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FORMULATION, EVALUATION AND ESTIMATION OF PROPRANOLOL HYDROCHLORIDE AND FLUNARIZINE DIHYDROCHLORIDE CONVENTIONAL TABLETS IN COMBINED DOSAGE FORM AND ITS COMPARISON WITH MARKETED FORMULATIONS

Dipali Malhotra* and Ravi Sharma

Department of Pharmaceutical Analysis, ASBASJSM College of Pharmacy, BELA (Ropar) 140111, Punjab, India

Keywords:

Oral route, Conventional tablets, Propranolol Hydrochloride, Flunarizine Dihydrochloride,

Correspondence to Author:
Dipali Malhotra

Department of Pharmaceutical Analysis, ASBASJSM College of Pharmacy, BELA (Ropar) 140111, Punjab, India

E-mail: dipalimalhotra68@yahoo.com

ABSTRACT: Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. This study was aimed at development of Propranolol hydrochloride and flunarizine dihydrochloride conventional dissolving tablets in combined dosage form. Propranolol competes with sympathomimetic neurotransmitters such as catecholamines for binding at beta (1)-adrenergic receptors in the heart, inhibiting sympathetic stimulation and Flunarizine is a selective calcium entry blocker with calmodulin binding properties and histamine H1 blocking activity both are effective in the treatment of coexistence of hypertension & migraine.

INTRODUCTION: Migraine is a neurologic disease, associated with throbbing intense headache in one half of the head. It is characterized by recurrent attacks of intense headache and nausea that occur at irregular intervals and last for several hours. Flunarizine is a selective calcium channel blocker and coupled with its antihistaminic property it is claimed to be effective in prophylaxis of migraine. It is effective in migraine by reducing intra-cellular Ca^{2+} overload due to brain hypoxia and thus prevents the deleterious effects of cellular calcium overload. With a very long half-life, flunarizine may be given once daily; and drowsiness, the main side effect, can be minimized by taking the daily dose in the evening [1].

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Propranolol hydrochloride is a non-specific beta-adrenergic blocking agent used in the treatment of hypertension. The absolute bioavailability is only approximately 26% due to extensive hepatic metabolism. So, conventional tablet of both drugs can be effective in the treatment of coexistence of migraine and hypertension [2]. Chemical structures of Propranolol hydrochloride and Flunarizine dihydrochloride are given in (**Fig.1)**.

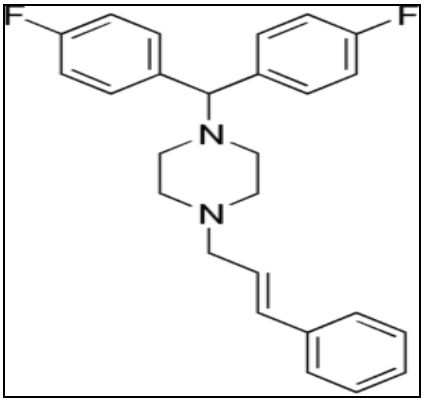

FIG.1. (a) FLUNARIZINE

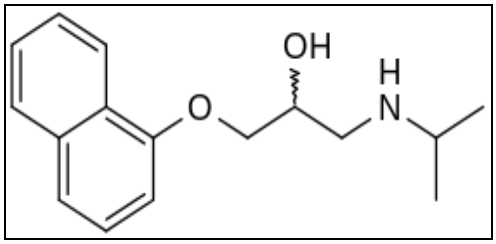

FIG.1. (b) PROPRANOLOL

MATERIALS AND METHODS:

Propranolol Hydrochloride and Flunarizine Dihydrochloride were obtained as a gift sample from Tanpal Pharmaceuticals Nabha. Lactose, Talcum and Magnesium stearate were obtained from ASBASJSM College of Pharmacy Bela (Ropar). All chemicals and reagents used were of Analytical grade.

Formulation of Conventional Tablets:

Propranolol Hydrochloride, Flunarizine Dihydrochloride and excipients like lactose, Talcum, Magnesium stearate, blank dummy granules were co-grounded in pestle mortar (except talc and magnesium stearate) and were passed through mesh. No.60. Finally talc and magnesium stearate were added and mixed for 5 min. The mixed blends of excipients were compressed using a single punch tablet machine to produce convex faced tablets weighing 225 mg each with thickness between 3.0-3.4 mm and 8 mm in diameter by direct compression method. Composition of conventional tablets is shown in **(Table 1)**.

Composition of Blank Dummy:

It is composed of starch forming paste, gelatin, methyl paraben sodium, propyl paraben sodium, starch, dibasic calcium phosphate, microcrystalline cellulose phosphate.

TABLE 1: COMPOSITION OF CONVENTIONAL TABLETS TABLE

Ingredient	Amount (in mg)
Propranolol Hydrochloride	20
Flunarizine Dihydrochloride	10
Lactose (1%)	2.25
Talcum (2%)	4.5
Magnesium Stearate (1%)	2.25
Blank Dummy Granules	186
Total Weight	225

Evaluation of MDTs:

Pre-compression characterization:

Bulk Density: [3, 4]

Apparent bulk density was determined by pouring the 5gm of powder into a 100 ml granulated cylinder. The bulk volume (V) poured drug was determined. The bulk density was calculated using the formula. Result is shown in **(Table 2)**.

$\rho_b = M / V$

Where: ρ_b - bulk density, M- is the weight of powder, V- is the volume of powder.

Tapped Density: [3, 4]

Weight 5gm of powder and placed in a measuring cylinder. Measuring cylinder containing known mass (5gm) of powder was tapped for 100 times or fixed time. The minimum volume (V_t) occupied was measured. The tapped density was calculated using following formula. Result is shown in **(Table 2)**.

$\rho_t = M / V_t$

Where: ρ_t - tapped density, M- is the weight of powder, V_t- is the volume of powder

Compressibility Index: [4, 5]

The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by Compressibility Index. The value below 15% indicates a powder with give rice to good flow properties, whereas above 25% indicate poor flowability. This is calculated as follow. Result is shown **(Table 2)**.

$\% C.I. = \rho_t - \rho_b / \rho_t \times 100$

Hausner ratio: [4]

Hausner ratio is an indirect index of ease of powder flow. Hausner ratio is the ratio of tapped density (ρ_t) to bulk density (ρ_b). Lower the value of Hausner ratio better is the flow property. Powder with Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (> 1.25). It is calculated by following formula. Result is shown in **(Table 2)**.

Hausner ratio = ρ_t / ρ_b

Angle of repose: [4, 6]

The angle of repose was determined using funnel method. Funnel can be fit vertically with stand at 6.3cm height. The opening end of funnel is closed

with thumb until drugs are poured. The 5 gm of powder was poured into funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (Θ) was calculated using the formula. Result is shown in **(Table 2)**.

$\Theta = \tan^{-1} (h / r)$

TABLE 2: PRE-COMPRESSION PARAMETERS (CHARACTERIZATION OF BLENDS)

Formulation codes	Bulk density(g/cc)	Tapped density(g/cc)	Hausner's ratio	Compressibility index (%)	Angle of repose(°)
Conventional Tablet Blend	0.390±0.001	0.457±0.005	1.17±0.007	14.66±0.537	34.04±1.004

Infrared spectral assignment (Drug polymer interaction studies):

The IR analysis of sample was carried out for qualitative compound identification. The infrared spectra of Propranolol hydrochloride and Flunarizine Dihydrochloride was performed on Fourier transformed infrared spectrophotometer. The infrared absorption spectra of drug and mixture of polymer and drug were run between 4000 – 400 cm^{-1}. Results are shown in **(Fig. 2, 3)** and **(Table 3)**

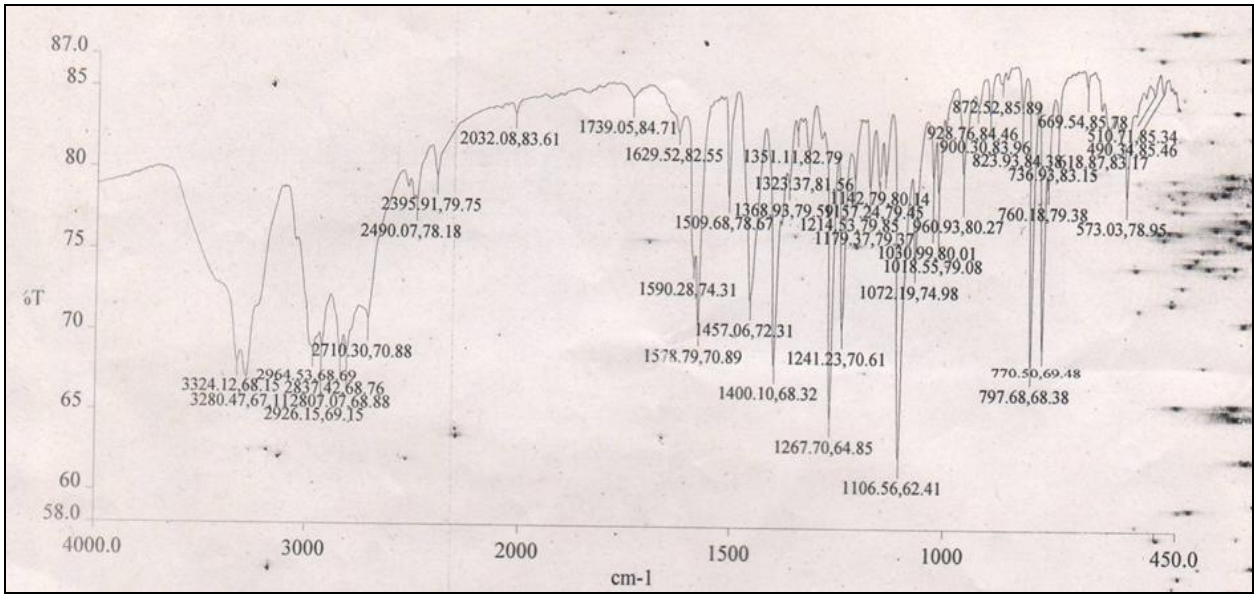

FIGURE 2: IR SPECTRA OF PURE PROPRANOLOL HYDROCHLORIDE

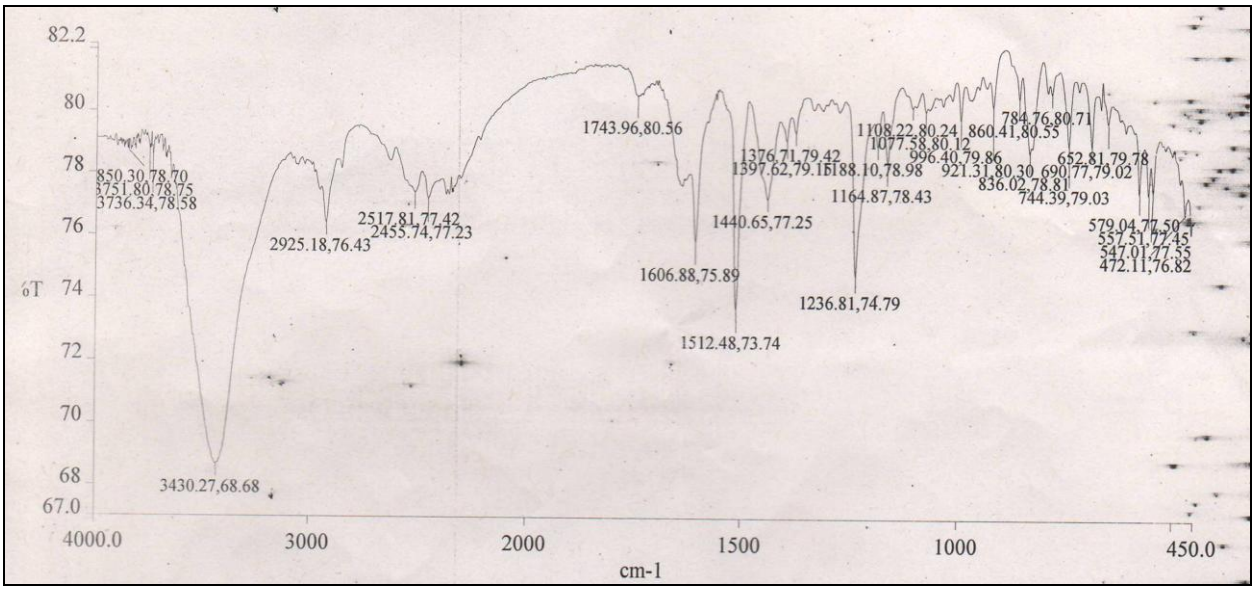

FIG. 3: IR SPECTRA OF PURE FLUNARIZINE DIHYDROCHLORIDE

TABLE 3: IR Study Data

Drug	FTIR peaks (cm^{-1})
Propranolol Hydrochloride	3324.12 (N-H stretching) 1629.52 (C=C aromatic stretching) 1267.70 (C-O stretching) 797.68 (C-H aromatic out of plane bending)
Flunarizine Dihydrochloride	1236.81 (C-F stretching) 1164.87 (C-N stretching) 1606.88 (C=C aliphatic stretching)

Post- Compression Characterization: [7]

Hardness:

The test is done as per the standard methods. The hardness of three randomly selected tablets from each formulation is determined by placing each tablet diagonally between the two plungers of tablet hardness tester (with the nozzle) and applying pressure until the tablet broke down into two parts completely and the reading on the scale is noted down in kg/cm^2. Result is shown in **(Table 4)**.

Thickness:

The thickness of three randomly selected tablets from each formulation is determined in mm using a vernier caliper. The average values are calculated. Result is shown in **(Table 4)**.

Uniformity of Weight: [8, 9]

Weight variation test is done as per standard procedure. Twenty tablets from each formulation are weighed using an electronic balance and the average weigh are calculated.

Result is shown in **(Table 4)**.

Friability:

The friability of tablets using 10 tablets as a sample is measured using a Roche Friabilator. Tablets are rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets are then taken out, dedusted and reweighted. The percentage friability is calculated from the loss in weight as given in equation below. The weight loss should not more than 1%.

%Friability = (initial weight- final weight)/ (initial weight) x 100

Result is shown in **(Table 4)**.

TABLE 4: POST-COMPRESSION PARAMETERS (CHARACTERIZATION OF CONVENTIONAL TABLETS)

Formulation	Thickness (mm)	Average Weight(mg)	Hardness (kg/cm^2)	Friability (%)
Conventional tablets	4.57±0.01	226.59±0.99	4.134±0.094	0.61

Drug Content determination by Absorbance ratio method:

Absorption maximum, isopiestic point determination and Preparation of calibration curves in Methanol and distilled water.

Standard stock solutions of FLU and PRO were prepared separately by dissolving 10 mg of each drug in 10ml of methanol to get standard stock solution of 1000µg/ml respectively and 1 ml was pipette out and further volume was made up to 10 ml with distilled water to obtain concentration of 100µg/ml.

Further dilutions were made in distilled water from stock solution to get concentrations 8-48µg/ml for propranolol hydrochloride and 6-36 µg/ml for flunarizine dihydrochloride. Results are shown in **(Fig. 4, 5, 6, 7, 8, 9, 10)**.

Curve in Methanol and Distilled water:

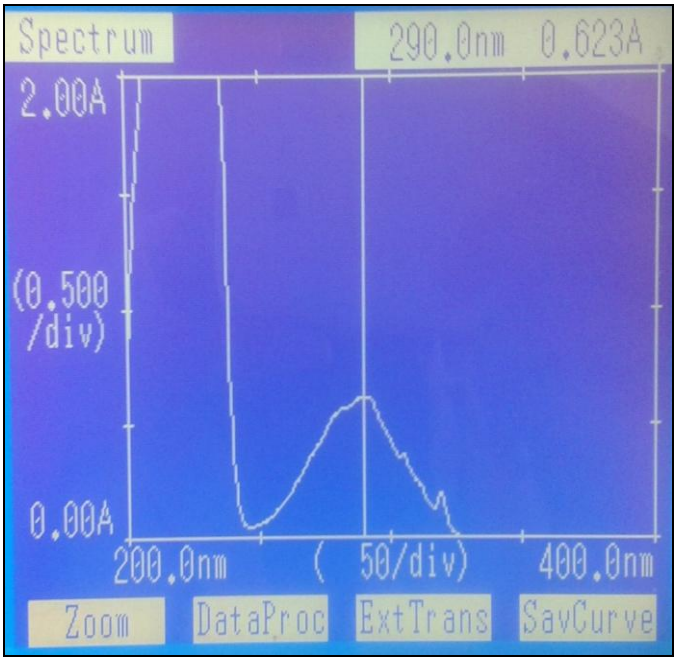

FIG.4: ABSORPTION MAXIMA OF PROPRANOLOL HYDROCHLORIDE

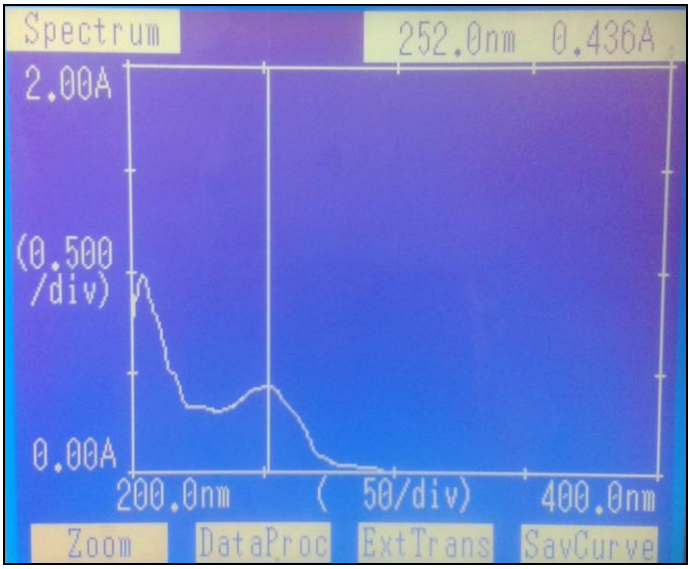

FIG. 5: ABSORPTION MAXIMA OF FLUNARIZINE DIHYDROCHLORIDE

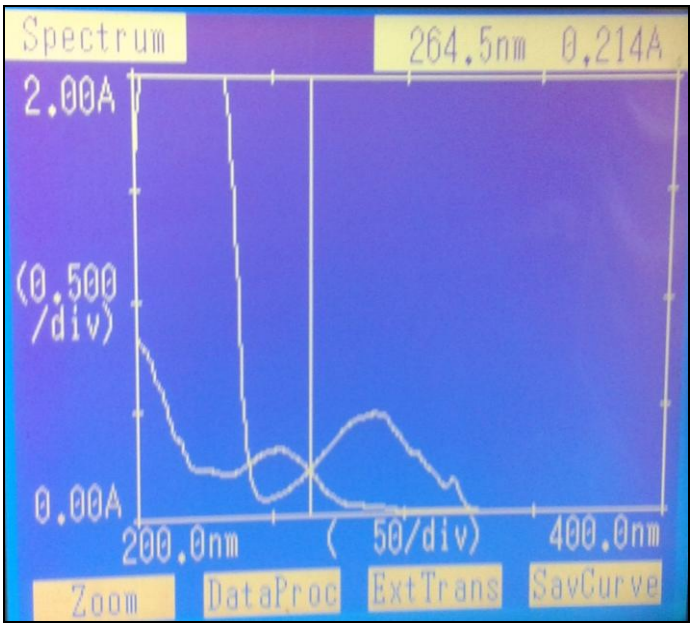

FIG.6: ISOBESTIC POINT OF PROPRANOLOL HYDROCHLORIDE AND FLUNARIZINE DIHYDROCHLORIDE

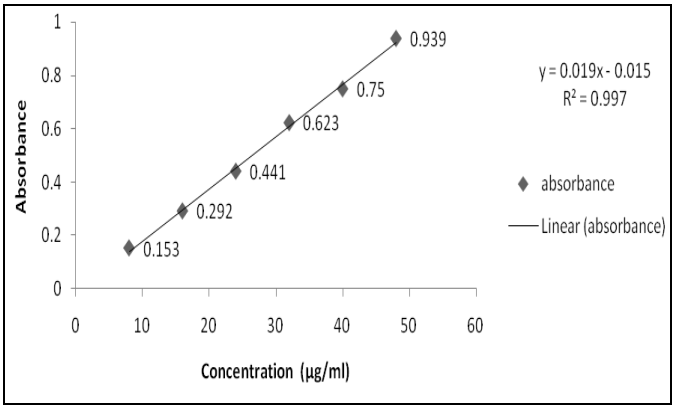

FIG. 7: CALIBRATION CURVE OF PROPRANOLOL HYDROCHLORIDE AT 290nm

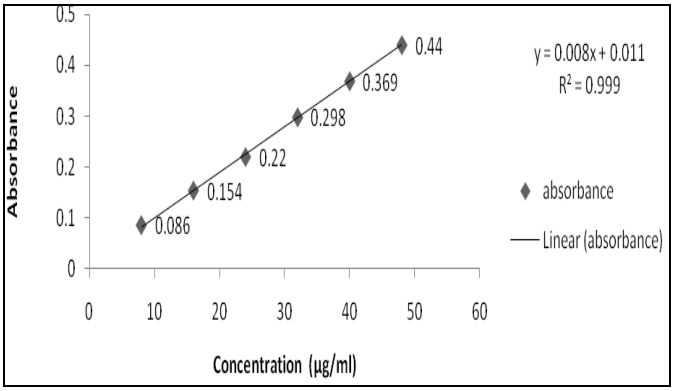

FIG. 8: CALIBRATION CURVE OF PROPRANOLOL HYDROCHLORIDE AT 264.5nm

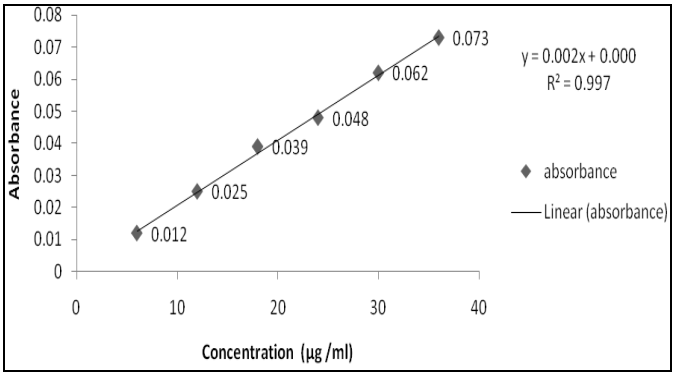

FIG. 9: CALIBRATION CURVE OF FLUNARIZINE DIHYDROCHLORIDE AT 290nm

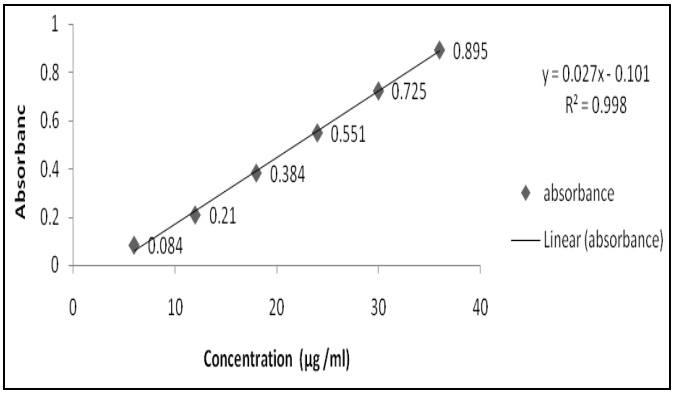

FIG. 10: CALIBRATION CURVE OF FLUNARIZINE DIHYDROCHLORIDE AT 264.5

Preparation of calibration curves in 0.1 M HCl

Standard stock solutions of FLU and PRO were prepared separately by dissolving 10 mg of each drug in 10ml of 0.1N to get standard stock solution of 1000 µg/ml respectively and 1 ml was pipette out and further volume was made up to 10 ml with 0.1HCl to obtain concentration of 100µg/ml. Further dilutions were made in distilled water from stock solution to get concentrations 8-48ug/ml for propranolol hydrochloride and 6-36 ug/ml for flunarizine dihydrochloride. Results are shown in **(Fig. 11, 12, 13, 14)**.

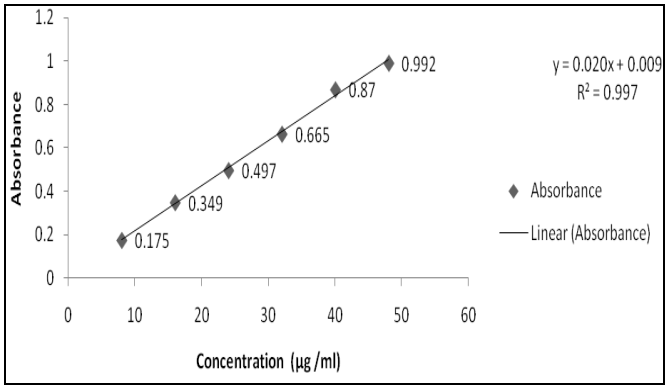

FIG. 11: CALIBRATION CURVE OF PROPRANOLOL HYDROCHLORIDE AT 290nm

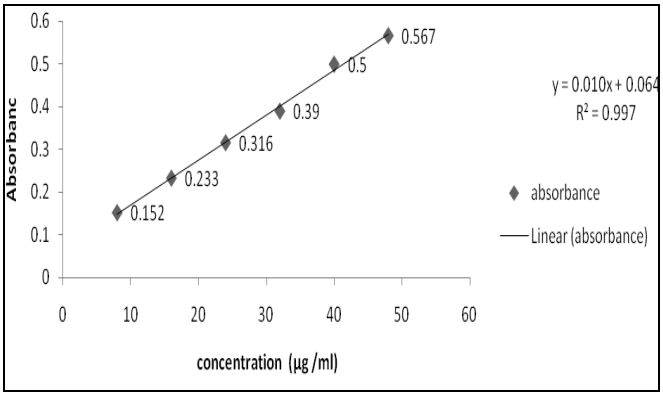

FIG. 12: CALIBRATION CURVE OF PROPRANOLOL HYDROCHLORIDE AT 264.5

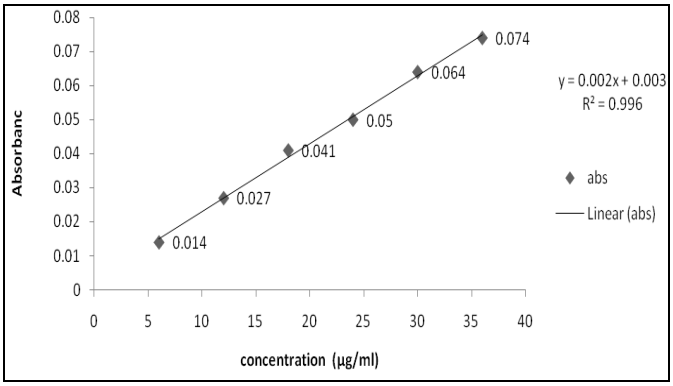

FIG.13: CALIBRATION CURVE OF FLUNARIZINE DIHYDROCHLORIDE AT 290nm

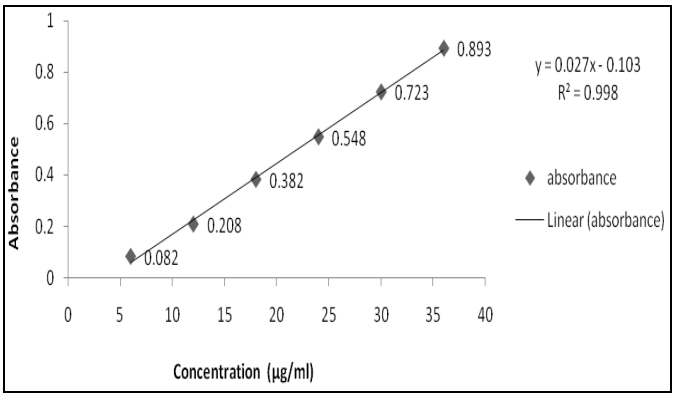

FIG. 14: CALIBRATION CURVE OF FLUNARIZINE DIHYDROCHLORIDE AT 264.5

For the content uniformity test, 20 tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 10 mg of Propranolol Hydrochloride and Flunarizine Dihydrochloride was accurately weighed, transferred into a 100 ml flask, dissolved in methanol to get concentration of 100ug/ml and this solution was sonicated for about 30 minutes then volume was made up to 10 ml and filtered to separate any insoluble matter .The clear solution obtained was diluted to get appropriate concentration with distilled water. The concentrations of two drugs in the mixture were calculated by using Absorbance ratio method at 290nm (λ_{max} of Propranolol Hydrochloride) and 264.5nm (isobestic point of Propranolol Hydrochloride and Flunarizine dihydrochloride)

$$C_X = \frac{Q_M - Q_Y}{Q_X - QY} \times \frac{A_1}{ax_1}$$

$$C_Y = \frac{Q_M - Q_X}{Q_Y - Q_X} \times \frac{A_2}{ay_2}$$

Where, $Q_M = A_2/A_1$; $Q_X = ax_2/ax_1$; $Q_Y = ay_2/ay_1$
A_1 and A_2 are the absorbance of diluted samples at λ_1 and λ_2, ax_1 and ax_2 are the absorptivity of X, ay_1 and ay_2 are the absorptivity of Y. Result is shown in **(Table 5)**.

Wetting Time: [7]

The tablets wetting time is measured by a procedure modified from that reported by Bi et al. The tablet is placed at the center of two layers of absorbent paper fitted into a dish. After paper is thoroughly wetted with distilled water, excess water is completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet is then recorded using a stopwatch. Result is shown in **(Table 5)**.

***In- vitro* Disintegration Time:**

Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The water was maintained at a temperature of 37°±2°C and time taken for the entire tablet to disintegrate completely was noted. Result is shown in **(Table 5)**.

TABLE 5: POST-COMPRESSION PARAMETERS (CHARACTERIZATION OF MOUTH DISSOLVING AND CONVENTIONAL TABLETS)

Formulation	Disintegration Time(sec)	Wetting Time (sec)	Drug Content (%)
Conventional tablets	720±1.25	43.33±0.47	Propranolol - 99.20±0.43 Flunarizine – 99.10±0.41

***In- vitro* drug release study:**

The release rate of Propranolol Hydrochloride and Flunarizine Dihydrochloride from conventional tablets was determined using USP XXIV dissolution testing apparatus II (paddle method) using 900 ml of in 0.1M HCl as a dissolution medium at 37 ± 0.5˚C and 75 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at different time interval (min). The samples were filtered through a Whatman filter paper. Absorbance of these solutions was measured at 290 nm ((λ_{max} of Propranolol Hydrochloride) 264.5nm (isobestic point of Propranolol Hydrochloride and Flunarizine Dihydrochloride). Results are shown in **(Table 6) (Fig.15)**.

TABLE 6: DISSOLUTION PROFILE OF CONVENTIONAL TABLETS

Time in minutes	Cummulative %drug release Propranolol Hydrochloride	Cummulative %drug release Flunarizine dihydrochloride
0	0	0
5	18.65	18.45
10	30.78	30.56
15	43.56	42.32
20	54.89	53.21
25	63.65	63.35
30	71.46	70.34
35	78.20	78.10
40	82.56	82.49
45	83.67	84.74

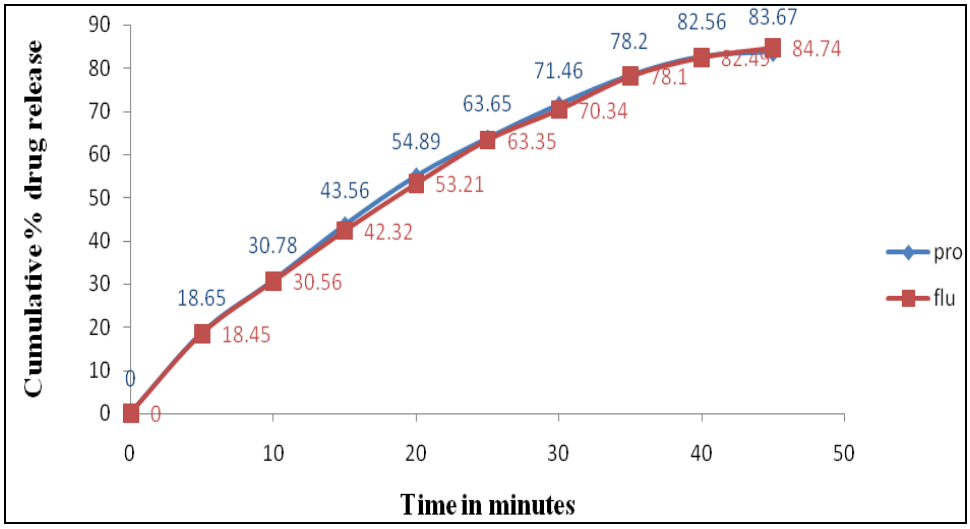

FIG.15: PERCENT RELEASE OF CONVENTIONAL TABLETS

Comparison with marketed formulations:

In vitro drug release and drug content of conventional tablets was determined and compared with marketed conventional tablets of Provanol Plus 10(Propranolol 20mg, Flunarizine 10mg). Results are shown in **(Table 7)** and **(Figure 16)**

Stability Studies:

Temperature dependent stability studies:

The Combined conventional tablets of Propanolol Hydrochloride and Flunarizine Dihydrochloride were packed in wide mouth air tight glass container and stored at (40 ± 2 ˚C and 75 ± 5 % RH) for a period of 3 months.

The tablets were withdrawn after a repeated period of 15 days and analyzed for physical

characterization and drug content spectrophotometrically at 290nm and 264.5nm. Among several methods investigated for dissolution profile comparison, *f2* is the simplest.

$$f_2 = 50 \bullet \log \{[1+1/n\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \bullet 100$$

Where R_t and T_t are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively.

When the two profiles are identical, *f2*=100. An average difference of 10% at all measured time point's results in an *f2* value of 50. FDA has set a public standard of *f2* value between 50-100 indicate similarity between two dissolution profiles. Results are shown in **(Table 8, 9, 10) (Fig. 17)**.

TABLE 7: COMPARISON OF *IN VITRO* DRUG RELEASE WITH MARKETED FORMULATION

Time (min)	Cummulative %drug release of Propranolol hydrochloride in conventional tablet	Cummulative %drug release of Flunarizine Dihydrochloride in conventional tablet	Cummulative %drug release of Propranolol hydrochloride in marketed conventional tablet- Provanol Plus 10	Cummulative %drug release of Flunarizine Dihydrochloride in conventional tablet- Provanol Plus 10
0	0	0	0	0
5	18.65	18.45	14.33	14.23
10	30.78	30.56	24.76	25.21
15	43.56	42.32	33.24	33.14
20	54.89	53.21	41.57	40.56
25	63.65	63.35	52.34	52.24
30	71.46	70.34	61.21	60.89
35	78.20	78.1	70.89	69.98
40	82.56	82.49	72.34	72.23
45	83.67	84.74	79.98	78.91

TABLE 8: EFFECT OF STORAGE CONDITIONS ON CONVENTIONAL TABLETS

No. of days	Avg. weight (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (sec)	Drug Content (%)
0	226.72 ±1.07	4.13±0.094	0.61	142±1.25	99.20±0.32
15	226.79±0.78	4.13±0.1	0.57	140±1.15	99.15±0.014
30	226.96±0.84	4.13±0.2	0.56	140±1.55	99.10±0.008
45	226.61±1.24	4.12±0.4	0.57	139±1.10	98.60±0.023
60	226.57±0.30	4.12±0.4	0.57	139±1.46	98.58±0.032
75	226.49±0.91	4..08±0.3	0.63	139±1.13	98.51±0.017
90	226.46±0.36	4.08±0.3	0.65	139±1.58	99.42±0.007

Comparison of drug release data before and after storage of Conventional tablets:

TABLE 9: BEFORE STORAGE

Times in minutes	Cummulative %drug release Propranolol Hydrochloride	Cummulative %drug release Flunarizine dihydrochloride
0	0	0
5	18.65	18.45
10	30.78	30.56
15	43.56	42.32
20	54.89	53.21
25	63.65	63.35
30	71.46	70.34
35	78.20	78.10
40	82.56	82.49
45	83.67	84.74

TABLE 10: AFTER STORAGE

Times in minutes	Cummulative %drug release Propranolol Hydrochloride	Cummulative %drug release Flunarizine dihydrochloride
0	0	0
5	17.64	17.43
10	29.76	29.54
15	42.58	41.30
20	53.87	52.19
25	62.57	62.33
30	70.43	69.33
35	77.23	77.09
40	81.57	81.47
45	82.69	83.73

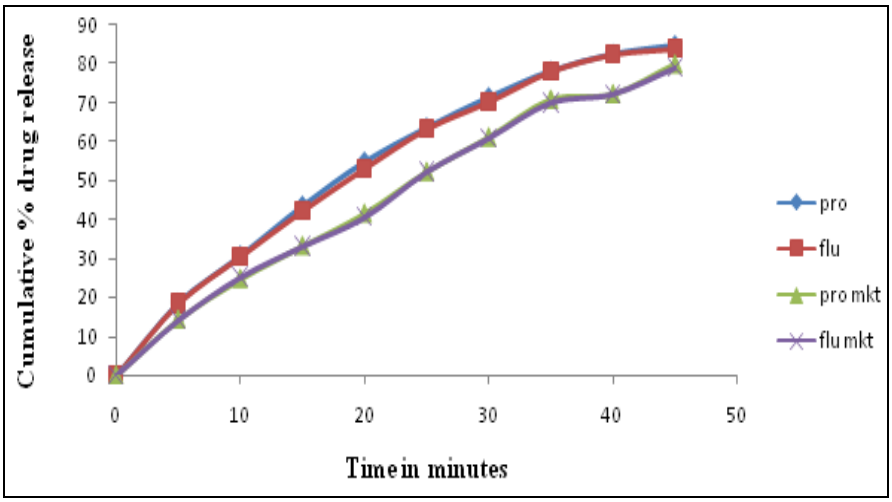

FIG. 16: PERCENT RELEASE OF PROPRANOLOL HYDROCHLORIDE AND FLUNARIZINE DIHYDROCHLORIDE IN COMBINED CONVENTIONAL TABLET AND COMBINED CONVENTIONAL MARKETED FORMULATED TABLET

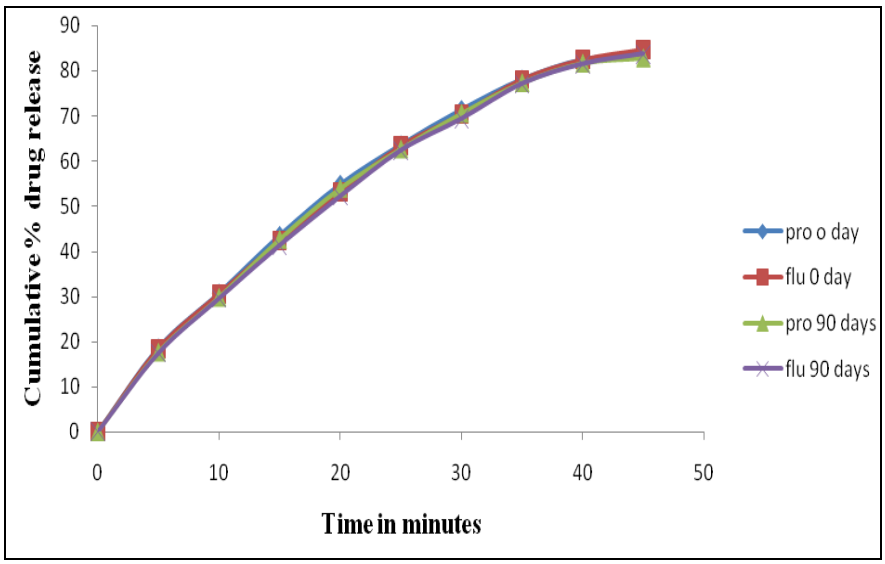

FIG. 17: COMPARISON OF DRUG RELEASE BEFORE AND AFTER STABILITY STUDIES OF MOUTH DISSOLVING TABLETS

RESULT AND DISCUSSION: Combined Conventional tablets of Propranolol Hydrochloride and Flunarizine Dihydrochloride were prepared by direct compression method. **Table 1** shows the composition of Conventional tablets and **Table 2** shows the Pre-compression evaluation of tablets.

Conventional tablets were evaluated for various pre and post compression parameters.

Pre – Compression parameters like bulk density, tapped density, Hausner's ratio, compressibility index, angle of repose, IR studies of pure drugs for identification are shown in **Fig. 2, 3** and **Table 3**. Post- compression parameters such as hardness, friability, wetting time, disintegration time, dissolution studies, and drug content were evaluated shown in **Table 4, 5**. Drug content was determined by Absorption ratio method by selecting two wavelengths 290 (λ_{max} of Propranolol Hydrochloride) and 264.5 (isobestic point of Propranolol Hydrochloride and Flunarizine Dihydrochloride) and the standard plots in methanol and in 0.1M HCl are shown in **Fig.** 7,8,9,10,11,12,13,14. The *in- vitro* disintegration time is within the prescribe limit and comply with the criteria for Conventional tablets, the value as 720±1.25 seconds). *In- vitro* dissolution study is shown in Table 6 and in **Fig.15**. It shows highest drug release of Propranolol Hydrochloride 83.67%, Flunarizine Dihydrochloride 84.74% at 45minutes.

Comparison of the *in- vitro* drug release of combined Conventional tablet of Propranolol Hydrochloride and Flunarizine Dihydrochloride with marketed combined tablet: - Provanol plus 10 (Propranolol 20mg, Flunarizine 10mg) is shown in **Table 7** and in **Fig.16**. Stability studies of Conventional tablets are shown in **Table** 8,9,10 and **Fig. 17**.

CONCLUSION: Formulated conventional tablet was having high percentage of drug release as compare to marketed formulation. Simultaneously and quantitatively estimated by U.V. spetrophotometric Q- Absorbance Ratio Method.

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