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Formulation and Evaluation of Fexofenadine Hydrochloride Fast Disintegrating Sublingual Tablets for Improving Bioavailability

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ABSTRACT

Objectives:

To improve the dissolution and bioavailability of fexofenadine HCl, an attempt was made to prepare its sublingual tablets by using different super disintegrants.

Methods:

The tablet is prepared by direct compression method by using different super disintegrants such as cross povidone, sodium starch glycolate and extracted mucilage powder of Plantago ovata seeds for increase the rate of dissolution. Different characterization parameters viz. FTIR, hardness, weight variation, drug content, in- vitro dissolution, in- vivo plasma drug concentration and stability were evaluated.

Key findings:

The evaluated parameters were in compliance with the pharmacopoeia limits. The most successful formulation F2, shows within 60seconds of complete disintegration and drug release in specified time 60min. The In-vitro drug release of Fexofenadine sublingual tablet F2 formulation containing cross povidone was found to be 98.55±0.89% for 60min.The In-vivo study of Fexofenadine sublingual tablet was performed for the best formulation F2 using three healthy albino rabbits. The Cmax was found to be 0.079µg/ml from oral route and 0.101µg/ml from sublingual route. The stability studies for best formulations were carried out for 90 days at 40 ± 2 ℃ /75% ± 5% RH. There was no significant change in disintegration, drug content and drug release.

Conclusion:

The results indicated that the prepared fast disintegrating sublingual tablets of Fexofenadine hydrochloride could perform therapeutically better than conventional oral tablets with improved efficacy and better patient compliance. The In-vivo animal study showed the better bioavailability by sublingual route when compare to oral route.

Key Words: Fexofenadine hydrochloride, super disintegrants, sublingual tablet, taste masking, In-vivo drug concentration.

I. INTRODUCTION:

The concept of sublingual drug administration emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules, especially patients like pediatrics and geriatrics, un cooperative patients, mentally retard and patients advised with less intake of water have more beneficial of the sublingual medication. In terms of permeability, the sublingual area of the oral cavity is more permeable than cheek and palatal areas of mouth. The drug absorbed via sublingual blood vessels bypasses the hepatic first-pass metabolic processes giving acceptable bioavailability with low doses and hence decreases the side effects. The main mechanism for the absorption of the drug into oral mucosa is via passive diffusion into the lipoidal membrane. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route. Introduction of Sublingual Drug Delivery The literal meaning of sublingual is 'under the tongue'. Sublingual mucosa is the membrane of the ventral surface of tongue and the floor of the mouth. Sublingual drug delivery refersto a mode of drug delivery by which the drug substances are placed under the tongue and are directly absorbed via the blood vessels under the tongue. Sublingual drug delivery offers various advantages such as avoidance of the gastrointestinal and hepatic pre systemic elimination and fast onset of drug action. In comparison to other non-invasive routes of delivery into the systemic circulation such as transdermal drug delivery, drug delivery via sublingual mucosa offers higher permeability to drug, easier access to the administration site, and cost effectiveness. Therefore, as a site of drug administration, sublingual region is an attractive

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and logical alternative route for delivering drugs into the body[1].

Fexofenadine HCl, a BCS class II drug, indicated for the symptomatic relief of seasonal allergic rhinitis and for the treatment of elementary skin manifestations of chronicidiopathic urticaria. These conditions are commonly found in pediatric patients, where palatability is of main concern. Fexofenadine HCl has been shown to have potent antiallergic or antihistaminic activities similar to levocetirizine and desloratadine with an advantage that it does not cross the blood-brain barrier to any appreciable degree. Thus, it has better safety as compared to levocetirizine and desloratadine. However, a major limitation of Fexofenadine HCl is its water solubility which may result in poor dissolution and low bioavailability. In the light of above facts, in the present investigation, lyophilization technique was employed to prepare Fast dissolving tablets of Fexofenadine HCl to achieve better patient compliance, enhanced bioavailability, instant onset of action, reduced first-pass metabolism, convenience in administration and good mouthfeel.[2]

MATERIALS AND METHODS

Fexofenadine hydrochloride was purchased from yarrow chemicals Mumbai, Stevia, Cross povidone, sodium starch glycolate, extracted mucilage powder of Plantago ovata seeds, were used as super disintegrant agents. All other reagents used were of analytical grade. Sublingual tablets were prepared by direct compression method.

Compatibility study

A most successful formulation of excipients to facilitate release of drug and also protect it from degradation. In the formulation drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Pre formulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Fexofenadine and the selected polymers.

FORMULATION OF SUBLINGUAL TABLETS

Fexofenadine sublingual tablets were prepared by the direct compression method using different super disintegrants. The excipients used were Cross povidone, Sodium starch glycolate, Isapgol mucilage powder (Super disintegrate),Magnesium stearate, Talc, Micro crystalline cellulose, Stevia (Sweetening agents). Compositions of various formulations are shown in Table 1. All the ingredients of the sublingual tablets of Fexofenadine HCl were weighed and mixed in mortar with the help of pestle. Then the blended material was compressed on the 6mm flat–biconvex punch using a Rimek MINI PRESS-I MT tablet machine (Karnawati Engg. Ltd., Mehsana, India).

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Fexofenadine HCL	30	30	30	30	30	30	30	30	30
Cross povidone	3.6	6	9.6	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	3.6	6	9.6	-	-	-
Isapgol mucilage powder	-	-	-	-	-	-	3.6	6	9.6
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1
Microcrystalline cellulose	76.2	73.8	70.2	76.2	73.8	70.2	76.2	73.8	70.2
Stevia	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2

TABLE 1 Formulation of Fexofenadine Hydrochloride Sublingual tablet

PRE-COMPRESSIONAL STUDIES OF SUBLINGUAL TABLETS OF FEXOFENADINE HCL

The evaluations of pre-compression studies of sublingual tablets of Fexofenadine HCL were done as per standard procedure. The following parameters were evaluation.

Bulk density: It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve #20) in to a measuring cylinder and the initial volume was noted, it is bulk volume. The results are presented in **Table 2**. The bulk density is calculated by given formula

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Bulk density (ρ) = Mass of the powder (M) / Bulk volume (V)

Tapped density: It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. The results are presented in Table 2. It is expressed by given formula

Tapped density (ρ) = Mass of the powder (M) / Tapped volume (V)

Carr's Index: It is the simple test to evaluate the bulk density and tapped density of a powder and the rate at which it packed down. The results are presented in Table 2. It is expressed by the given formula

Carr's Index (%) = [(Tapped density – Bulk density) × 100] / tapped density

Hausner's Ratio: It is the ratio of tapped density to the bulk density. The results are presented in Table 2.

Hausner's Ratio = Tapped density / Bulk density

Angle of repose: Angle of repose of powdered blend was determined by the funnel method. The accurately powdered blends were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powdered blend was allowed to through the funnel freely on to the surface. the diameter of the powder cone was measured and angle of repose was calculated by using the following formula and the results are presented in Table 2.

$\tan \Theta = h/r$

h = height of the powder cone, r = radius of the powder cone

POST-COMPRESSIONPARAMETERS OF SUBLINGUAL TABLETS OF FEXOFENADINE HCL

The evaluations of post-compression studies of sublingual tablets of Fexofenadine HCL were done as per standard procedure. The following parameters were evaluation.

Hardness: The test was done as per the standard methods. The hardness of three randomly selected tablets from each formulation (F1 to F4) was 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 was noted down in Kg/cm. The results are presented in Table 3.

Thickness: The thickness of three randomly selected tablets from each formulation was determined in mm using a Vernier caliper (Pico India). The average values were calculated. The results are presented in Table 3.

Weight variation (or) Uniformity of Weight: Weight variation test was done as per standard procedure. Ten tablets from each formulation (F1 to F9) were weighed using an electronic balance and the average weight was calculated. The results are shown in Table 3.

Friability: The friability of tablets using 10 tablets as a sample was measured using a Roche Friabilator. Tablets were rotated at 25 rpm for 4 minutes or up to 100 revolutions. The tablets were taken out, dedusted and reweighted. The percentage friability was calculated from the loss in weight as given in equation below. The weight loss should not more than 1%. The results are shown in Table 3.

%Friability = (Initial weight – Final weight) x 100 (Initial weight)

Drug Content: Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and powder equivalent to 100mg of Fexofenadine Hydrochloride was accurately weighed and transferred to 100 ml volumetric flasks containing 50 ml of phosphate buffer (pH 6.8). The flasks were shaken to mix the contents thoroughly. The volume was made up to the mark with phosphate buffer pH 6.8 and filtered. One ml of the filtrate was suitably diluted and Fexofenadine Hydrochloride content was estimated at 224nm using a double beam UV-Visible Spectro photo-meter. This procedure was repeated thrice and the average value was calculated.

The results are presented in Table 3.

In-vitro drug release studies for Fexofenadine sublingual tablet [3,]

In-vitro release rate of Fexofenadine Hydrochloride sublingual tablets was carried out using United State Pharmacopoeia (USP) dissolution testing apparatus (Paddle method). The dissolution test was carried out using 900 ml of 6.8 pH phosphate buffer, at 37±5˚ C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 5,10,15,30,45 and 60 min. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through Whatman filter paper No 40 and analyzed for Fexofenadine Hydrochloride after appropriate dilution by UV spectrophotometer at 224 nm. The percentage drug release was calculated using an equation obtained from the calibration curve.

The results are presented in Table 4.

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In-vivo study on animals.[4]

Animals used

Rabbit

Species: Albino
Sex: Male
Weight: 1.5 – 2.0 kg
Color: White
Number of animals per dose group: 3 males
Acclimatization: 8-10 days in experimental room

Source

Rabbits used for the study were obtained from the animal house of Mallige College of Pharmacy (MCP 056/2016-17)

General procedure

Three healthy albino rabbits weighing about 1.5 to 2.0 kg were selected, marked and fasted for overnight. All the animals were administered with the oral dose of Fexofenadine as a standard drug and the time was noted. Then 0.5 ml of blood was withdrawn from the marginal ear vein at an interval of 5, 10, 15, 30, 45 and 60 min. The serum was separated and Fexofenadine was estimated by using HPLC. After the washout period of 10 days again the same rabbits were administered with prepared Fexofenadine sublingual formulation. Rabbits were anaesthetized using Ketamine hydrochloride and the Fexofenadine fast disintegrating sublingual tablets (1.71mg/kg) was placed at sublingual region, then 0.5 ml of blood was withdrawn from the marginal ear vein at an interval of 5, 10, 15, 30, 45 and 60 min. The serum was separated and Fexofenadine was estimated by using HPLC.

The obtained data was subjected to Ramekin software to find out $T_{max,}$ $t_{1/2}$, $C_{max,}$ AUC, AUMC, MRT of pharmacokinetics parameters. The results are presented in Table 5.

Stability Studies:

Stability studies are done to understand how to design a product and its packaging such that product has appropriate physical, chemical and microbiological properties during a defined shelf life when stored and used. The optimized formulation was subjected for two months stability study according to ICH guidelines**.** The selected formulations were packed in aluminum foil in tightly closed container. They were then stored at 40ºC/75% RH for three months and evaluated for their release study. The results are presented in Table 6.

II. RESULTS AND DISCUSSION:

Compatibility studies: The incompatibility between the Drug and Excipients were studied by FTIR spectroscopy. The spectral data of pure drug and various drug-excipient mixtures are presented in Fig. 1- 3. The results indicate that there was no chemical incompatibility between drug and excipients used in formulation

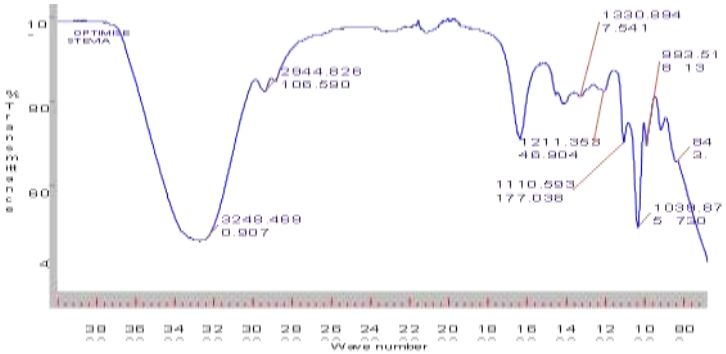

Fig 1: FT-IR spectra of Fexofenadine Hydrochloride with stevia.

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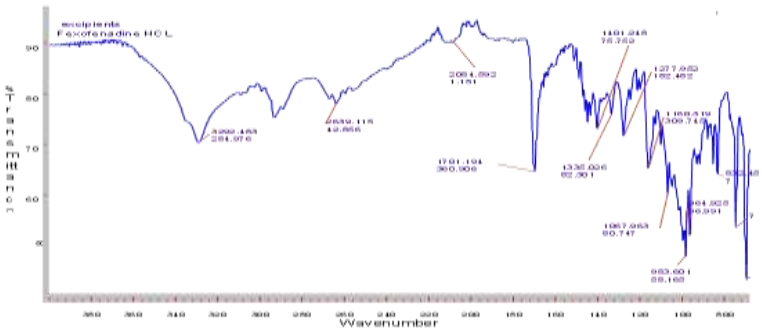

Fig.2: FT-IR spectra of successful formulation F2.

PRE-COMPRESSION STUDIES:

Pre-compression parameters of all formulations F1 to F9 are satisfactory. Bulk density, tapped density, angle repose, Carr's index and Hausner's ratio are within the limits. The results are shown in Table 02.

Bulk density (gm/ml): 0.49 to 0.57

Tapped density (gm/ml): 0.60 to 0.74

Angle of repose: 22.0 to 31.23

%Compressibility: 15.72 to 23.04

Hausner's ratio: 1.20 to 1.299

The results obtained confirm that the batches which exhibit good flow properties have good packing characteristics.

Table2: Pre-CompressionparametersofFexofenadine Hydrochloride sublingual tablets

Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index%	Hausner's ratio	Angle of repose (°)
F1	0.538±0.024	0.684±0.077	21.331	1.271	22.013±0.983
F2	0.571±0.021	0.742±0.038	23.045	1.299	27.500±0.196
F3	0.569±0.024	0.733±0.072	22.373	1.288	24.706±1.357
F4	0.523±0.022	0.676±0.056	22.633	1.292	24.260±0.980
F5	0.492±0.018	0.608±0.019	19.078	1.235	23.720±0.168
F6	0.541±0.005	0.642±0.024	15.732	1.207	31.230±1.143
F7	0.531±0.014	0.653±0.030	18.683	1.229	29.273±0.671
F8	0.532±0.021	0.668±0.030	20.359	1.255	29.113±1.183
F9	0.510±0.018	0.658±0.018	22.511	1.290	27.513±1.072

POST COMPRESSION STUDIES:

The post compression parameters of all formulations F1-F9was found to be satisfactory and all were within pharmacopeias limits. The Hardness for all formulations found to be 4.0kg/cm to 5.0 kg/cm

The Thickness of tablet was found to be between 3.2mm to 3.9 mm.

The Friability was found to between 0.44% to 0.78 %.

The Weight variation was found to between 119±1.25 % to 120±0.115 %.

Assay values of the formulations were observed in the range of 94.73% to 97.75%. The results are shown in Table 3.

Table3: Post Compression parameters of Fexofenadine Hydrochloride sublingual tablets

Code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	3.8±0.063	5.0±0.181	0.74±0.013	119.3±0.500	96.11±1.782
F2	3.8±0.026	5.0±0.130	0.56±0.001	119.5±0.287	95.00±0.272
F3	3.9±0.015	5.0±0.194	0.44±0.002	120.2±0.310	97.75±0.795
F4	3.8±0.035	4.0±0.136	0.57±0.013	119.6±1.096	95.99±1.638
F5	3.8±0.059	5.0±0.178	0.69±0.071	120.5±1.050	96.71±1.587

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F6	3.8±0.048	5.0±0.083	0.74±0.021	119.9±0.577	95.53±0.504
F7	3.8±0.061	5.0±0.120	0.69±0.017	120.6±0.115	96.00±0.950
F8	3.8±0.022	5.0±0.158	0.78±0.092	119.1±1.258	94.73±0.556
F9	3.8±0.064	5.0±0.196	0.90±0.042	120.3±1.050	95.91±0.615

In-vitro dissolution study: The in-vitro dissolution studies of all formulations (F1 to F9) were conducted and the results are shown in Table 5. The percentage of drug release for formulations, F1to F9 was found to be 35.3 % to 99.97% during 5min to 60 min. The maximum percentage of drug release was found to be 99.97% in formulation, F3 during 60 min.

From the above studies, it was observed that increase in concentration of super disintegrant i.e., Cross povidone, the percentage of drug release increased. Among the all formulations (F1 to F9), the best in-vitro drug release observed in formulation, F3 was found to be 99.97%, as increase the concentration of Cross povidone that is due to result of rapid disintegration. During the dissolution studies, it was observed that the tablets were initially swelled and erodible over period of time.

Table4: In-vitro drug release study of Fexofenadine Hydrochloride sublingual tablets

Time (min)	% Drug Release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
5	74.2 ±0.14	90.2 ±0.17	93.6 ±0.42	68.3 ±0.44	75.2 +0.23	88.3 ±0.31	35.3 +0.47	42.3 ±0.33	45.5 ±0.16
10	79.3 ±0.36	95.5 ±0.28	88.6 ±0.65	72.2 +0.83	78.2 +0.37	90.5 +0.53	36.71 +0.73	45.2 +0.53	50.5 ±0.28
15	84.3 +0.57	97.5 +0.64	90.66 ±0.88	78.66 +0.62	82.6 +0.62	93 +0.83	42.3 +0.92	50.2 +0.93	55.3 +1.13
30	89 +1.11	97.9 +1.16	98.13 +0.78	82.0 +1.04	84.2 +1.02	95.2 +1.16	48.2 +1.30	53.6 ±1.07	60.2 +1.35
45	92.3 +1.17	98.4 +1.21	98.14 +1.03	87.3 +1.23	89.3 ±1.21	97.4 +1.10	54.6 +1.09	58.2 +1.25	69.2 ±1.29
60	93 +1.09	99.6 +1.04	99.97 ±0.83	90.3 +1.23	91.3 ±1.15	98.8 +1.30	60.8 +1.12	62.3 ±1.09	70.1 +1.02

In- vivo study of Fexofenadine Hydrochloride sublingual tablet:

The In-vivo study of Fexofenadine sublingual tablet was performed for the best formulation F2 using three healthy albino rabbits as described in the methodology section. The C_{max} was found to be 0.079µg/ml from oral route and 0.101µg/ml from sublingual route.

Table5: Data for pharmacokinetic parameters

Pharmacokinetics parameters	Fexofenadine (1.71mg/kg)	
	Oral route	**Sublingual route**
C_{max} (µg/ml)	0.080	0.12
T_{max} (hr)	4	8
AUC (µg/ml/hr)	2.366	4.233
AUMC (µg/ml/hr)	4.978	9.897
T1/2 (hr)	2.34	4.27
MRT (hr)	19.021	21.045

Stability studies:

The stability studies for best formulations F2 were carried out for 90 days at 40 ± 2 °C /75% ± 5% RH. There was no significant change in color and odor, hardness, drug content and %CDR. 90 days of stability studies revealed that; there was no any significant degradation of the drug. The results found to be satisfactory.

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Table6: Stability study of formulation F2

Time (Days)	Hardness (Kg/cm^2)	Drug content (%)	In-vitro Drug Release (%)
0	4.0 ± 0.294	97.75 ± 0.795	97.90 ± 0.52
15	4.0 ± 0.351	96.89 ± 0.235	97.21 ± 0.24
30	4.0 ±0 .128	97.25 ± 0.254	96.89 ± 0.26
45	5.0 ± 0.245	97.10 ± 0.851	98.62 ± 0.45
60	4.0 ± 0.254	97.52 ± 0.421	97.21 ± 0.91
90	5.0 ± 0.012	97.23 ± 0.028	97.02 ± 0.34

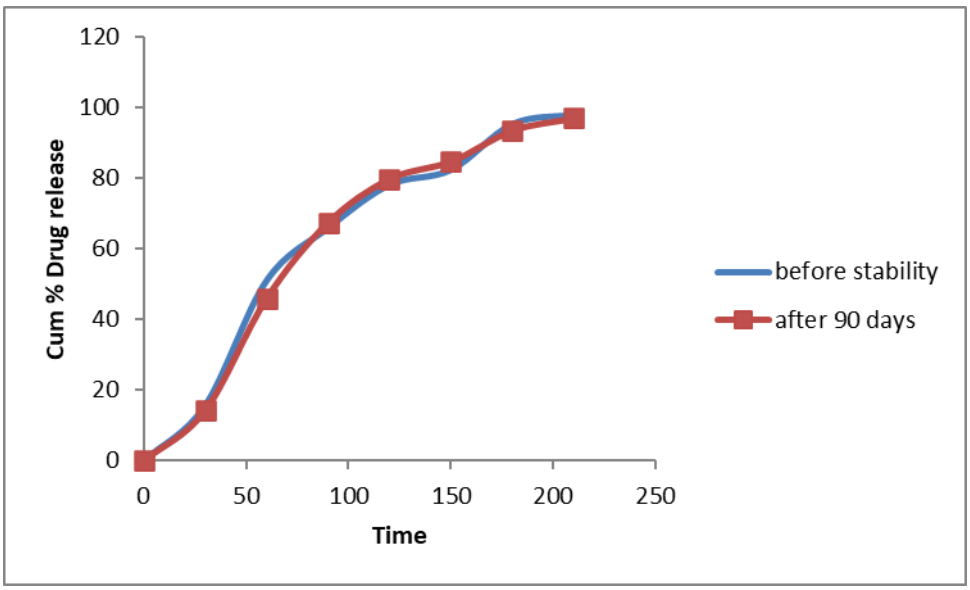

Fig3: In-vitro drug release of F2 before and after stability studies

III. CONCLUSION:

The fast-disintegrating sublingual tablet of Fexofenadine were prepared by direct compression method using various polymers such as cross povidone, sodium starch glycolate, isapgol mucilage powder and Stevia. A total of nine different formulations were prepared.

The following conclusions can be drawn from the results obtained.

The FT-IR studies revealed that there was no chemical interaction of pure drug (Fexofenadine) with the polymers and excipients. The Pre-compression parameters like Bulk density, tapped density, angle of repose, Hausner's ratio and Carr's index of all the formulations were found to be within the standard limits. The Post-Compression parameters like thickness, hardness, friability, weight variation, disintegrating time, drug content, and In-vitro dissolution of all the formulations were within the standard limits of official books. The formulation F2 containing cross povidone showed the 98.55±0.89 % of drug release within 60min so it is considered as best formulation.

The In-vivo study was performed using 3 albino rabbits and the bioavailability of Fexofenadine was found to be increased by sublingual route when compared to oral route. The formulation F2 was selected for stability studies on the basis of their better and satisfactory evaluation studies parameter. Results showed there was not much variation in physical parameters even after the period of 90 days. All formulation of sublingual tablet bitterness was masked by Stevia.

From the results obtained it was concluded that, formulations F2 containing cross povidone are found to be stable and retained their original properties during their study period.

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