Research Article

Formulation, Evaluation and Estimation of Propranolol Hydrochloride and Flunarizine Dihydrochloride Mouth Dissolving Tablets in Combined Dosage form and its Comparison with Marketed Formulations

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Abstract

Mouth dissolving tablets (MDTs) have received ever increasing demand during last decade and it is a rapidly a growing area in the pharmaceutical industry due to its convenience in self administration, compactness and ease of manufacturing. This study was aimed at development of Propranolol hydrochloride and Flunarizine dihydrochloride mouth dissolving tablets in combined dosage form which can disintegrate or dissolve rapidly once placed in the oral cavity. 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. The tablet was prepared with two superdisintegrants: crosscarmellose sodium and sodium starch glycolate. The blend was evaluated for pre- compression, post-compression and for stability studies.

Keywords: Mouth dissolving tablets; Propranolol Hydrochloride; Flunarizine Dihydrochloride; Superdisintegrants; Stability studies

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 chan-nel 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]. Propranolol hydrochloride is a non-specific beta-adrenergic blocking agent used in the treatment of hypertension. The ab-solute bioavailability is only approximately 26% due to extensive hepatic metabolism. So, combined mouth dissolving tablet of both drugs can be effective in the treatment of coexistence of migraine and hypertension [2].

The aim of proposed work was to formulate, evaluate and estimate the combined mouth dissolving tablets of Propranolol Hydrochloride and Flunarizine Dihydrochloride to avoid extensive first pass metabolism and improvement in dissolution efficacy, disintegration time which results in improvement in bioavailability and with reducing dosing frequency to minimize side effects.

Materials and Methods

Propranolol Hydrochloride and Flunarizine were obtained as a gift sample from Tanpal Pharmaceuticals, Nabha. Crosscarmellose, So-dium starch glycolate, Lactose, Dextrose, Magnesium stearate, Mannitol, Pineapple flavor and Aspartame were obtained from ASBASJSM College of Pharmacy Bela (Ropar). All chemicals and reagents used were of Analytical grade.

Formulation, Evaluation and Estimation of Propranolol Hydrochloride and Flunarizine Dihydrochloride Mouth Dissolving Tablets in Combined Dosage form and its Comparison with Marketed Formulations

06

Figure 1: (a) Propranolol Hydrochloride (b) Flunarizine Dihydrochloride

Formulation of Mouth Dissolving Tablets

Propranolol Hydrochloride, Flunarizine Dihydrochloride and excipients like lactose, dextrose, mannitol, crosscarmellose sodium, sodium starch glycolate, pineapple flavour and aspartame 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 tablets is given in table 1.

Ingredient	Amount (in mg)
Propranolol Hydrochloride	20
Flunarizine Dihydrochloride	10
Lactose (1%)	2.25
Dextrose (2%)	4.5
Talcum (2%)	4.5
Magnesium Stearate (1%)	2.25
Manitol (1%)	2.25
Crosscarmellose Sodium (2%)	4.5
Sodium Starch Glycolate (2%)	4.5
Pineapple Flavour (1%)	2.25
Aspartame	2.25
Blank Dummy Granules	167.75
Total Weight	225

Table 1: Composition of Mouth Dissolving Tablets.

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.

Evaluation of Mdts

Bulk Density [3,4]

Composition of Blank Dummy

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 reported 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 5 gm of powder and placed in a measuring cylinder. Measuring cylinder containing known mass (5 gm) 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 for-mula. Result is reported 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 reported in table 2.

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

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 Hausner ratio less than 1.18, 1.19, 1.25, 1.3, 1.5 and greater than 1.5 indicate excellent, good, passable, and very poor,

Formulation, Evaluation and Estimation of Propranolol Hydrochloride and Flunarizine Dihydrochloride Mouth Dissolving Tablets in Combined Dosage form and its Comparison with Marketed Formulations

07

respectively. It is calculated by following formula. Result is reported in table 2.

$$\text{Hausner ratio} = \rho_t/\rho_b$$

Angle of repose [4,6]

The angle of repose was determined using funnel method. Funnel can be fit vertically with stand at 6.3 cm 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 reported in table 2.

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

Figure 3: IR spectra of pure Flunarizine Dihydrochloride.

Formulation codes	Bulk density (g/cc)	Tapped density(g/cc)	Hausner's ratio	Compressibility index (%)	Angle of repose(°)
MDTs Blend	0.395 ± 0.002	0.464 ± 0.003	1.17 ± 0.001	14.87 ± 0.075	32.59 ± 0.907

Table 2: Pre-compression Parameters (Characterization of blends).

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. It is therefore necessary to confirm that drug are not interacting with the polymer. The infrared absorption spectra of drug and mixture of polymer and drug were run between 4000 – 400 cm^{-1}.

Figure 4: IR spectra of Propranolol Hydrochloride and Crosscarmellose sodium.

Figure 2: IR spectra of pure Propranolol Hydrochloride.

Figure 5: IR spectra of Flunarizine Dihydrochloride and Crosscarmellose sodium.

Formulation, Evaluation and Estimation of Propranolol Hydrochloride and Flunarizine Dihydrochloride Mouth Dissolving Tablets in Combined Dosage form and its Comparison with Marketed Formulations

08

was no interaction between the functional groups of drugs and polymers, so selected drugs and polymers were compatible for the formulation of combined mouth dissolving tablet.

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 reported 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 reported 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 reported 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 min-utes 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%. Result is reported in table 4.

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

Figure 6: IR spectra of Propranolol Hydrochloride and Sodium starch glycolate.

Figure 7: IR spectra of Flunarizine Dihydrochloride and Sodium starch glycolate.

Mixture	FTIR peaks (cm^{-1})
Propranolol Hydrochloride + Crosscarmellose sodium	3327.09 (N-H stretching) 1608.97 (C = C aromatic stretching) 1267.66 (C-O stretching) 797.67 (C-H aromatic out of plane bending)
Propranolol Hydrochloride + sodium starch glycolate	3434.98 (N-H stretching) 1650.61 (C = C aromatic stretching) 1267.27 (C-O stretching) 797.30 (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)
Propranolol Hydrochloride + Crosscarmellose sodium	1236.62 (C-F stretching) 1164.25 (C-N stretching) 1607.07 (C = C aliphatic stretching)
Flunarizine Dihydrochloride + Sodium starch glycolate	1232.43 (C-F stretching) 1150.96 (C-N stretching) 1645.70 (C = C aliphatic stretching)

Table 3: Drug Excipients Compatibility Study Data.

From the above information as given in Table 5, it was confirmed that there

Formulation	Thickness (mm)	Average Weight (mg)	Hardness (kg/cm^2)	Friability (%)
Mouth dissolving tablets	4.59 ± 0.05	226.72 ± 1.07	3.267 ± 0.094	0.74

Table 4: Post-compression parameters (Characterization of mouth dissolving tablets).

Formulation, Evaluation and Estimation of Propranolol Hydrochloride and Flunarizine Dihydrochloride Mouth Dissolving Tablets in Combined Dosage form and its Comparison with Marketed Formulations

09

Drug content determination by absorbance ratio method

Absorption maximum, isobestic 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 10 ml of methanol 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 distilled water to obtain concentration of 100 μg/ml. Further dilutions were made in distilled water from stock solution to get concentrations 8-48 μg/ml for propranolol hydrochloride and 6-36 μg/ml for flunarizine dihydrochloride.
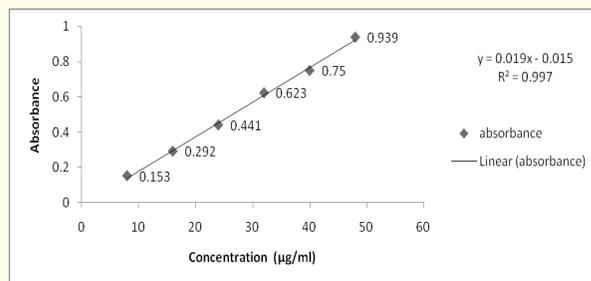
Figure 11: Calibration curve of Propranolol hydrochloride at 290 nm.

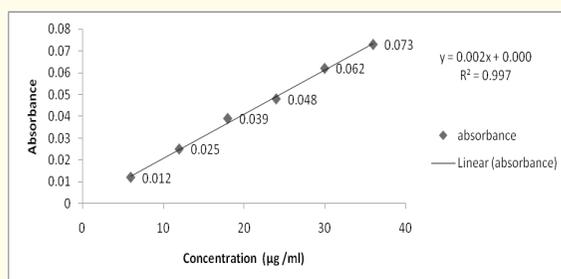**Figure 8:** Absorption maxima of Propranolol hydrochloride.
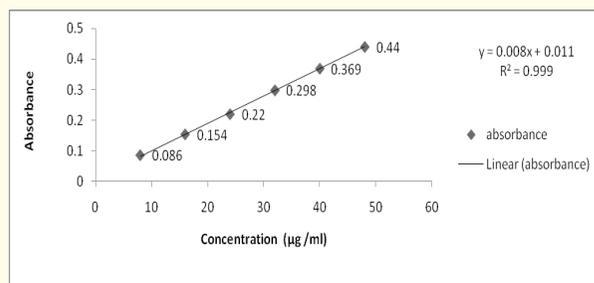
Figure 12: Calibration curve of Propranolol hydrochloride at 264.5 nm.

Figure 9: Absorption maxima of Flunarizine Dihydrochloride.

Figure 13: Calibration curve of Flunarizine Dihydrochloride at 290 nm.

Figure 10: Isobestic point of Propranolol hydrochloride and Flunarizine Dihydrochloride.

Formulation, Evaluation and Estimation of Propranolol Hydrochloride and Flunarizine Dihydrochloride Mouth Dissolving Tablets in Combined Dosage form and its Comparison with Marketed Formulations
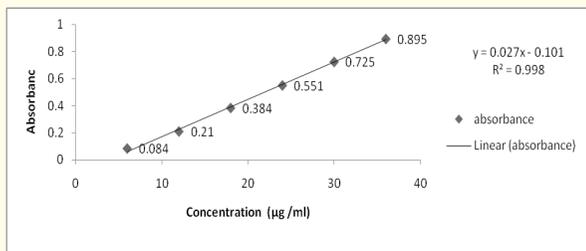
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Figure 14: Calibration curve of Flunarizine Dihydrochloride at 264.5.
Preparation of calibration curves in 0.1 M HCl.

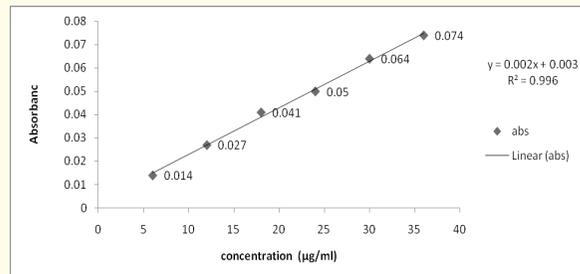**Figure 17:** Calibration curve of Propranolol hydrochloride at 264.5.

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 0.1 HCl to obtain concentration of 100 µg/ml. Further dilutions were made in distilled water from stock solution to get concentrations 8-48 µg/ml for propranolol hydrochloride and 6-36 µg/ml for flunarizine dihydrochloride.
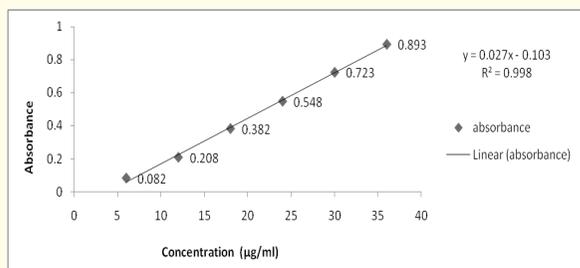

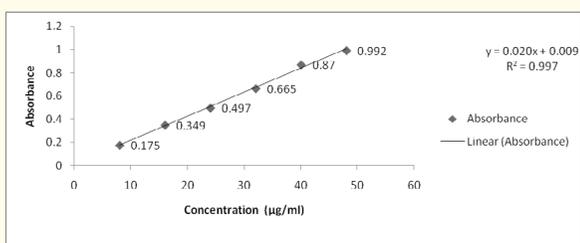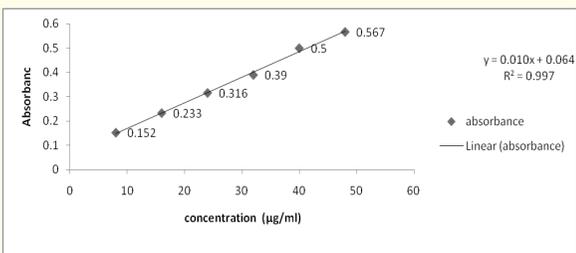**Figure 18:** Calibration curve of Flunarizine Dihydrochloride at 264.5.

Figure 15: Calibration curve of Propranolol hydrochloride at 290 nm.

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 100 ug/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 290 nm (λ_{max} of Propranolol Hydrochloride) and 264.5 nm (isobestic point of Propranolol Hydrochloride and Flunarizine dihydrochloride). Result is reported in table5.

$$C_x = \frac{QM - Q_Y A_1}{Q_X - Q_Y ax_1} \times -----$$

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

Figure 16: Calibration curve of Propranolol hydrochloride at 290 nm.

Formulation, Evaluation and Estimation of Propranolol Hydrochloride and Flunarizine Dihydrochloride Mouth Dissolving Tablets in Combined Dosage form and its Comparison with Marketed Formulations

11

Where, $Q_M = A_2/A_1$; $QX = ax_2/ax_1$; $Q_Y = ay_2/ay_1$

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.

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 reported in table 5.

***In- vitro* Disintegration Time**

Disintegration of mouth dissolving tablets is achieved in the mouth owing to the action of saliva, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate *in- vivo* conditions. A modified method was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10-meshscreen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve. To determine disintegration time, 6 ml of phosphate buffer (pH 6.8), was placed inside the vessel in such way that 2 ml of the media was below the sieve and 4 ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined.

Formulation	Disintegration Time (sec)	Wetting Time (sec)	Drug Content (%)
Mouth dissolving tablets	37 ± 0.68	34.33 ± 1.24	99.90 ± 0.33

Table 5: Post-compression parameters (Characterization of mouth dissolving tablets).
Dissolution profile of Mouth dissolving tablets of Propranolol Hydrochloride and Flunarizine dihydrochloride in combined dosage form

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

The release rate of Propranolol Hydrochloride and Flunarizine Dihydrochloride from mouth dissolving 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) 264.5 nm (isobestic point of Propranolol Hydrochloride and Flunarizine Dihydrochloride).

Time in minutes	Cumulative %drug release Propranolol Hydrochloride	Cumulative %drug release Flunarizine dihydrochloride
0	0	0
1	42.67	40.56
2	54.73	53.67
3	67.56	66.89
4	80.73	79.67
5	94.58	93.78

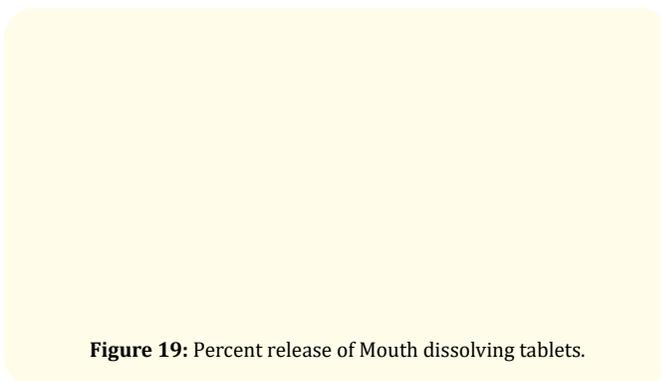**Table 6:** Dissolution profile of MDTs .

Figure 19: Percent release of Mouth dissolving tablets.

Comparison with marketed formulations

In vitro drug release and drug content of mouth dissolving tablets was determined and compared with single mouth dissolving marketed tablets: Inderal (Propranolol 20 mg) and Sibelium (Flunarizine 10 mg).

Time in minutes	Cumulative %drug release Propranolol Hydrochloride (combined mouth dissolving tablet)	Cumulativ Cumulative %drug release Propranolol Hydrochloride (single mouth dissolving tablet – Inderal) e %drug release Flunarizine dihydrochloride
0	0	0
1	42.67	32.56

Formulation, Evaluation and Estimation of Propranolol Hydrochloride and Flunarizine Dihydrochloride Mouth Dissolving Tablets in Combined Dosage form and its Comparison with Marketed Formulations

12

2	54.73	47.67
3	67.56	59.89
4	80.73	68.67
5	94.58	89.78

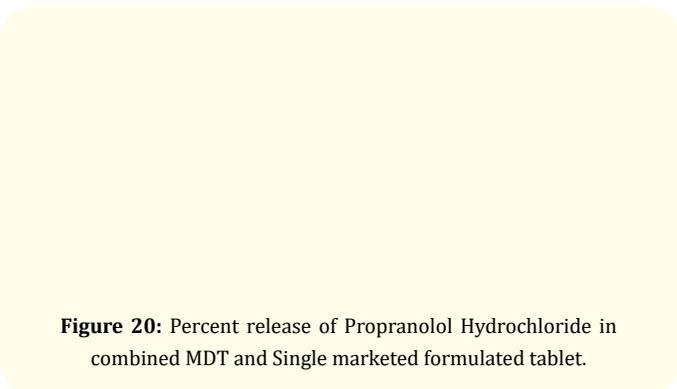**Table 7:** Comparison of *In vitro* drug release with marketed formulations.

Figure 20: Percent release of Propranolol Hydrochloride in combined MDT and Single marketed formulated tablet.

Time in minutes	Cumulative %drug release Flunarizine Diydrochloride (combined mouth dissolving tablet)	Cumulative %drug release Flunarizine Diydrochloride (single mouth dissolving tablet –Sibelium)
0	0	0
1	40.56	32.56
2	53.67	47.67
3	66.89	59.89
4	79.67	68.67
5	93.78	89.78

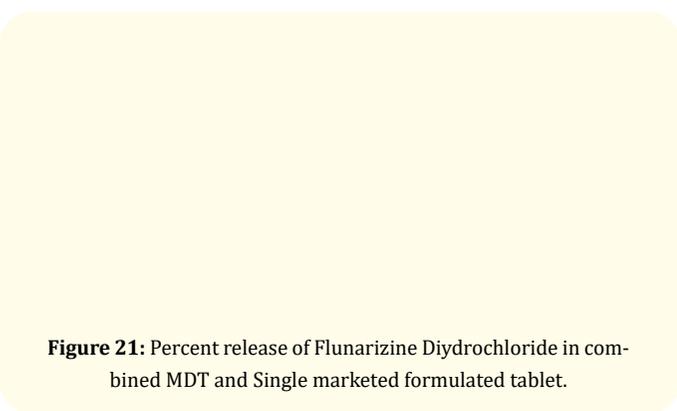**Table 8:** Comparison of *in- vitro* drug release with marketed formulations.

Figure 21: Percent release of Flunarizine Diydrochloride in combined MDT and Single marketed formulated tablet.

Stability Studies

Temperature dependent stability studies

The Combined Mouth dissolving 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 spectro-photometrically at 290 nm and 264.5 nm. Among several methods investigated for dissolution profile comparison, f2 is the simplest.

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

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, $f_2 = 100$. An average difference of 10% at all measured time point's results in an f_2 value of 50. FDA has set a public standard of f_2 value between 50-100 indicate similarity between two dissolution profiles. Results are reported in table 9, 10, 11 and figure 22.

No. of days	Avg. weight (mg)	Hardness (kg/cm²)	Fri-ability (%)	Disinte-gration Time (sec)	Drug Content (%)
0	226.72 ± 1.07	3.26 ± 0.094	0.74	37 ± 0.68	99.90 ± 0.33
15	226.78 ± 0.76	3.26 ± 0.1	0.70	36 ± 1.09	99.53 ± 0.017
30	226.98 ± 0.85	3.26 ± 0.2	0.69	36 ± 1.55	99.35 ± 0.009
45	226.63 ± 1.24	3.25 ± 0.2	0.75	35 ± 1.10	99.23 ± 0.014
60	226.57 ± 0.31	3.25 ± 0.2	0.75	35 ± 1.44	99.20 ± 0.021
75	226.52 ± 0.92	3.21 ± 0.3	0.76	35 ± 1.12	99.20 ± 0.015
90	226..46 ± 0.38	3.21 ± 0.3	0.78	35 ± 1.57	99.09 ± 0.008

Table 9: Effect of storage conditions on Mouth dissolving tablets.

Comparison of drug release data before and after storage of Mouth dissolving tablets.

Formulation, Evaluation and Estimation of Propranolol Hydrochloride and Flunarizine Dihydrochloride Mouth Dissolving Tablets in Combined Dosage form and its Comparison with Marketed Formulations

13

Time in minutes	cumulative %drug release Propranolol Hydrochloride	cumulative %drug release Flunarizine dihydrochloride
0	0	0
1	42.67	40.56
2	54.73	53.67
3	67.56	66.89
4	80.73	79.67
5	94.58	93.78

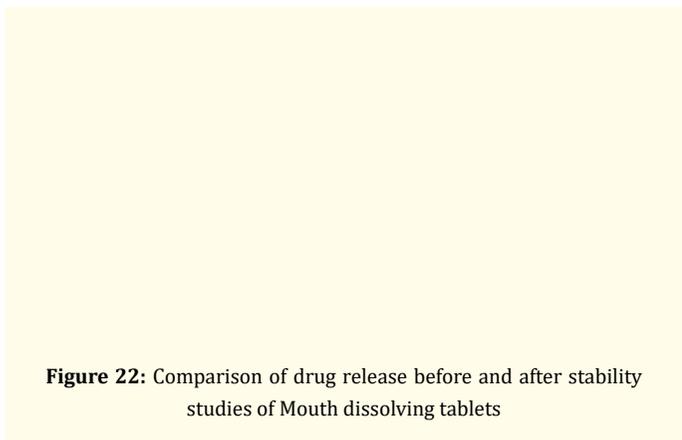**Table 11:** Drug release data before storage of Mouth dissolving tablets.

Figure 22: Comparison of drug release before and after stability studies of Mouth dissolving tablets

Result and Discussion

Combined MDTs of Propranolol Hydrochloride and Flunarizine Dihydrochloride were prepared by direct compression method. Table 1 shows the composition of mouth dissolving tablets and table 2 shows the pre- compression evaluation of tablets. MDTs 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 for drug-polymer interaction are shown in figures 2,3,4,5,6,7 and in 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 figures 11,12,13,14,15,16,17, 18.

The *in- vitro* disintegration time is within the prescribe limit and

comply with the criteria for MDTs, the value as 37 ± 0.68 seconds fulfills the European Pharmacopoeia (describes orally disintegrating tablet as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed and as tablets which should disintegrate within 3 minutes).

In-vitro dissolution study is shown in Table 6 and figure 19. It shows highest drug release of Propranolol Hydrochloride 94.58% and Flunarizine Dihydrochloride 93.78% at 5 minutes. Comparison of the *in-vitro* drug release of combined MDTs of Propranolol Hydrochloride and Flunarizine Dihydrochloride with marketed single tablets viz Inderal (Propranolol 20 mg) and Sibelium (Flunarizine 10 mg) is shown in (table 7, figure 20) and (table 8, figure 21).

Stability studies of MDTs are shown in tables 9,10,11 and figure 22.

Conclusion

The formulated mouth dissolving tablets were meeting with all the ideal requirements such as improved bioavailability, disintegration time, and dissolution efficacy patient compliance and reducing dosing frequency to minimize side effects.

Acknowledgement

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