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ANALYSIS OF FLUNARIZINE DIHYDROCHLORIDE IN PHARMACEUTICAL DOSAGE FORM BY ULTRAVIOLET SPECTROPHOTOMETRY AND ITS APPLICATION TO DISSOLUTION STUDIES

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Abstract:

Flunarizine Dihydrochloride (FNZ) is a selective calcium entry blocker with histamine H1 blocking activity intended for the treatment of migraine, occlusive peripheral vascular disease and as an adjuvant in the therapy of epilepsy. Existing methods analyzed Flunarizine in bulk and pharmaceutical dosage forms either as single component or in binary mixture, its related impurities and its degradation products by chromatographic techniques and spectroscopic techniques including AUC methods. Only fewer techniques to analyze Flunarizine Dihydrochloride have been reported. Hence we focused on analysis of FNZ in its conventional tablet dosage form by UV spectrophotometry. FNZ was estimated in commercial tablets (Flunarin 5) by a simple, accurate, precise and economical validated method. Excellent linearity was established in the concentration range of 3- 15 mcg/ ml at λ_{max} of 253.20 nm using 0.1 M Hydrochloric acid as solvent (R^2= 0.9995). The assay results were satisfactory (95.42 ± 0.1%). Precision, recoveries were good and within limits (%RSD < 2.0). LOD and LOQ were 0.2471 mcg and 0.7489 mcg respectively. Further dissolution studies for FNZ tablets were carried out using rotating paddle apparatus with 0.1M Hydrochloric acid as dissolution medium pertaining to the ease of applicability of the developed method. These studies provide scope for analyzing FNZ in different pharmaceutical dosage forms and by varied analytical approaches.

Key words: *Flunarizine Dihydrochloride, Method development, Validation, Dissolution.*

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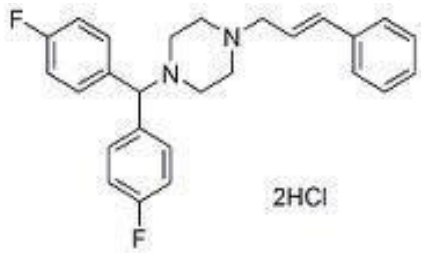
INTRODUCTION:

Flunarizine Dihydrochloride, chemically 1-[bis(4-fluorophenyl)methyl]-4-[(2E)-3-phenylprop-2- en-1-yl]piperazine dihydrochloride. It is a selective calcium entry blocker with calmodulin binding properties and histamine H1 blocking activity hence employed in the treatment of migraine and as an adjuvant in the therapy of epilepsy [1].

Flunarizine Dihydrochloride is official in British and European Pharmacopoeia[2]. Several HPLC works like method development and validation, analysis of Flunarizine and its main production impurities, analysis of Flunarizine Dihydrochloride in the presence of its degradation products[3,4,5]. Several Spectroscopic [6,7]and HPTLC[8,9] methods has been developed in combination with other drugs like Propranolol hydrochloride.

The principal aim of the study is to develop, validate a simple, accurate, precise, economical method by UV spectrophotometry for routine analysis in quality control laboratories. It is further aimed to apply the developed method for dissolution studies of commercial formulation.

Fig 1 Structure of Flunarizine Dihydrochloride



EXPERIMENTAL:

Chemicals and Reagents:

FNZ API was kindly received as gift sample from Vance & Health Pharmaceuticals Pvt Ltd, India. Flunarin 5 tablets were purchased commercially from FDC Limited, India. Hydrochloric acid was purchased from Merck, India. Freshly prepared distilled water was utilized throughout the work.

0.1 M Hydrochloric acid was prepared by dissolving accurately 8.65 ml of concentrated HCl in freshly prepared distilled water and made upto the mark in 1000 ml volumetric flask [10].

Apparatus and Instrument:

Denver instrument Analytical balance was used to weigh chemicals.

Bhanu Quartz distiller was utilized for distilling water time to time prior to analysis.

Shimadzu UV-1800 double beam spectrophotometer with matched pair of 10mm quartz cells was used throughout the experimental work. UV Probe 2.34 software was used to acquire data.
Electrolab Dissolution Test Apparatus was used to perform *invitro* dissolution studies.

All apparatus including glassware and instruments were calibrated to ensure correct procurement of data and results.

METHOD DEVELOPMENT:

Preparation of Flunarizine Dihydrochloride standard stock solution:

25 mg of FNZ API was accurately weighed into 100 ml volumetric flask and dissolved in freshly prepared 0.1 M HCl and made upto the volume to get concentration of 250 mcg/ ml (stock solution- I). 20.0 ml from the above stock solution was pipetted into 50 ml volumetric flask and made upto volume with freshly prepared 0.1 M HCl to get 100 mcg/ ml concentration (stock solution- II).

From stock solution- II 0.3 ml, 0.6 ml, 0.9 ml, 1.2 ml and 1.5 ml were accurately transferred to respective 10 ml volumetric flasks and made upto volume with freshly prepared 0.1 M HCl which corresponds to concentrations of 3, 6, 9, 12, 15 mcg/ ml respectively. The absorbance for the above dilutions was measured at 253.20 nm.

METHOD VALIDATION:

Precision:

Intra- day and inter- day precision was calculated at three points of calibration curve (3, 9 and 15 mcg/ ml respectively) within 1 day and on 3 different days respectively.

Accuracy:

Accuracy of the method was confirmed by recovery study from marketed formulation at three levels of standard addition from 50%, 100% and 150 % of label claim. The recovery studies were carried out in triplicate.

LOD:

Lowest limit of detection was calculated using the formula

$$LOD = 3.3\delta / m$$

LOQ:
Lowest limit of quantitation was calculated using the formula

$$LOD = 10\delta / m$$

Where δ= standard deviation, m= slope from the line equation of standard calibration curve [11]

Assay Of Formulation (Flunarin 5 mg Tablets):
20 tablets were weighed accurately and average weight of tablet was noted that constitutes 5 mg FNZ and was finely powdered. The tablet powder equivalent to 2.5 mg of FNZ was accurately weighed and transferred to 25 ml volumetric flask and dissolved in about 10 ml of the solvent (0.1 M HCl). It was then vortexed for 45 minutes to enhance maximum extraction of the active pharmaceutical ingredient from the dosage form and filtered through Whatmann No 1 filter paper to remove insoluble excipients to the maximum extent. It was then made upto the volume with the same solvent that constitutes 100 mcg/ ml of FNZ. From the stock solution, aliquot corresponding to medium concentration of standard curve (9 mcg/ ml) was prepared and made upto the mark with the solvent. The absorbance was noted and the corresponding concentration was then determined from the standard calibration curve.

Dissolution studies of flunarin tablets:
Dissolution studies were carried out using rotating paddle apparatus (USP type- II) by dissoluting each Flunarin tablet in a dissoluting jar containing 900 ml of 0.1 M HCl (dissolution medium) maintaining the temperature at 37 ± 2° C rotating the paddle at a speed of 50 rpm for 60 min [12,13]. 5 milliliters of sample was withdrawn at time intervals of 0, 5, 15, 30, 45 and 60 min respectively. ,Each 5 ml of withdrawn sample is replaced by 5 ml of 0.1 M HCl to maintain sink condition. The samples were then filtered through Whatmann No 1 filter paper to avoid interference of excipients. The absorbance of the resulting solutions was measured at 253.20 nm against 0.1 M HCl as blank.

RESULTS AND DISCUSSION:

Method Development and Validation:
Correlation coefficient within concentration range of 3- 15 mcg/ ml (n= 5) was found to be 0.9995. It represents that there exists linear relationship between concentrations and their corresponding absorbance.

Fig 2 Overlay spectra of FNZ (3- 15 mcg/ ml)

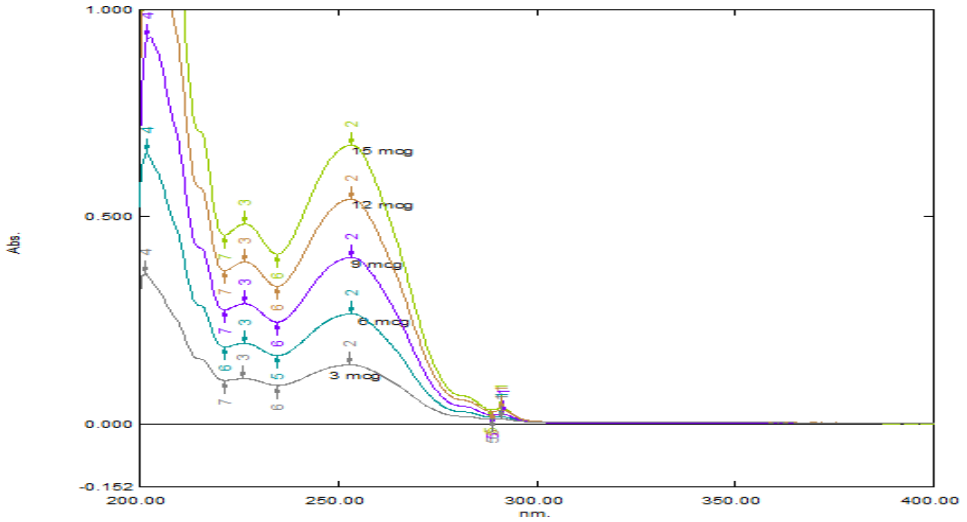


Fig 3 Standard Calibration curve of FNZ

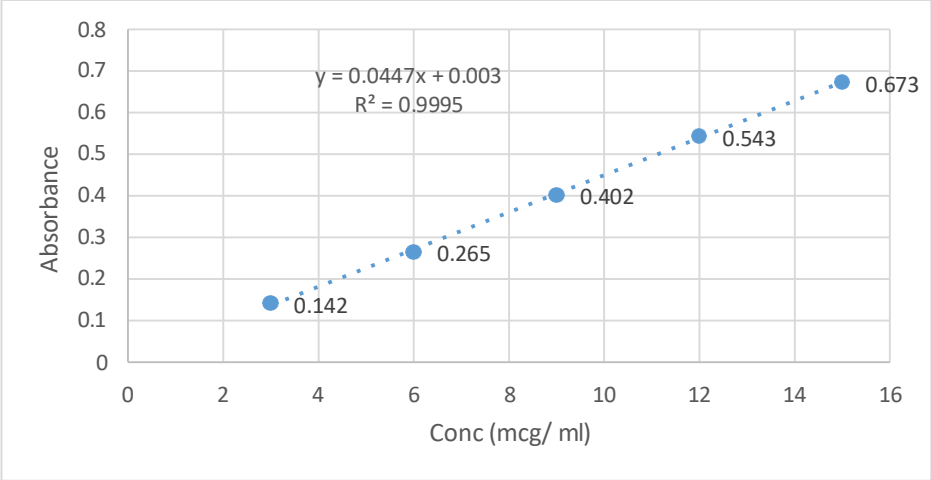


Table 1 Linearity data of FNZ by UV spectrophotometry

Linearity range	3- 15 mcg/ ml
Correlation coefficient (r^2)	0.9995
y- intercept (C)	0.003
Slope (m)	0.0447

The method was precise and the % RSD of intra- day and inter- day precision were within limits (<2.0).

Table 2 Precision data

Precision		% RSD	
Intra- day (n= 9)	Day 1	Day 2	Day 3
3 mcg/ ml	1.40	0.44	1.39
9 mcg/ ml	0.27	0.07	0.67
15 mcg/ ml	0.18	0.09	0.24
Inter- day (n= 6)			
3 mcg/ ml		1.80	
9 mcg/ ml		0.99	
15 mcg/ ml		0.90	

Recovery studies yielded good results within limits (98- 102%).

Table 3 Accuracy data of FNZ

FNZ in dosage form (µg ml^{-1})	% Pure FNZ added	Pure FNZ added(µg ml^{-1})	Concentration of FNZ found (µg ml^{-1})	FNZ Recovered% ±RSD*
6	50%	3	9.171	101.90 ± 0.44
6	100%	6	12.05	100.42 ± 0.07
6	150%	9	14.85	99.00 ± 0.17

*Average of 3 experiments LOD and LOQ were 0.2471 mcg and 0.7489 mcg respectively.
Drug content of molsidain tablets from the assay was found to be 95.42% (limits: 95- 105%).

Table 4 Percent label amount of FNZ in tablets

Formulation	Label claim	Amount found	% Assay ± RSD*
Flunarin 5	5 mg	4.771 mg	95.42 ± 0.10

*Average of 3 experiments

Dissolution studies:
invitro dissolution studies using simulated gastric fluid (0.1 M HCl) provided data relating the % drug release with respect to time (fig 4 , table 5). It might be helpful to predict and study *invivo* dissolution profile.

Fig 4 Graph showing % drug release of FNZ with time

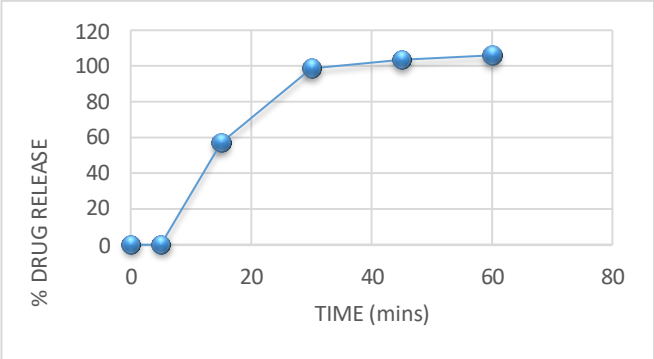


Table 5 Dissolution profile of Flunarin tablets

Time (mins)	Absorbance	Concentration (mcg/ ml)	Amount of drug released (mg)	Cumulative amount of drug dissolved (mg)	% drug release
0	0.000	0.000	0.000	0.000	0.000
5	0.000	0.000	0.000	0.000	0.000
15	0.145	3.176	0.003176	2.8584	57.16
30	0.248	5.48	0.00548	4.932	98.64
45	0.260	5.749	0.005749	5.1741	103.482
60	0.266	5.883	0.005883	5.2947	105.89

CONCLUSION:

A simple, accurate, precise, economical method was developed and validated to analyze Flunarizine Dihydrochloride in tablet dosage form in conjunction with dissolution studies. The developed method can be utilized for routine analysis in quality control laboratories. Application of developed method for dissolution studies enhances the scope to monitor invivo dissolution profile and bioavailability of the drug in biological systems.

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