Research Article

In-vitro comparative degradation study of different brands of Flunarizine dihydrochloride tablet using UV Spectrophotometer

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Abstract

The objective of this study was to develop the degradation studies of different brands of Flunarizine dihydrochloride tablet available in market. 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. Flunarizine dihydrochloride is a calcium channel blocker which reduces arterial and arteriolar smooth muscle spasm by reducing intracellular Ca^{2+} overload due to brain hypoxia. It is widely used in cerebral and peripheral vascular disorders and also as antihistaminic & sedative. This drug was subjected to different stress conditions as per International Conference on Harmonization guidelines (ICH). An ultraviolet UV spectroscopic method was developed for analysis of the drug in the presence of the degradation products. Ethanol was used as a solvent. The amount of degraded drugs was calculated by taking the absorbance at 253 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. In case of acidic pH and basic pH except Fluver and Minium other brands were degraded. In addition to heat exposure only brand Norium was Stable. It was concluded that all brands weren't degraded from ranges for all the stresses applied for degradation studies.

Keywords: Flunarizine, calcium channel blocker, degradation studies, Assay, USP

1. Introduction

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 testing data to understand 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 pathways, and to validate the stability indicating procedures used [1].

Flunarizine Dihydrochloride (FLU); 1-[Bis (4-fluorophenyl) methyl]-4-[(2E)-3-phenylprop-2-enyl] piperazine dihydrochloride (Fig. 1) [1]. It is a calcium channel blocker which reduces arterial and arteriolar smooth muscle spasm by reducing intracellular Ca^{2+} overload due to brain hypoxia. It is widely used in cerebral and peripheral vascular disorders and also as antihistaminic & sedative. The compound has undergone the most extensive evaluation, and it may reduce the frequency of either classical or common migraine attacks by as much as 90%. It may also be effective in preventing more complicated syndromes, such as childhood hemiplegic migraine [3-6]. Flunarazine has molecular formula $C_{26}H_{26}N_2F_2$. 2HCl and molecular weight 477.4. It is widely used in

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treatment of cerebral and peripheral vascular insufficiency. It is white crystalline powder soluble in DMSO (25 mg/ml), 100% ethanol (5 mg/ml) or chloroform: methanol (1:1; 50 mg/ml) [5-6].

Literature survey revealed several analytical methods such as GC [7], HPLC [8], and UV–spectrophotometry [9] have been reported in bulk, pharmaceutical dosage form and in biological fluids for determination of Flunarizine. The aim of the study was to perform forced degradation studies of the different brands of Flunarizine hydrochloride under hydrolytic (acidic and basic), and thermal stress conditions, defined under ICH guideline by using a spectrophotometer. This work also serves as an analytical tool for a drug. Our research group done these types of degradation studies of drugs on different brand such as atorvastatin, rabeprazole, amytriptyline, domperidone [10-13] and these are very helpful for health care professionals [10-16].

2. Materials and Methods

2.1 Reagents

Analytical grade reagents were used 0.1N sodium hydroxide, 0.1N hydrochloric acid, de-mineralized water and distilled water.

2.2 Glassware

Volumetric flask, funnel, beakers, Measuring cylinder, pipette, and stirrer used were of Pyrex type and were washed followed by thorough washing with laboratory grade detergent and finally rinsed with distilled or de-mineralized water which was freshly prepared in the laboratory.

2.3 Instruments: Theses include

- Spectrophometer: UV-Vis spectrophotometer, UV mini-1240, Shimadju.
- Corvettes
- Weighing Balance: Precision balance, LF224DR, Shinko Denshi Co., ltd.
- Water Bath: Stainless-steel, thermo station, HH-S.

2.4 Wavelength Selection

About 100 ppm of Flunarizine dihyrochloride was accurately prepared in ethanol. The wavelength maxima (λmax) was observed at 253 nm and this wavelength was adopted for absorbance measurement.

2.5 Preparation of 0.1 N Sodium Hydroxide

0.4 grams of sodium hydroxide were taken and transferred it in a 100 ml volumetric flask and dissolved it in small quantity of water and finally make up the volume up to the mark of the flask with de-mineralized water.

2.6 Preparation of 0.1 N Hydrochloric Acid

8.36 ml analytical grade hydrochloric acid (37%, 12N) was taken in a volumetric flask and de-mineralized water was added to make up the volume.

2.7 Standard Stock Solution

The four different brands were purchased from a local medicine shop located in Bayezid Bostami, Chittagong. All tablets of brand were labeled to contain Flunarizine 10 mg per tablet. Showing manufacturing and expire date of different brands (Table 1). Weigh and finally crushed tablets accurately for making primary solutions of Flunarizine dihydrochloride 10 mg. Fluver (0.1236 gm) ACI Ltd., Norium (0.1869 gm) Eskayef Bangladesh Ltd., Flurizin (0.1411 gm) Square Pharmaceuticals Ltd., Minium (0.1027 gm) Opsonin Pharma Ltd. was weighed accurately and introduced in 100 ml volumetric flasks. Ethanol was added and shaken vigorously and was making up the volume up to 100 ml to make the strength of the solution 100 ppm in 100 ml.

2.8 Procedure

2.8.1 For Acid

To study the effect of acid, 5 ml of 100 ppm solution of each brand was taken in four separated test tubes, then 5ml of 0.1N HCl was added in each test tube. They were then left for a period of 1 hour. Upon completion of the time period, solutions were transferred to a cuvette separately and then absorbance of the solutions was recorded at the wavelength of 253 nm.

2.8.2 For Base

To study the effect of base, 5 ml of 100 ppm solution of each brand was taken in four separated test tubes, then 5 ml of 0.1N NaOH was added in each test tube. The samples were then left for a period of 1 hour. Upon completion of the time period, solutions were transferred to a cuvette separately and then absorbance of the solutions was recorded at the wavelength of 253 nm.

2.8.3 For Heat

To study the effect of heat, 5 ml of 100 ppm solution of each brand was taken in four separated test tubes, each containing 5 ml of water, then place these solutions in water bath at 40 degree centigrade temperature for 1 hour and absorbance of the solutions was recorded at the wavelength of 253 nm.

3. Results

This research was performed with the purpose to compare the degree of degradation in four different brands of Flunarizine dihydrochloride. The variation in absorbance after the effect of different degradation parameters shown in table 2. The percent of the assay for acidic pH effect was found 76.83-104.18% and for basic pH effect percent of the assay was found 71.46%-96.63% (Table 3, 4 & Fig. 2, 3). In case of the effect of heat, percent of the assay was found 79.17%-101.84% (Table 5 & Fig. 4).

Table 1: Showing manufacturing and expire date of different brands

Sl No.	Brand name	Mfg. Date	Exp. Date
1.	Fluver	July , 2014	July, 2017
2.	Norium	May, 2014	May, 2017
3.	Flurizin	May, 2014	April, 2016
4.	Minium	December, 2013	December, 2015

Table 2: Showing absorbance of drug in different parameters

Sl No.	Brand name	Absorbance of standard	Absorbance after acidic pH effect	Absorbance after basic pH effect	Absorbance after heat effect
1.	Fluver	2.439	2.541	2.357	2.224
2.	Norium	2.439	2.240	2.149	2.484
3.	Flurizin	2.439	1.874	1.739	2.931
4.	Minium	2.439	2.319	2.325	2.288

Table 3: Showing effect of acidic pH

Sl No.	Brands	% Assay
1.	Fluver	104.18%
2.	Norium	91.84%
3.	Flurizin	76.83%
4.	Minium	95.07%

Table 4: Showing effect of basic pH

Sl No.	Brands	% Assay
1.	Fluver	96.63%
2.	Norium	88.10%
3.	Flurizin	71.46%
4.	Minium	95.32%

Table 5: Showing effect of heat

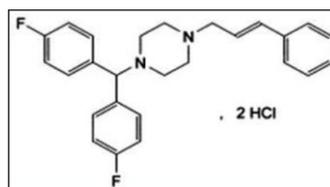| Sl No.	Brands	% Assay
1.	Fluver	91.18%
2.	Norium	101.84%
3.	Flurizin	79.17%
4.	Minium	93.80%

Fig. 1 *Structure of Flunarizine dihydrochloride*
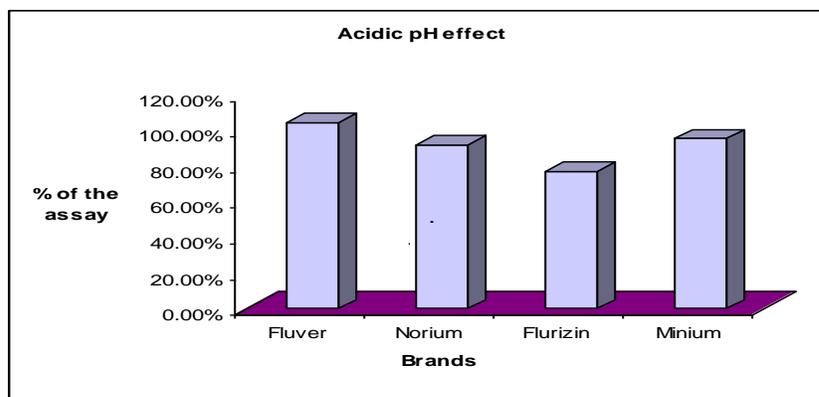
Fig. 2 *% of the assay upon the effect of acidic pH*
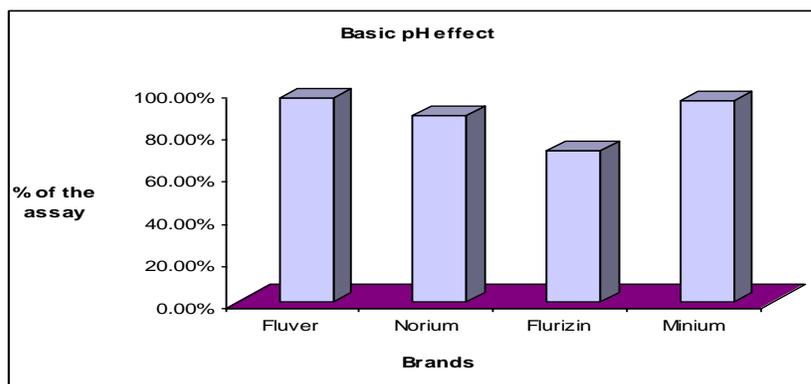

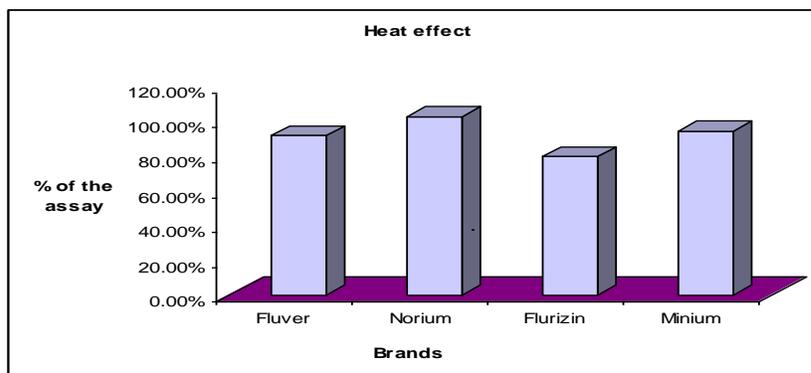**Fig. 3** *% of the assay upon the effect of basic pH*

Fig. 4 *% of the assay upon the effect of heat*

4. Discussion

The purpose of degradation studies is to investigate those changes, to get a shelf life of the drug product and to recommend storage conditions, which will be applicable to all future batches of the tested drug product manufactured and packaged under similar circumstances [10-13]. Acidic, basic, hydrolytic, oxidative, thermal and photolytic degradation was used to assess the stability indicating the power of the method. The drug was found to be stable in acidic, thermal, hydrolytic and photolytic stress conditions and showed slight degradation in oxidative stress condition and extensive degradation in basic medium by RP-UPLC [17]. In our study, we used UV spectrometry to investigate the degradation of Flunarizine dihydrochloride and the limit of the assay by USP specified that the content should not be less than 95% and not more than 105% of labeled amount. According to USP specified limit, in case of acidic pH and basic pH except Fluver and Minium other brands were degraded. In addition to heat exposure other than Norium all brands were degraded that means only brand Norium was Stable.

5. Conclusion

Some brands of Flunarizine dihydrochloride were found to be stable and some were degraded. This degradation study was the stress degradation studies as per ICH guidelines. The method was used 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 all brands weren't degraded from ranges for all the stresses applied for degradation studies.

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