl tablets by NIR spectrophotometry (NIRS) [24] Adsorptive stripping voltammetric determination of antihypertensive agent: diltiazem[25]. Enantiomeric Separation of Drugs by Mucopolysaccharide - Mediated Electro-kinetic Chromatography[26] Rapid liquid chromatography–tandem mass spectrometry method for the determination of a broad mixture of pharmaceuticals in surface water[27].

UV spectrophotometry has the advantage of being speedy, effortless, cost-effective with high precision, and accurateness. These advantages persuade the application of this method in routine analysis of drugs by UV-spectrophotometer .The method of analysis is based on the measuring absorption of a monochromatic light by colorless compounds in the near (UV) of spectrum (200-380 nm). UV spectrophotometry can be engaged for stress degradation studies of diltiazem. Two brands one of local company VS one of multinational company were subjected to a number of forced degradation conditions to include basic, acidic and photo degradative conditions as per International Conference Harmonization guidelines[28]. 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[29]. Forced degradation is carried out to produce representative samples for developing stability-indicating methods for drug substances and drug products. The preference of stress conditions should be reliable with the product's decomposition under normal industrialized, storage space, and use circumstances which are specific in each case[30,31].

EXPERIMENTAL

Diltiazem

The diltiazem 60mg tablets and brands used were LOCAL HERBESSER (High noon lab) MULTINATIOANL DILZEM (Pfizer lab).

Reagents

Analytical grade reagents were used which includes 1N sodium hydroxide, 1N hydrochloric acid and deionized water used was double distilled, deionized and filtered.

Instruments

- Spectrophometer: PG Instrument (T80 uv/vis spectrometer) along with a pair of 5 cm quartz cuvettes.
- Weighing Balance: Pioneer OHAIUS (Item PA214C).
- Water Bath: DT; Digital constant temperature tank HH-4.
- UV Lamp: Power: 8N, LF-204.LS, Serial N 045571, 4W-254 nm, 4W-365 nm.

Preparation of 1 N sodium hydroxide

Weigh 40 gm of NaOH, dissolve in small quantity of water taken in 100ml volumetric flask and make up the volume upto mark with de ionized water

Preparation of 1 N hydrochloric acid

Take 8.36ml analytical grade hydrochloric acid (37%, 12N) in a volumetric flask and add de-ionized water to make up the volume.

Preparation of stock solution

Separately weigh the 6 tablet of each of the brand in order to calculate average weight of each brand individually. Crush one 60 mg tablet of each brand triturate separately in mortar pestle and accurately weigh i.e HERBESSER Highnoon laboratories (0.063 gm) and DILZEM Pfizer laboratories (0.0495 gm).Weighed samples

were introduced into two separate 100ml volumetric flask and finally make up the volume to 100 ml respectively for each sample. Solutions obtained of desired concentration (200 ppm in 100ml) were transferred individually to cuvette to determine the absorbance at max 237nm by using spectrophotometer.

Procedure for degradation studies

Stress testing of the active pharmaceutical ingredient can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used.

For an active pharmaceutical ingredient the following approaches may be used:

(i) When an active pharmaceutical ingredient is described in an official pharmacopoeia monograph (British Pharmacopoeia, European Pharmacopoeia or the United States Pharmacopoeia) and fully meets its requirements no data are required on the degradation products if they are named under the headings "purity test" and / or "section on impurities".

(ii) For active pharmaceutical ingredients not described in an official pharmacopoeial monograph, there are two options:

(a) When available, it is acceptable to provide the relevant data published in the literature to support the proposed degradation pathways; as stated in ICH Q1AR-Stability testing guideline stability testing of new active pharmaceutical ingredients and products.

(b) When no data are available in the scientific literature, including official pharmacopoeias, stress testing should be performed. Results from these studies will form an integral part of the information provided to regulatory authorities.

For acid

To study the effect of acid, take 5 ml of 200 ppm solution of each brand separated test tubes then 5ml of 1 N HCl is added in each test tube. They were then left for a period of 30 minutes. Upon completion of time period, solutions were transferred to a curette separately and then absorbance of the solutions was recorded at the wavelength of 237nm. (See table 1.)

For base

To study the effect of acid, 5 ml of 200 ppm solution of each brand in separated test tubes then 5ml of 1 N NaOH is added in each test tube. The samples were then left for a period of 30 minutes. Upon completion of time period, solutions were transferred to a cuvette separately and then absorbance of the solutions was recorded at the wavelength of 237 nm. (See table 2.)

For UV light

To study the effect of UV light, take 5 ml of 200 ppm solution of each brand in six separated test tubes then 5 ml water is added in each test tube and place these solutions in UV light and absorbance of the solutions was recorded at the wavelength of 237 nm. (See table 3.)

For heat

To study the effect of heat, take 5 ml of 200 ppm solution of each brand in separate test tubes each containing 5 ml of water, than place these solutions in water bath for 30 min and absorbance of the solutions was recorded at the wavelength of 237 nm. (See table 4.)

Effect of time

To study the effect of time, take initial reading of stock solution of 200ppm of each brand in separate test tubes each containing 5 ml of water, and then set aside these stock solutions for 7days and absorbance of final reading after 1 week was recorded at the

wavelength of 237 nm. (See table 5 and figure 2.)

RESULTS AND DISCUSSIONS

This research was performed with the purpose to compare the degree of degradation in local vs. multinational brands of Diltiazem. The limit of assay by USP specified that the content should not be less than 95% and not more than 105% of labeled amount[32,33]. The results from the bar charts conclude that HERBESSER being manufactured goods of local pharmaceutical of Pakistan shows significantly more degradation when it undergoes accelerated stability studies under stress conditions such as (heat, acid and with time) and goes beyond the USP limits, comparatively to DILZEM which belongs to multinational pharmaceutical and seems to be degraded beyond the limits when kept for 7 days otherwise rest of results lies within the USP range. Ensuring uniformity in standards of quality, efficacy and safety of pharmaceutical products through shelf life in pharmaceutical equivalents (when the drug products contain the same active ingredients, are of the same dosage form, route of administration and are identical in strength or concentration but manufacturing company is different) is the fundamental responsibility for all pharmaceutical industries to achieve desired bioavailability of the drug. Hence results revealed that local brand is prone to degrade more as compare to multinational when experience stress conditions and has less endurance[34].

CONCLUSION

Degradation products generated from forced degradation studies are potential degradation products that may or may not be formed under relevant storage conditions but they assist in the developing stability indicating method. It is better to start degradation studies earlier in the drug development process to have sufficient time to gain more information about the stability of the molecule. This information will in turn help improve the formulation manufacturing process and determine the storage conditions. We can conclude that local formulations of Diltiazem degrades most in acidic medium, under influence of heat and with time on storage temperature whereas slight degradation occurs in basic medium. Furthermore moderate degradation in active occurs when expose to U.V, where as its multinational formulation do not degrades in either of the stress conditions except showed degradation with the passage of time on storage conditions.

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Table 1. Showing effect o acid

Brands		% Assay
Local	HERBESSER (High noon lab)	108%
Multinational	Dilzem (Pfizer lab)	104%

Table 2. Showing effect of base

Brands		% Assay
Local	HERBESSER (High noon lab)	106%
Multinational	DILZEM (Pfizer lab)	99.7%

Table 3. Showing the effect of UV

Brands		% Assay
Local	HERBESSER (Highnoon lab)	101%
Multinational	DILZEM (Pfizer lab)	99%

Table 4. Showing effect of heat

Brands		% Assay
Local	HERBESSER (High noon lab)	118%
Multinational	DILZEM (Pfizer lab)	101%

Table 5. Showing effect of time

Brands		Initial	Final after 7 days
Local	HERBESSER (High noon lab)	110%	120%
Multinational	DILZEM (Pfizer lab)	105%	117%

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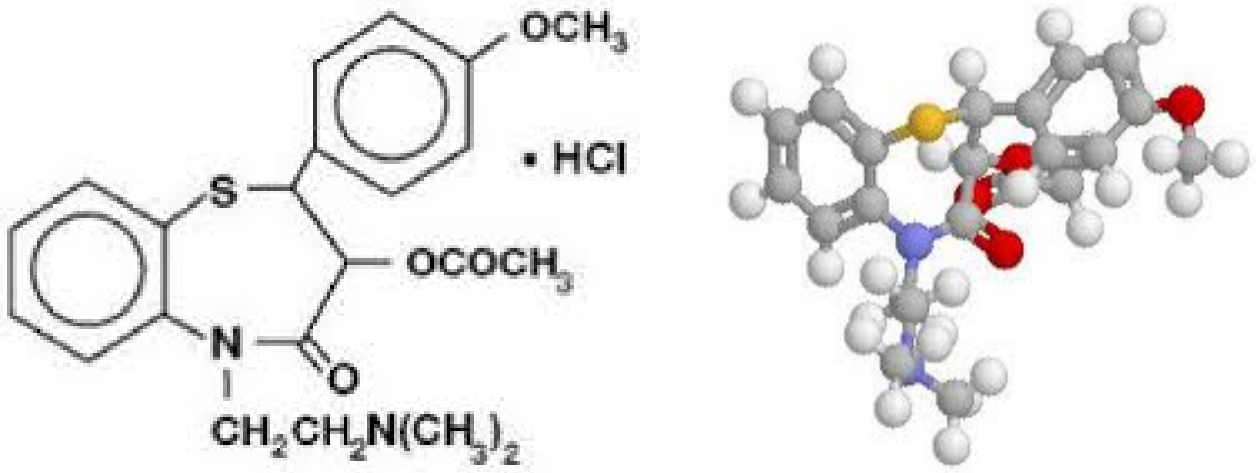

Figure 1. Diltiazem chemical structure and its 3D view

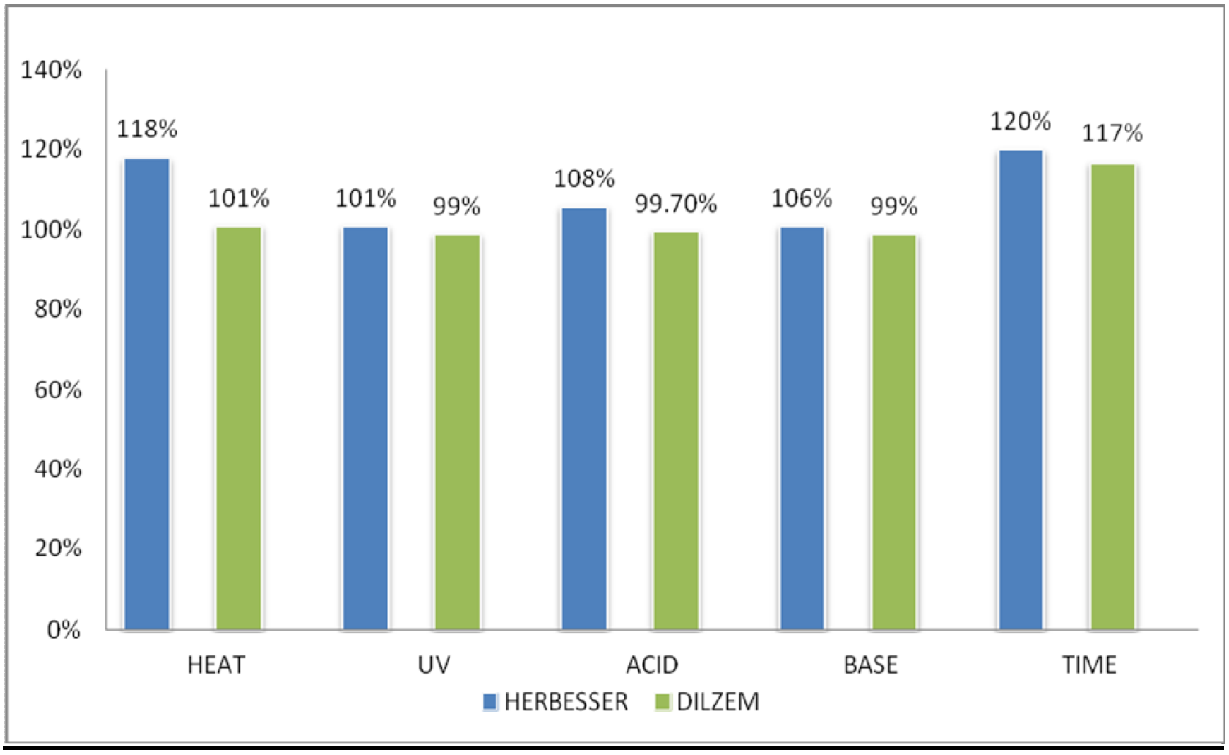

Figure 2. Showing effect of different stress parameters on local and multinational brand of Diltiazem