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DESIGN AND EVALUATION OF FAST DISSOLVING FILMS OF ANTI-HISTAMINE

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ABSTRACT

Among other skin allergies, hay fever (allergic rhinitis) and urticaria (hives) are symptoms of allergies that can be treated with loratadine, a second-generation non-sedating antihistamine. In an effort to create a dosage form for fast action that is helpful in controlling severe allergy symptoms, aids in enhancing bioavailability, and is highly easy for administration—without the need for water—a quick release film formulation of loratadine was attempted. The artificial sweetener aspartame, which also works as a saliva stimulant, was used in an effort to cover up the drug's salty flavour. Polymers like hydroxyl propyl methylcellulose (HPMC K4M), polyvinyl pyrrolidone-K30 (PVP-K30), and poly vinyl alcohol were used to make loratadine films via solvent casting (PVA). They passed all of the physical and chemical tests that were performed on them, including those for tensile strength, weight uniformity, thickness, folding

endurance, drug content uniformity, surface pH, swelling index, and percentage elongation. The IR research found no evidence of a drug-polymer interaction. The formulations were also examined for their release characteristics in vitro using a USP dissolving equipment and in vivo blood histamine levels in animals. Fast-dissolving films of loratadine made using the polymers HPMC K4M, PVP-K30, and PVA showed a notable increase in dissolution rate when compared to commercial tablets. The stability analyses showed that when the formulations were maintained at refrigerator temperatures of 2–8 °C and room temperatures of 25–30 °C, the drug concentration did not noticeably alter. Further *in vivo* study was carried out to determine blood histamine level in animal and compared its rapid action with marketed product. The formulations were also subjected for *in vivo* blood histamine level estimation in animals. The *in vivo* blood histamine level estimation in animals exhibited rapid pharmacological response to justify the fast release of the drug from formulations than marketed product.

Keywords: Fast dissolving films, Loratadine, Sublingual films, Solvent casting, Animals

INTRODUCTION:

Fast dissolving oral delivery methods are, solid dose forms that dissolve or disintegrate within a minute. Because they are simple to use and may be taken sublingually, fast mouth dissolving films have gained popularity as a novel delivery method. Rapid medication absorption and fast bioavailability are achievable due to the sublingual mucosa's thin membrane and high blood flow, which makes the drug act more quickly. Drug breakdown in the GI tract and the first pass effect can be avoided since the medication is immediately absorbed into the systemic circulation. Additionally, higher patient compliance is anticipated because this approach does not involve swallowing, as with a traditional tablet, making it advantageous for patients who have dysphagia or difficulties swallowing **[1]**. Some businesses introduced stronger variations of fast-dissolving medication delivery. Lavipharm Laboratories Inc. (Lavipharm), for instance, created a perfect fast-dissolving drug delivery system that addressed the market's unmet demands. This innovative intraoral medication delivery device, branded Quick-DisTM, is a thin, flexible, and quickly dissolving film and is a proprietary, patented technology of Lavipharm. The tongue's floor or top is where the film is applied **[2]**. This film instantly dissolves when placed on the tongue, releasing the medication, which dissolves in the saliva. As saliva travels from the mouth, throat, and oesophagus into the stomach, certain medications are absorbed.

When this occurs, the drug's bioavailability is substantially higher than what is typically seen for tablets **[3]**. Oral thin films, or OTFs, have become a popular and practical replacement for conventional OTC drug forms including liquids, pills, and capsules among pharmaceutical businesses and customers today. OTFs provide quick, precise dosage without the need for measuring tools or water in a manner that is safe, effective, and portable. OTFs for the fast release of one or more APIs are generally the size of a postage stamp and dissolve on a patient's tongue in a matter of seconds (active pharmaceutical ingredients) **[4]**.

MATERIALS AND METHODS

Materials

A free sample of loratadine was offered by Vasudha Pharma Chem Ltd. in Hyderabad. Hydroxypropyl methylcellulose (HPMC K4M (15cps), polyvinyl pyrrolidone (PVP-K30), and polyvinyl alcohol (PVA) were supplied by HiMedia Laboratories Pvt. Ltd., Mumbai, to CDH Laboratories in New Delhi. The other compounds were all of the analytical variety.

METHODS:

FORMULATION OF FAST DISSOLVING FILMS OF LORATADINE

In the current investigation, solvent casting was used to create loratadine fast-dissolving films. For casting the films, a flat, square-shaped, aluminium foil-coated glass mould with a surface area of 25 cm^2 was created.

Preparation of casting solutions:

In a beaker, 10 ml of ethanol was used to dissolve the weighed amounts of medication and aspartame **(as mentioned in Tables 1, 2, 3, and 4)** before the addition of the polymer(s). dissolved after being stirred. Using ethanol, propylene glycol was produced up to a volume of 20 ml and applied as a plasticizer. To get rid of air bubbles, the solution was let to stand overnight in a beaker wrapped with aluminium foil.

Preparation of fast dissolving films:

For controlled solvent evaporation, the casting solution (20 ml) was put into a petri dish and set to the side. The films were peeled off and cut into squares of 2 × 2 cm (4 cm^2), containing around 10 milligrams of medication per square. These films were sealed in self-sealing covers and placed in a desiccator for an additional two days to dry completely **[5]**.

Table 1: Formulations of HPMC K4M

Formulation Code	Polymer(mg)	HPMC K4M(mg)	Drug (mg)	Propylene glycol (ml)	Aspartame (mg)
FA1	HPMC K4M	200	65	0.25	50
FA2	HPMC K4M	300	65	0.25	50
FA3	HPMC K4M	400	65	0.25	50

Table 2: Formulations of HPMC K4M and PVP K-30 combination

Formulation Code	Polymer Ratio	HPMC K4M (mg)	PVP K-30 (mg)	Drug (mg)	Propylene glycol (ml)	Aspartame (mg)
FB1	2.5:1.5	250	150	65	0.25	50
FB2	3:1	300	100	65	0.25	50
FB3	3.5:0.5	350	50	65	0.25	50

Table 3: Formulations of HPMC K4M and PVA combination

Formulation Code	Polymer Ratio	HPMC K4M (mg)	PVA (mg)	Drug (mg)	Propylene glycol (ml)	Aspartame (mg)
FC1	2.5:1.5	250	150	65	0.25	50
FC2	3:1	300	100	65	0.25	50
FC3	3.5:0.5	350	50	65	0.25	50

Table 4: Formulations of PVA and PVP K-30 combination

Formulation Code	Polymer Ratio	PVA (mg)	PVP K-30 (mg)	Drug (mg)	Propylene glycol (ml)	Aspartame (mg)
FD1	2.5:0.5	250	50	65	0.25	50
FD2	2:1	200	100	65	0.25	50
FD3	1.5:1.5	150	150	65	0.25	50

IN VIVO DISSOLUTION STUDY [24, 25]:

The study was conducted on six healthy human volunteers. (Age group was from 21 to 28 year. The volunteers were not allowed to take water and food starting from half an hour before the study till the end of the study. The study was carried out for 30 s. They were instructed to keep the film below the tongue for about 30 s without moistening the film before application. The volunteers were asked to record the time of film insertion and the time of erosion of the film.

In vivo studies:

Determination of Blood Histamine Level [26]:

Animals were randomly divided into seven groups, 4 rats in each group. Group 1, was normal control (treated with normal saline). Group 2, was control (Toxic), induced with OVA (ovalbumin) for increasing histamine level in blood. Group 3, was treated with marketed product (tablet 10 mg) in the form solution (dissolution study of loratadine tablets for 30 s) and dose was administered in such a way, each ml contains 0.5 mg of drug and hence 1.2 ml of solution was administered so that 0.6 mg of drug, which is corresponding to animal dose. Group 4, 5, 6, and 7 were treated with prepared formulations of loratadine films (each film of 4 cm^2 contains 10 mg of drug and upon dissolution completely in 20 ml during dissolution study, each ml contains 0.5 mg of drug, and hence 1.2 ml of administered quantity contains 0.6 mg of drug which is corresponding to animal dose). The rats were exposed by gavage to OVA (ovalbumin, 1 mg protein/ ml tap water; 1 ml/animal) for 6 weeks, without the use of an adjuvant. The blood samples for plasma histamine level were collected 7 days after

the last dose of the OVA, and determined by fluorimetry method. The formulations were administered orally in the form of solutions of 1.2 ml containing 3 mg/kg dose level (dissolution study for 30 s) 10 min after the withdrawal of blood on 7th day for determining the OVA induced histamine level. Again the blood samples were withdrawn 30 min after the administration of the drug formulations, to determine the reduction of histamine level with respect to time factor.

This study was conducted in accordance with CPCSEA guidelines and experimental protocol was approved by approved by Institutional Animal Ethics Committee.

EVALUATION OF FAST DISSOLVING FILMS

Physical appearance:

The films were all visually examined for smoothness, homogeneity, homogeneity, and colour.

Uniformity of weight & film thickness:

The average weight of the films' separate weights from formulation was computed. Micro meter screw gauge was used to measure the thickness of the films made from each recipe.

Surface pH:

Since an acidic or alkaline pH may irritate the buccal mucosa, the surface pH of the film was measured to evaluate the probability of any negative effects related to change in pH in vivo. The test film was put in a petri dish, soaked with 10 ml of distilled water, and allowed to stand for 30 seconds. After allowing the pH metre electrode to come into touch with the formulation's surface and reaching equilibrium for one minute, the pH was recorded. For each formulation, the average of three measurements was obtained **[6, 7]**.

Folding endurance:

This test shows if the films can withstand mechanical manipulation and maintain their pliability when used in the oral cavity. The folding durability was tested by repeatedly folding one film at the same location until it broke, or folded up to 300 times, which is regarded sufficient to demonstrate good film qualities. The value of the folding endurance is determined by how many times the film could be folded in the same position without breaking **[8, 9]**.

Uniformity of drug content:

This value was obtained by homogenising a film with a surface area of 2×2 cm (4 cm^2) containing 10 mg of loratadine for 20–30 ml of simulated salivary fluid with a pH of 6.8 for 30 s while continuously shaking. A UV spectrophotometer was used to detect the absorbance at 247.2 nm after the solution had been filtered and properly diluted with simulated salivary fluid. For each formulation, the tests were performed in triplicate **[10]**.

Measurement of swelling index:

In simulated salivary fluid with a pH of 6.75, investigations for the film's swelling index were carried out. A pre-weighed stainless steel wire sieve with an estimated mesh size of 800 m was used to filter the film sample, which had a surface area of 4 cm^2. A porcelain dish with 15 ml of simulated salivary medium was used to immerse the mesh containing the film sample. The stainless steel mesh was removed, the surplus moisture was carefully wiped away with an absorbent tissue, and the scales were reweighed at predetermined intervals. Up until a steady weight was noticed, the film's weight increase was calculated at each time interval **[11]**. The algorithm was used to determine how much oedema there was.

$SI = W_t - W_o / W_o$

W_o = weight of film at time t = 0

W_t = weight of film at time t

SI = Swelling index

Tensile strength and %Elongation:

The highest tension (applied at one location) needed to break the film is its tensile strength. The 2 x 2 cm (4 cm^2) film, which was flawless physically, was put between two clamps that were spaced 10 mm apart. When the film broke, the force and elongation were measured. The film was pulled by clamps at a rate of 5 mm/min. Calculations did not take into account the results from film samples that ruptured at the clamps rather than between them. For every film, the measurements were carried out three times.

For the assessment of the film, two mechanical properties—tensile strength and % elongation—were calculated. The applied load at rupture as the mean of three measurements and the cross sectional area of the broken film from the following equation may be used to calculate the tensile strength, which is the maximum stress applied to a point at which the film specimen breaks **[12]**.

According to the equation below, it is computed by dividing the applied load at rupture by the strip's cross-sectional area.

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross sectional area of the sample } (mm^2)}$$

Percentage elongation:

A film sample expands when tension is applied, and this is referred to as a strain. Basically, strain is the distortion of a film divided by the sample's initial dimension **[12]**.

Percentage elongation can be obtained by following equation

$$\%\text{Elongation at break} = \frac{\text{Increase in length}}{\text{original length}} \times 100$$

***IN VITRO* DISINTEGRATION STUDIES:**

A film with a surface area of 2 x 2 cm (4 cm^2) was laid on a glass petri dish containing 10 ml of pH 6.8 phosphate buffer. In vitro disintegration time was recorded as the amount of time needed to break the film **[13]**.

***In vitro* dissolution studies:**

Loratadine's fast release films' dissolution profile was tested in a beaker with 20–30 ml of simulated salivary fluid (pH 6.8) acting as the dissolving medium and being kept at 37±0.5°C. At 100 rpm, medium was swirled. Every 5 s, aliquots (5 ml) of the dissolving media were removed and replaced with the equivalent volume of fresh medium **[5, 14]**.

By using a UV spectrophotometer set to 247.2 nm, the amount of medication in the withdrew samples was calculated. All samples underwent three trials, and an average value was calculated. The amount of medication that was dissolved on average during different time periods was quantified and shown against time.

***IN VITRO* DIFFUSION STUDY:**

Franz diffusion cells with an internal diameter of 2.5 cm were used to conduct an *in vitro* permeation research via cellophane membrane. Between the donor and receptor compartments, the cellophane membrane was installed. The donor compartment was filled with medication that had been dissolved (10 mg, which is equivalent to 4 cm^2) in 15 ml of salivary-simulating fluid with a pH of 6.8, which was kept at a constant 37 0.2 °C and had hydrodynamics that were maintained using a magnetic stirrer. At appropriate intervals of 10 s, samples (5 ml) were taken out of the receptor compartment and replaced with an equivalent quantity of phosphate buffer in the receptor compartment. By measuring the absorbance in a UV spectrophotometer at a maximum of 247.2 nm, it was possible to calculate the percentage of drug presence (diffused from donor to receptor compartment) in the receptor compartment **[15]**.

COMPARISON WITH MARKETED PRODUCT:

A USP type II (paddle apparatus) was used to determine the drug release profile of the commercially available form of loratadine (Lormeg-10 mg), with 900 ml of 0.1N hydrochloric acid solution (pH 1.2) serving as the dissolving medium and being kept at 37±0.5 °C. At 100 rpm, medium was swirled. Every 5 seconds, aliquots (5 ml) of the dissolving media were removed and

replaced with the equal volume of fresh medium **[16]**.

The amount of drug in the samples that were removed was measured using a UV spectrophotometer at 247.2 nm. The average result was calculated after three trials. Calculated percentages of drug dissolution at various time points were compared to the top formulation across all batches.

COMPATIBILITY STUDIES:

For the purpose of identifying any potential chemical interactions between the medication and polymers, an FT-IR spectra matching technique was applied. The three separate drug:polymer combination films as well as the individual sample of each were made and combined with the appropriate amount of potassium bromide. A translucent pellet was created from around 50 mg of this combination by compressing it under 15 tonnes of pressure in a hydraulic press. It was scanned in a Bruker FTIR spectrophotometer between 4000 and 600 cm^{-1}. To identify any peak appearance or removal, the IR spectrums of the formulations were compared to those of pure medicines.

STABILITY STUDIES:

On ready films held at various temperatures, stability experiments of the formed rapid dissolving films were conducted. For stability experiments, the film was packaged in aluminium foil and kept in a desiccator for 45 days at 2-8°C (45% RH) and 25-30°C (60% RH). At the conclusion of the 45-day period, the films were evaluated for drug content and other factors **[17, 18]**.

RESULTS AND DISCUSSION:

FORMULATION OF FAST DISSOLVING FILMS

Utilizing HPMC K4M, PVP K-30, and PVA as the polymers, twelve different fast-dissolving film formulations of loratadine were created using the solvent casting process on glass moulds. Aspartame was employed as a sweetener and propylene glycol as a plasticizer. By creating several formulations of rapid dissolving films, the effect of polymer type and concentration ratio was explored. A fixed dosage of the medication (65 mg) was kept consistent throughout all of these formulations. The casting solution (20 ml) was poured into a pan with a mould such that each 2 x 2 cm (4 cm^2) film-containing mould could hold 10 mg of medication. Different concentrations of polymers were utilised, but the concentration of other components like plasticizer and sweetener remained constant **(Tables 1, 2, 3 and 4)**.

EVALUATION OF FAST DISSOLVING FILMS

Physicochemical parameters:

Physical appearance:

The movie outside look was assessed. Indicating that the polymers utilised in the study were found to have good film forming

capabilities as mentioned in the literature, all the films formed with various polymer concentrations were found to be flexible, smooth, transparent, non-sticky, and homogenous **[19-21]**.

Uniformity of weight:

Ten samples of each type of formulation had their individual weights measured, and the average weight was computed. Each batch of formulas' film weight was determined to be uniform, it was noted. Due to the viscosity (a greater concentration of polymer causes a higher viscosity) and the thickness of the films, among the HPMC K4M formulations, the weight rose with increased amount of polymer utilised. Table 5 provides the findings of all formulations.

Film thickness:

Micro meter screw gauge was used to measure the thickness of 12 films of each formulation, and an average thickness was calculated. The findings for all formulations are shown in **Table 5**, and they are shown to be within the permitted range for rapid dissolving films **[8]** of 100 m to 200 m. additionally, each formulation's film thickness (HPMC K4M) was found to be consistent. The thickness of the films with more polymer content rose just little.

Surface pH:

Three films in each formulation had their surface pH measured. They may be less likely to irritate the sublingual mucosa **[8]** given that the surface pH was discovered to be in the range of 6.2 to 7.06, which is near to the neutral pH. Table 5 displays the average of 3 determinations for each formulation.

Folding endurance:

The process was followed to determine the folding endurance, and the results are shown in **Table 5**. All of the formulations had good folding endurance values of more than 300, it was discovered **[21]**.

Table 5: Data related to physicochemical properties

Formulation Code		Weight (mg)*	Thickness (mm)*	Surface pH#	Folding endurance	Disintegration (s)
FA	FA1	57.66±0.577	0.13 ±0.005	6.32 ±0.007	>300	8.05±1.07
	FA2	64.66 ±0.808	0.142 ±0.007	6.64 ±0.021	>300	8.40±2.03
	FA3	73.00 ±0.665	0.132 ±0.007	6.55 ±0.007	>300	8.70±2.03
FB	FB1	61.83±0.971	0.156 ±0.010	6.46 ±0.028	>300	7.02.±1.02
	FB2	62.90 ±0.750	0.144 ±0.015	6.72 ±0.021	>300	7.30.±2.01
	FB3	74.41 ±0.907	0.127 ±0.085	6.68 ±0.014	>300	8.01±1.30
FC	FC1	68.80 ±0.680	0.175 ±0.075	6.81 ±0.021	>300	10.05±1.21
	FC2	76.40 ±0.907	0.154 ±0.076	7.06 ±0.001	>300	9.80±2.14
	FC3	72.06 ±0.305	0.162 ±0.092	6.19 ±0.014	>300	9.20±2.58
FD	FD1	65.55±0.015	0.155±0.055	6.7±0.012	>300	11.65±1.11
	FD2	72.44±0.21	0.20±0.032	6.45±0.014	>300	10.03±1.23
	FD3	63.98±0.102	0.183±0.025	6.85±0.002	>300	9.50±1.05

*Each value is the mean ± SD; n = 12 determinations; #Each value is the mean ± SD; n = 3 determinations

Measurement of swelling index:

The polymer's hydration and swelling characteristics were said to be critical for its bio adhesive properties since the former is required to start close contact between the film and the mucosal surface. Up to a certain point, the degree of hydration causes the adhesion to rise until disentanglement at the polymer tissue interface causes a sudden decline in adhesive strength. The speed and degree of film hydration and swelling also have an impact on the film's adhesion, which has an impact on how quickly drugs are released from the film. According to studies, excessive moisture might impair the binding between the bio adhesive film and the mucosa by diluting the functional groups that are necessary for the adhesive contact **[22, 23]**.

The methods specified in the methodology was followed to calculate the swelling index, and the findings are shown in **Table 6** along with a graphical representation of the swelling index vs. time in **Figures 1-4**.

Table 6: Swelling index of films

Swelling Index*												
Time (Sec)	FA			FB			FC			FD		
	FA1	FA2	FA3	FB1	FB2	FB3	FC1	FC2	FC3	FD1	FD2	FD3
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	0.275	0.90	0.96	0.65	0.91	1.06	1.03	0.95	0.82	1.13	0.84	0.74
10	0.364	1.40	1.44	1.25	1.40	1.56	1.30	1.20	0.98	1.28	1.02	0.92
15	0.85	1.86	1.34	1.72	1.86	2.02	1.49	1.28	1.12	1.55	1.25	1.14
20	1.20	1.33	1.86	1.65	1.81	1.97	1.71	1.56	1.31	1.68	1.39	1.28
25	1.11	1.49	1.88	--	--	--	1.56	1.37	1.10	1.61	1.34	1.25
30	--	0.99	0.42	--	--	--	--	--	--	--	--	--

***Average of 3 determinations**

The formulations FA3 and FC1 with the highest amounts of the hydrophilic polymer HPMC K4M had greatest swelling indices of 1.88 and 1.71 after 25 and 20 s, respectively, among the FA and FC formulations. In comparison to the other HPMC K4M-PVP K-30 films, FB3 had the highest swelling index at the end of 15 s. This is likely because more PVP K-30, a hydrophilic polymer, was used, which enhanced the swelling index's overall extent. The FD1 formulation, which contains more PVA since it is only slightly soluble in water, was shown to have the highest swelling index of the FD formulations.

Further research revealed that the in vitro disintegration period was in the range of 7 to 11 s, demonstrating that the polymers used in the current study had the optimal characteristics for rapid disintegration upon contact with the damp surface.

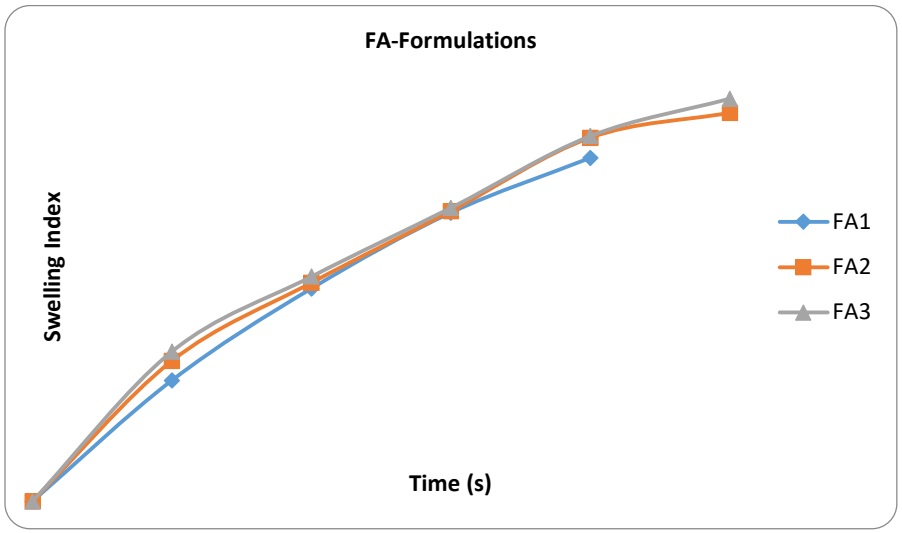

Figure 1: Swelling index of formulations FA

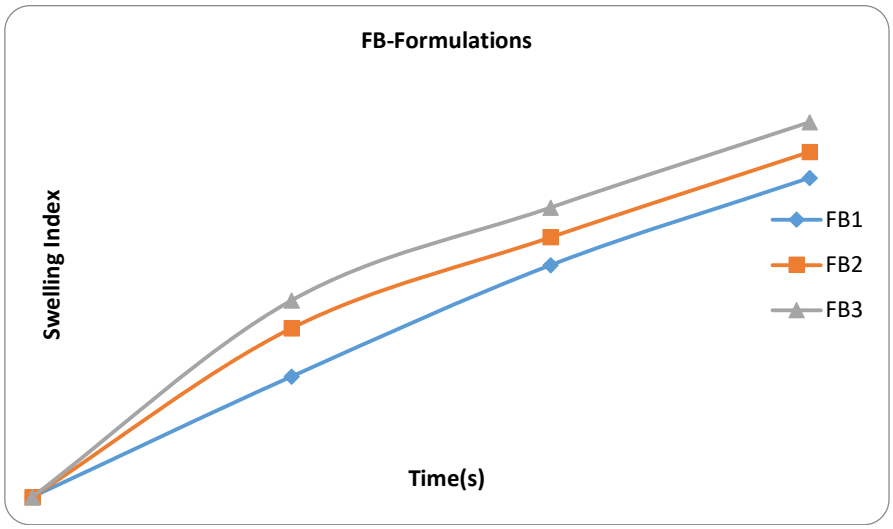

Figure 2: Swelling index of formulations FB

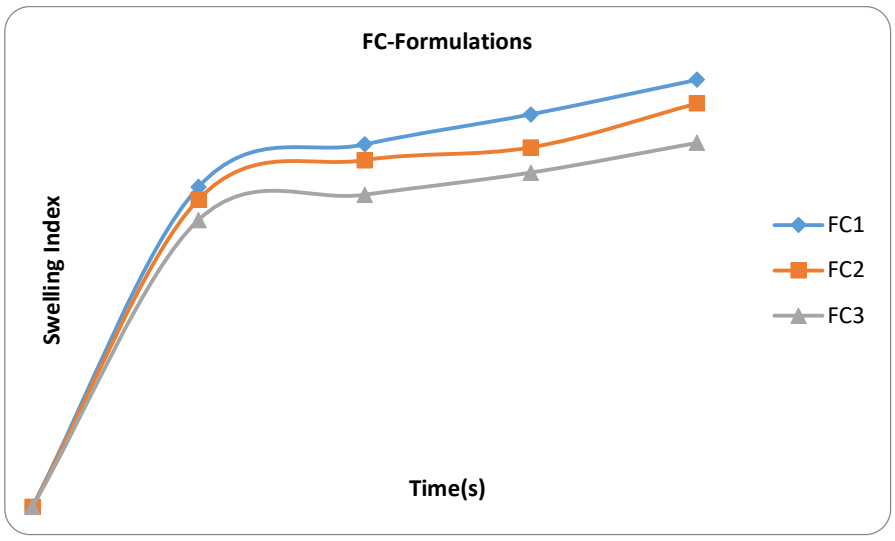

Figure 3: Swelling index of formulations FC

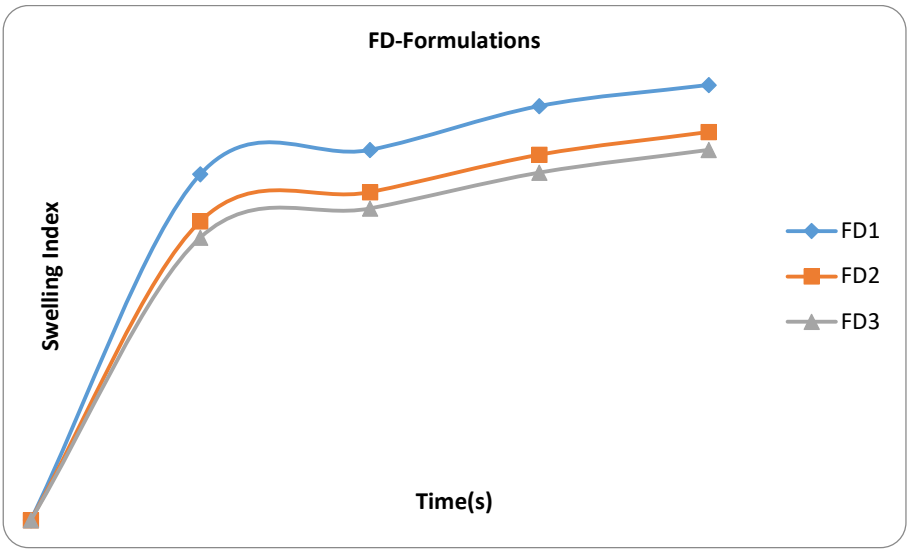

Figure 4: Swelling index of formulations FD

Content uniformity:

Table 7 displays the various formulations' % medication content. All formulations had a percentage drug content that was found to be between 91 and 98%.

Tensile strength measurement:

Tensile strength (TS) and elongation at break (E/B) characteristics provide information on the tensile strength and elasticity of the film. Low TS and E/B are indicative of weak and soft polymers; moderate TS and low E/B are indicative of hard and brittle polymers; and high TS and E/B **[14]** are indicative of soft and tough polymers. The findings of tensile strength and % elongation of all formulations are reported in the **Table 7**.

Table 7: Results of tensile strength, percentage elongation and percentage drug content of formulations

Formulation Code		Tensile strength* (kg/cm^2)	% Elongation*	Percentage Drug content in 4 cm^2
FA	FA1	1.153 ±0.030	31.86 ±0.472	98.17
	FA2	1.336 ±0.020	34.23 ±0.351	97.05
	FA3	1.486 ±0.025	41.13 ±0.404	92.95
FB	FB1	0.366 ±0.015	20.93 ±0.585	97.28
	FB2	0.503 ±0.025	25.73 ±0.416	95.64
	FB3	0.623±0.020	28.93±0.405	93.21
FC	FC1	1.053 ±0.025	51.83 ±0.450	90.90
	FC2	1.143 ±0.020	57.76 ±0.351	94.03
	FC3	1.223±0.015	64.16±0.602	96.13
FD	FD1	1.482±0.023	41.05±0.368	91.34
	FD2	1.351±0.030	37.42±0.40	93.21
	FD3	1.102±0.021	30.52±0.42	95.12

*Mean of 3 determinations ± SD

The findings demonstrated that the formulations FA and FC's tensile strength and% elongation rose with an increase in the percentage of the polymer HPMC K4M, but

these films become weaker when PVP K-30 proportions are larger than those utilised in them **[19]**. The HPMC K4M-PVP K-30 films' TS and E/B values, which are highest for FB3 and lowest for FB1, show that PVP K-30's addition reduced the tensile strength. Formulations FA and FC demonstrated higher TS than FB and increased with the addition of more HPMC K4M, demonstrating that HPMC K4M provides better TS to sublingual films than PVP K-30. These films are sturdy and durable enough to be used. The FD1 formulation among the FD formulations shown an increase in TS and E/B as a result of an increase in PVA and a reduction in PVP K-30.

***IN VITRO* DRUG RELEASE STUDIES:**

Table 8 displays the overall medication release percentage for all formulations. To create the release profiles seen in **Figure 5-8**, the proportion of drug release is plotted versus time.

Table 8: *In vitro* drug release profile data

Time (s)	Percentage drug released*											
	FA			FB			FC			FD		
	FA1	FA2	FA3	FB1	FB2	FB3	FC1	FC2	FC3	FD1	FD2	FD3
00	0.000	0.000	0.000	0.000	0.000	0.000	0.00	0.00	0.00	0.00	0.00	0.00
05	22.68	27.07	23.68	22.88	22.98	23.84	25.48	24.51	22.69	20.38	19.32	23.84
10	30.27	31.73	31.25	32.30	32.59	32.50	37.78	32.01	35.09	33.17	30.86	37.40
15	51.15	51.73	52.1	52.11	54.61	52.30	44.71	47.59	41.15	56.44	57.01	54.42
20	71.44	62.88	66.42	72.5	75.48	67.11	47.98	65.96	60.76	76.15	75.48	75.19
25	84.80	75.09	82.3	85.76	88.55	80.00	65.19	84.42	75.28	81.82	85.48	85.57
30	95.52	94.03	91.5	95.97	93.67	92.32	85.09	91.13	94.90	88.75	91.53	93.46

***Average of 3 determinations**

Formulations using just one polymer (FA1, FA2, and FA3) revealed that as polymer concentration rose, drug release reduced because more time was needed to wet and dissolve the drug molecules contained in the polymer matrix. The degree of the drug release was larger in the HPMC K4M-PVP K-30 films (FB1, FB2, and FB3) than in the other films. It was noted that the rate of drug release was found to be quicker with the higher amount of PVP K-30. This was caused by the water-soluble polymer PVP K-30, which increases the wettability and water penetration into the film matrices, resulting in greater drug diffusion. All HPMC K4M-PVA films (FC1, FC2, and FC3) showed slower release than the others; this may have been caused by the PVA's substantial swelling, which produced a high viscosity gel barrier to drug diffusion. It was discovered that among the two PVA and PVP K-30 formulations (FD1, FD2), FD3 exhibits slower release due to PVA's moderate solubility. This is especially true if PVA concentration is increased, since this results in a reduction in drug release.

Formulas FA1, FB1, FC3 and FD3 were determined to be the best formulations in

terms of drug release out of the twelve created (FA1, FA2, FA3, FC1, FC2 FC3, FD1, FD2 and FD3). Each pair of formulations' drug release sequence may be expressed as follows:

FA1 > FA2 > FA3
FB1 > FB2 > FB3
FC3 > FC2 > FC1
FD3 > FD2 > FD1

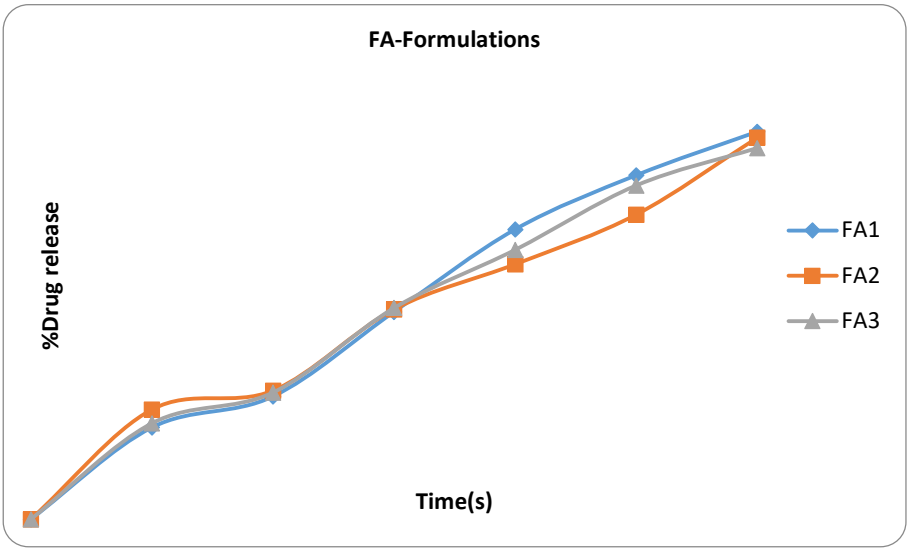

Figure 5: Dissolution profile of formulations FA

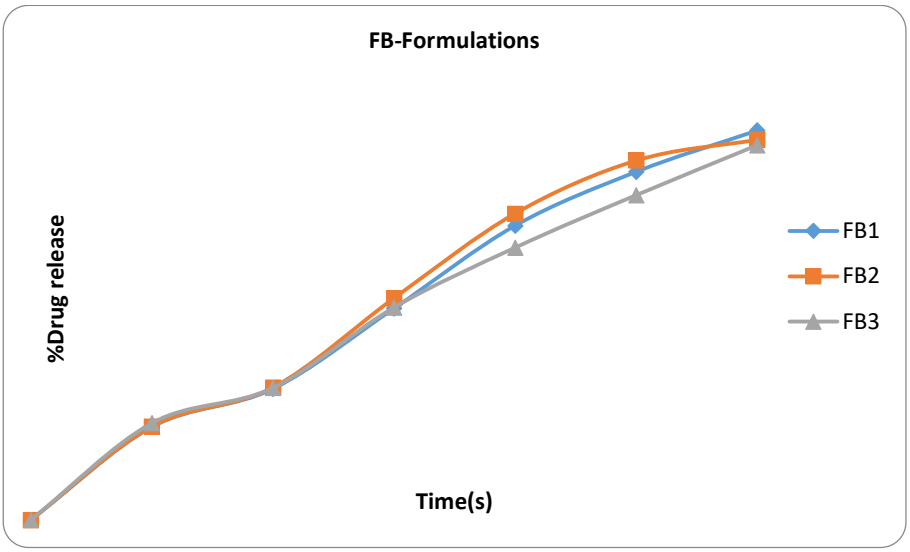

Figure 6: Dissolution profile of formulations FB

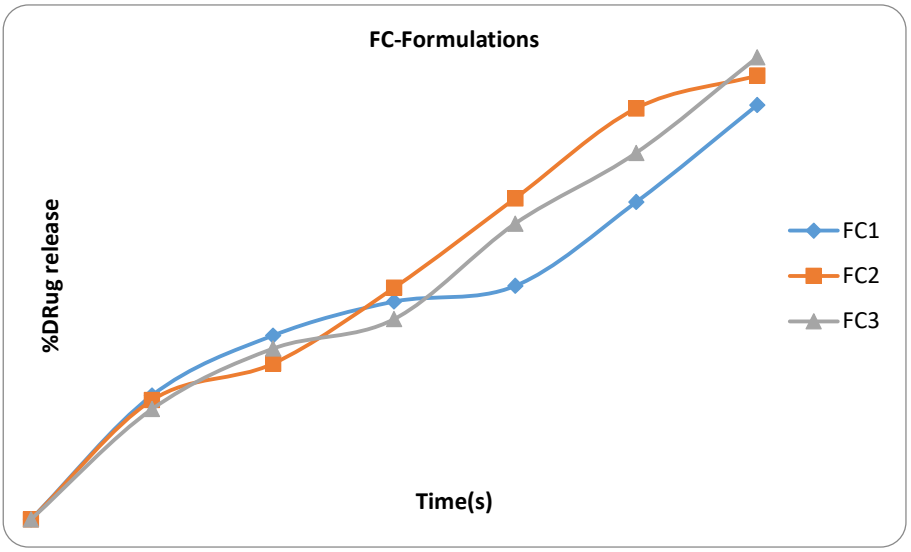

Figure 7: Dissolution profile of formulations FC

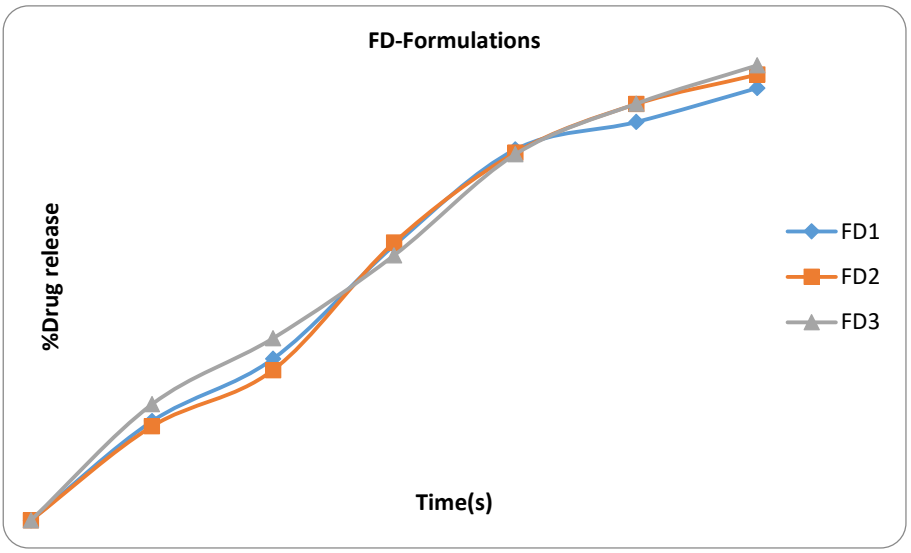

Figure 8: Dissolution profile of formulations FD

IN VITRO DIFFUSION STUDIES:

Table 9 lists the drug diffusion % for each formulation. In order to create the diffusion profile seen in **Figures 9–12**, the percentage quantity of drug diffusion is plotted against time. It was discovered that the full amount of medication released from the formulation diffused entirely in around 60 seconds, indicating an excellent diffusion coefficient, which is crucial for any pharmaceuticals designed to take effect more quickly, such as fast-acting formulations.

Table 9: *In vitro* diffusion profile data

Time (s)	Percentage drug diffused*											
	FA			FB			FC			FD		
	FA1	FA2	FA3	FB1	FB2	FB3	FC1	FC2	FC3	FD1	FD2	FD3
00	0.000	0.000	0.000	0.000	0.000	0.000	0.00	0.00	0.00	0.00	0.00	0.00
10	23.65	28.07	25.68	25.88	23.98	24.84	26.48	24.79	23.59	21.38	20.32	25.94
20	32.27	33.56	36.25	33.30	35.03	35.50	39.57	33.31	37.09	35.17	32.86	36.20
30	54.25	56.67	54.1	56.23	59.20	56.30	46.46	49.59	42.55	59.74	58.01	57.82
40	72.64	64.45	65.42	77.37	80.48	68.31	50.90	67.96	63.36	78.65	78.48	78.69
50	81.40	78.28	86.3	89.46	89.55	83.10	68.39	87.42	75.48	84.42	87.68	88.37
60	96.02	95.03	93.5	97.07	95.67	93.22	89.09	93.13	95.20	89.95	92.73	94.56

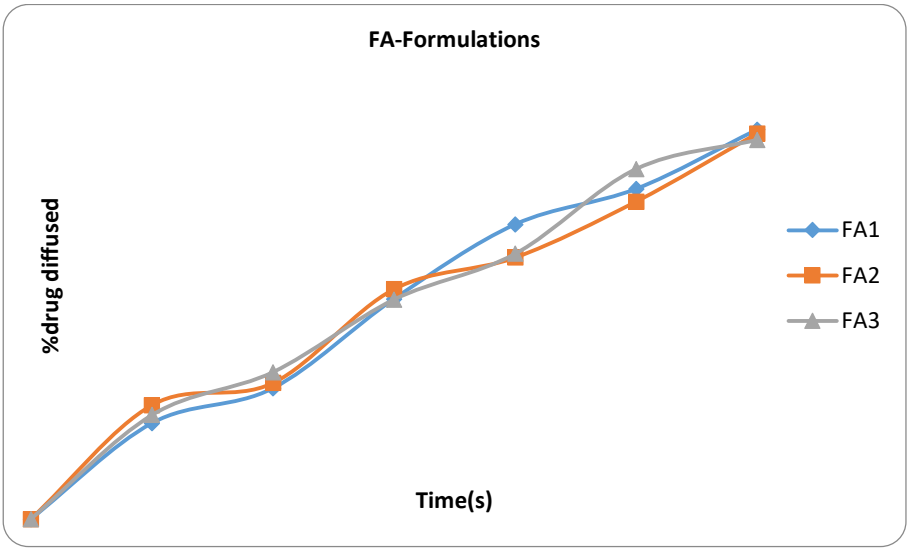

Figure 9: Diffusion profile of formulations FA

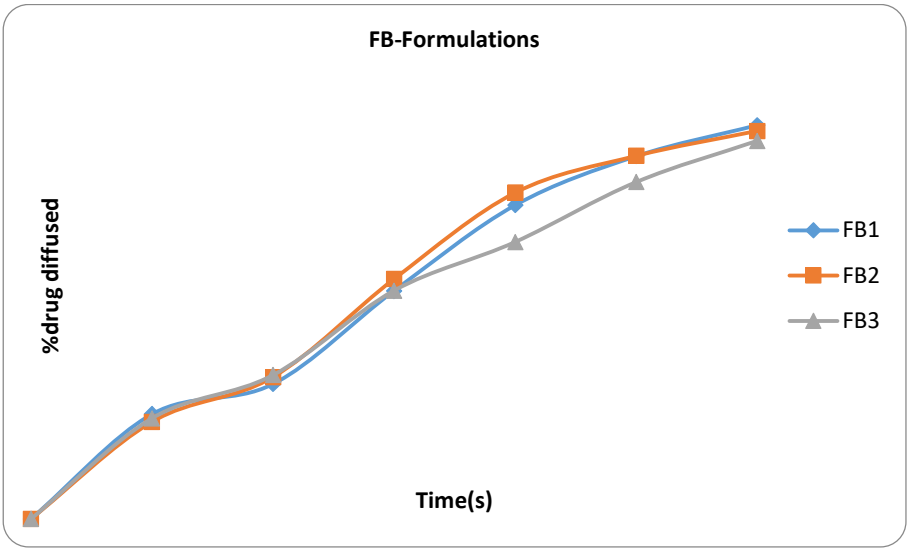

Figure 10: Diffusion profile of formulations FB

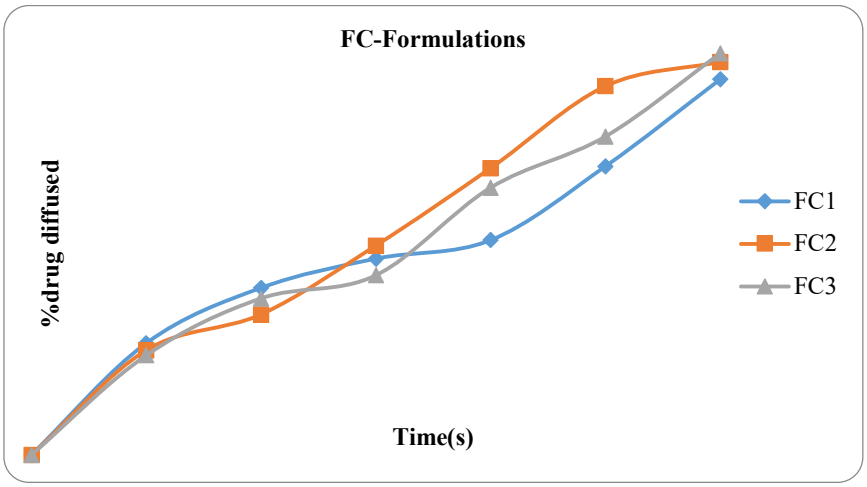

Figure 11: Diffusion profile of formulations FC

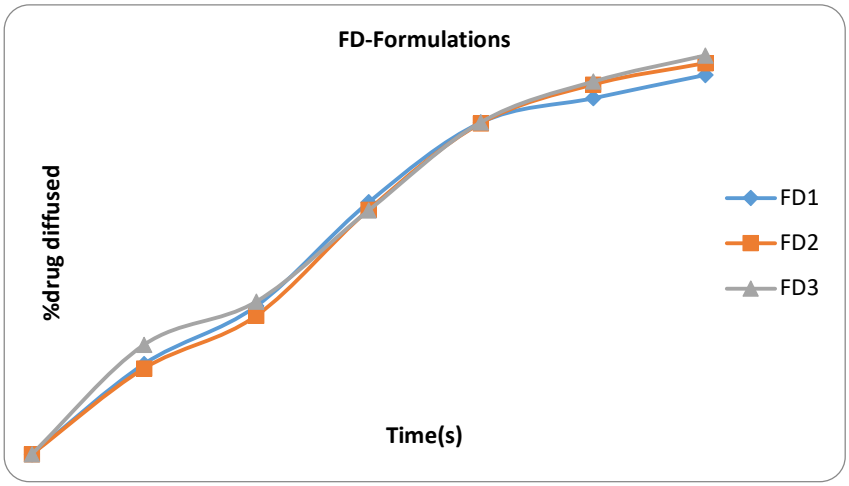

Figure 12: Diffusion profile of formulations FD

COMPARISON WITH MARKETED PRODUCT:

Additionally, the drug release profile of the commercially available version of loratadine (Lormeg-10 mg) was established and compared to the most effective formulation across all batches. The medication release from fast-dissolving film was found to be substantially quicker than that from tablets **(Table 10 & Figure 13)**.

Table 10: *In vitro* drug release profile data of marketed tablet

Time (s)	Concentration (µg/ml)	% drug released
00	0.000	0.00
05	0.565	5.08
10	0.915	8.23
15	1.320	11.88
20	1.795	16.15
25	2.410	21.69
30	3.105	27.94

*Average of 3 determinations

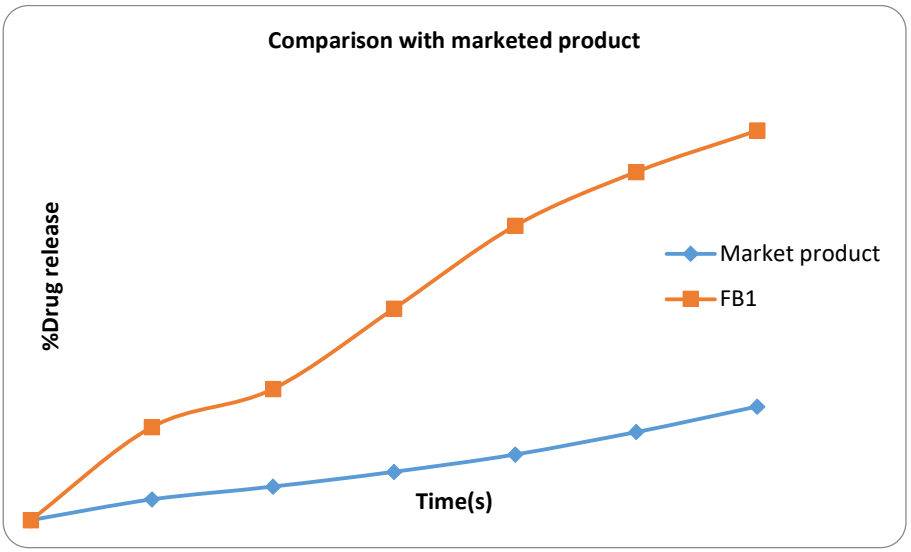

Figure 13: Comparison of dissolution profile of FB1 and marketed tablet

KINETIC ANALYSIS OF *IN VITRO* RELEASE DATA:

The in vitro release data were fitted to the Zero order, First order, and Higuchi models in order to identify the release mechanism that best describes the pattern of drug release. The Korsmeyer-Peppas model was also used to kinetically analyse the release data. Regression analysis of the data was performed using MS-EXCEL statistical functions. **Table 11** presents the findings of a kinetics study of in vitro drug release data for all formulations.

Table 11: Kinetic analysis of *in vitro* drug release data of all the formulations

Formulation Code	Zero Order R^2	First Order R^2	Higuchi Model R^2	Korsmeyer-Peppas Model 'n' value	Best fitting model
FA1	0.9251	0.9773	0.9710	0.73	First
FA2	0.9258	0.9919	0.9686	0.63	First
FA3	0.9619	0.9937	0.9897	0.69	First
FB1	0.9118	0.9668	0.9929	0.72	First
FB2	0.9820	0.9923	0.9902	0.72	First
FB3	0.9209	0.9844	0.9882	0.68	First
FC1	0.9859	0.9842	0.9896	0.56	Higuchi
FC2	0.9792	0.9853	0.9809	0.68	First
FC3	0.9887	0.9915	0.9875	0.67	First
FD1	0.9224	0.5648	0.7986	0.73	First
FD2	0.9212	0.6184	0.8057	0.77	First
FD3	0.9011	0.6427	0.8297	0.68	First

With the exception of FC1, the kinetics of drug release for all formulations was determined to be first order. In FC1, a Higuchi matrix model was visible. In light of the fact that these films are essentially hydrophilic polymer matrices, it can be said that the mechanism of drug release from the films followed the matrix diffusion process. Using the Korsmeyer and Peppas model, Case-1 or Fickian diffusion occurs if n=

0.45, anomalous behaviour or non-Fickian transport occurs if n= 0.45 to 0.89, Case 11 transport occurs at 0.89, and Super Case 11 transport occurs at 0.89. A chemical potency gradient often causes molecular diffusion of the medication to cause fickian release. The drug transport process known as Case 11 relaxation release is connected to stresses and state transition in hydrophilic glassy polymers, which expand when exposed to water or biological fluids. This phrase also covers erosion and polymer disentanglement. According to Korsmeyer and Peppa's model, the release from the hydrophilic polymers in the current study followed a mix of diffusion and erosion, which further supported the applicability of polymers for the creation of quickly dissolving films. The 'n' values varied from 0.56 to 0.77.

COMPATIBILITY STUDIES:

To understand the interaction between the drug and the polymers, IR tests were conducted on the pure drug, HPMC K4M, PVP K-30, PVA, and the formed films **Figure 14-19.** lists the values for the IR spectrum. The main peaks in the IR spectra of the pure medication "Loratadine" were seen at 1699 cm^{-1} owing to carbonyl group stretching in the C=O direction, 1646 cm-1 in the C=N direction, 1429 cm^{-1} in the C=C direction, and 1220 cm^{-1} in the C-N vibration direction. Peak at 770 cm^{-1} is caused by stretching of the C-Cl bond. When mixed with polymers for the formulation, it was seen that there was no appreciable change in the major peaks of loratadine **(Figure 10, 12 and 13)**, indicating that there was no drug-polymer interaction.

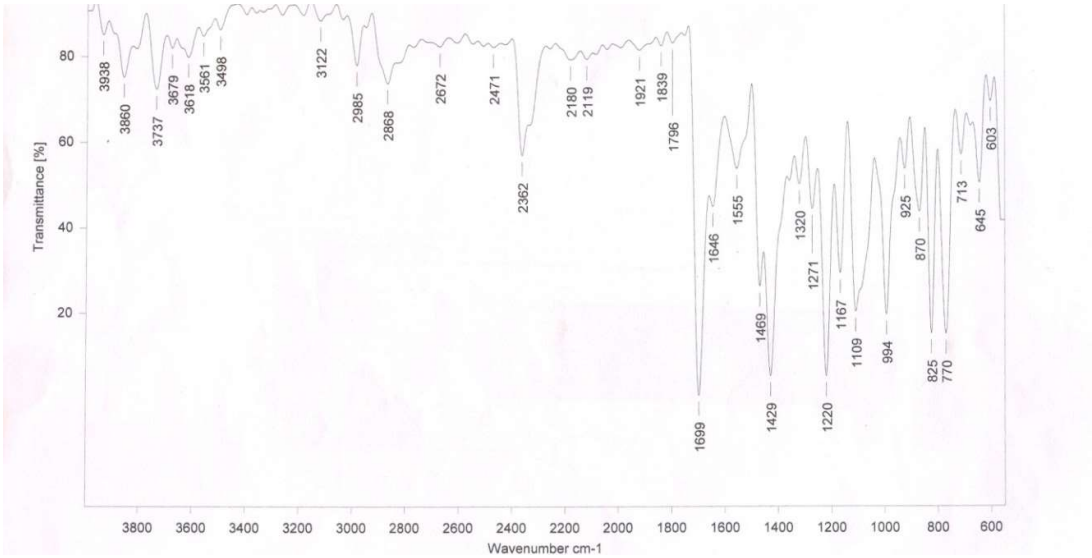

Figure 14: FTIR spectrum of Loratadine

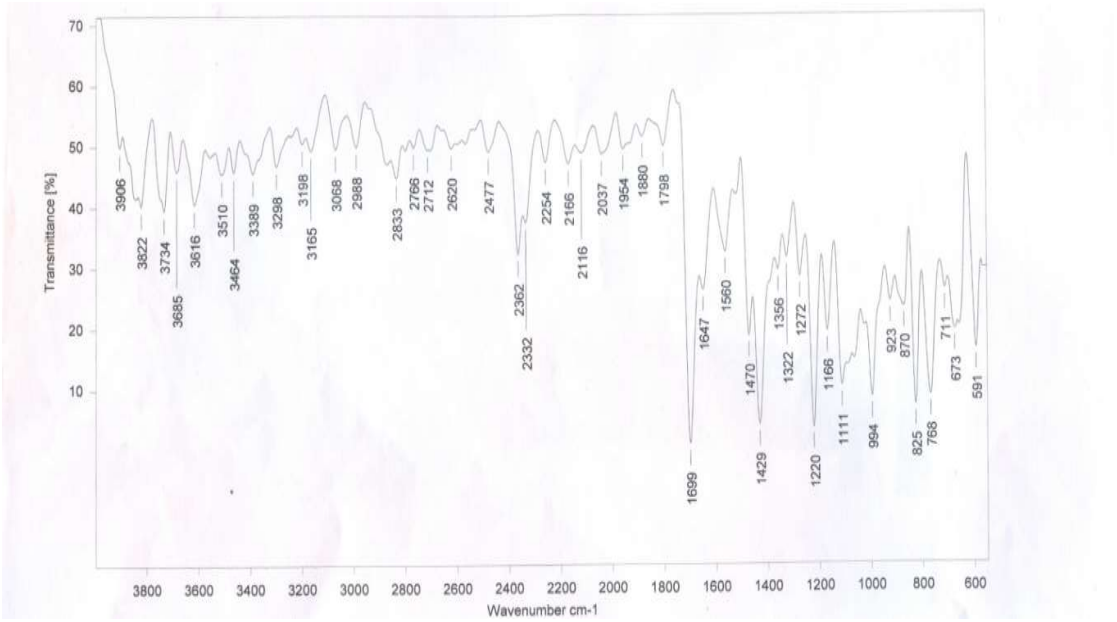

Figure 15: FTIR spectrum of FA

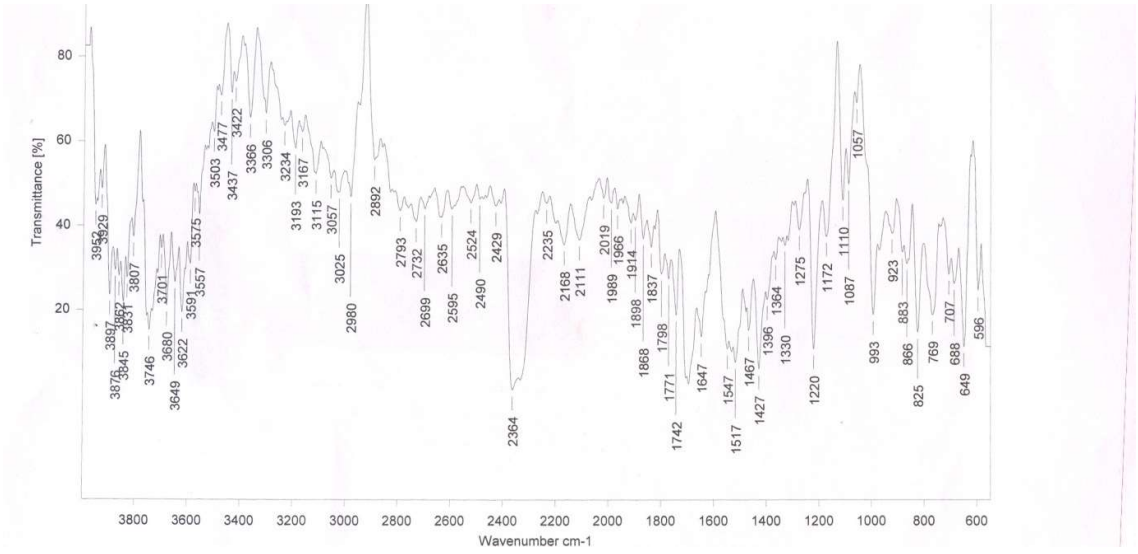

Figure 16: FTIR spectrum of FB

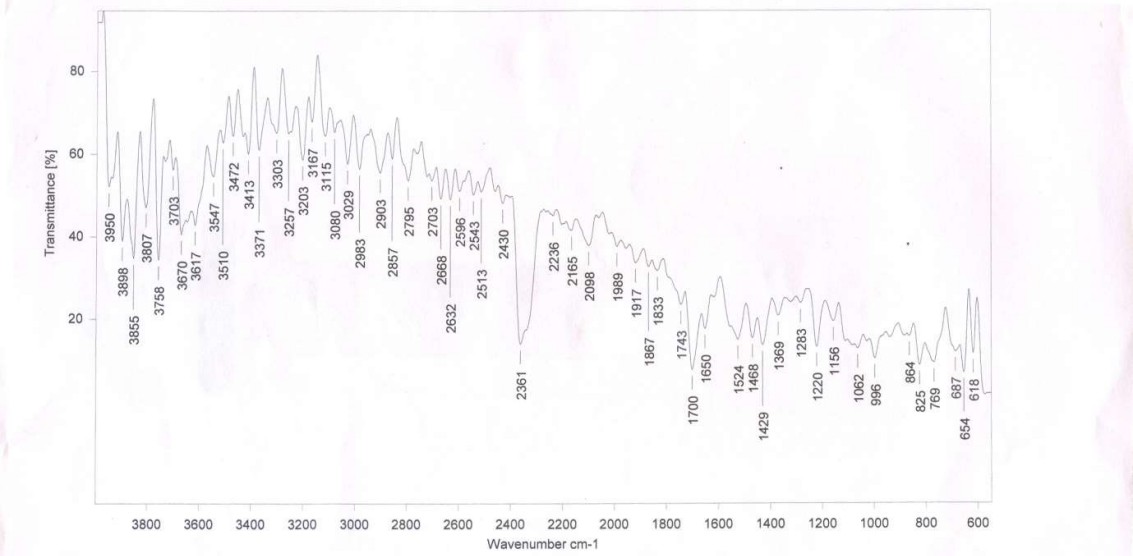

Figure 17: FTIR spectrum of FC

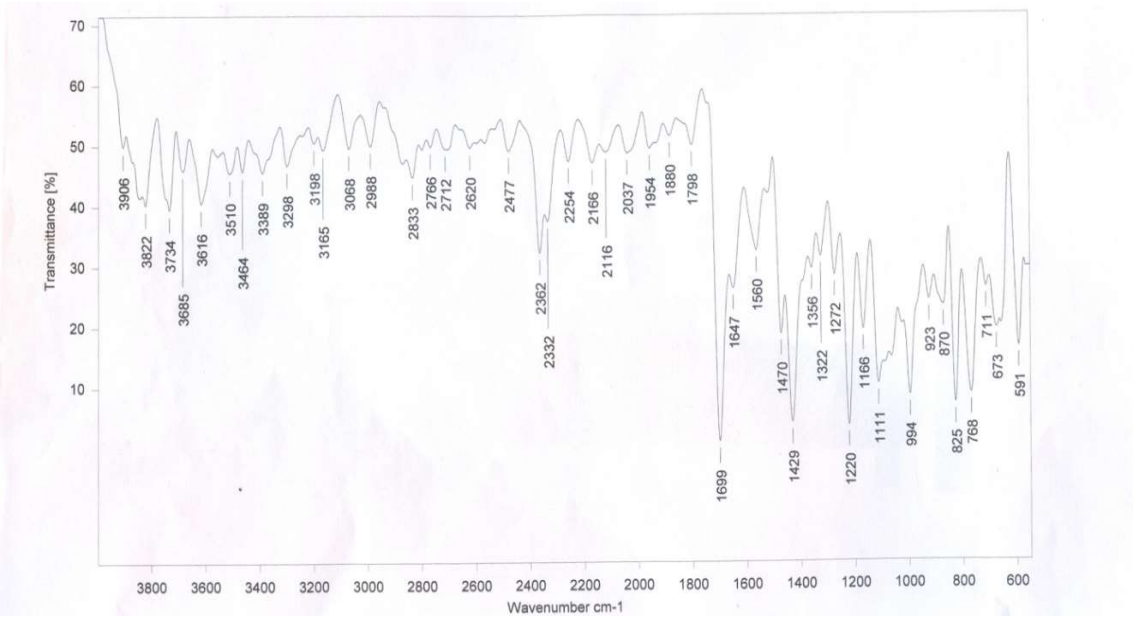

Figure 18: FTIR spectrum of FD

STABILITY STUDIES:

45 days of stability experiments were conducted at 2-8°C (45% RH), and 25-30°C (60% RH). The physical alteration, drug content, and drug release in the movies were all observed. Fast-dissolving films of loratadine were discovered to be physically and chemically stable and did not exhibit any appreciable changes in terms of their physical properties, percentage of drug content **(Table 12)**, or percentage of drug release **(Table 13)**.

Table 12: Stability study data (Drug content)

Formulation Code	Initial % drug content	2-8°C (45% RH)			25-30°C (60% RH)		
		15 days	30 days	45 days	15 days	30 days	45 days
FA1	94.43	94.40	94.38	94.37	94.40	94.38	94.35
FA2	97.00	96.99	96.97	96.96	96.78	96.75	96.73
FA3	94.16	94.12	94.05	94.00	94.13	94.04	93.92
FB1	93.86	93.81	93.77	93.74	93.82	93.69	93.62
FB2	96.03	95.97	95.91	95.85	95.96	95.85	95.81
FB3	95.03	94.98	94.90	94.88	94.85	94.80	94.78
FC1	94.93	94.79	94.73	94.68	94.83	94.71	94.65
FC2	95.93	95.88	95.78	95.71	95.83	95.70	95.56
FC3	95.20	95.16	95.10	95.05	95.25	95.08	95.04
FD1	94.22	94.18	94.11	94.04	94.26	94.11	94.09
FD2	95.33	95.26	95.19	95.09	95.37	95.22	95.19
FD3	94.12	94.11	94.08	94.03	94.20	94.12	94.05

Table 13: Stability study data (*in vitro* release)

Formulation Code	Initial % drug release	2-8°C (45% RH)			25-30°C (60% RH)		
		15 days	30 days	45 days	15 days	30 days	45 days
FA1	89.49	89.45	89.41	89.35	89.43	89.37	89.34
FA2	75.78	75.76	75.72	75.68	75.74	75.70	75.68
FA3	65.88	65.81	65.77	76.73	65.85	86.82	65.79
FB1	78.30	78.30	78.20	28.18	78.26	78.22	78.20
FB2	83.88	83.81	83.79	83.77	83.86	83.82	83.76
FB3	92.79	92.73	92.68	92.61	92.75	92.66	92.60
FC1	90.09	90.05	90.01	89.98	90.03	89.97	89.94
FC2	80.13	80.09	80.04	79.95	80.10	80.06	80.01
FC3	68.40	68.38	68.33	68.30	68.35	68.29	68.26
FD1	75.43	75.42	75.38	75.32	75.40	75.37	75.34
FD2	82.65	82.62	82.59	82.53	82.60	82.55	82.52
FD3	90.22	90.19	90.15	90.11	90.12	90.07	90.03

IN VIVO BLOOD HISTAMINE LEVEL

The study was performed to determine the effectiveness of loratadine to reduce the increased blood histamine level with respect to the time factor. The blood histamine level increase during allergic condition, resulting in hypersensitivity reactions. In the present study, blood histamine level was increased by injecting OVA (ovalbumin) as described under methodology section. It was observed that the blood histamine level increased in all group of animals except normal control, to 70-82 ng/ml, which is above the normal blood histamine level of 25-65 ng/ml **[27]**. The formulation (fast dissolving films) treated groups (Group 4-7) showed marked reduction to the normal range compared to the tablet formulation (group 3), indicated that the ability of the fast dissolving films to initiate the onset of action of drug faster **(Table 14)**. Thus, fast dissolving films have the potential of relieving the clinical symptoms of the allergic reactions like rhinitis, urticaria etc much faster compared to the marketed tablet formulations. This test is used as a yard stick to understand the faster on set of action produced by the formulations (fast dissolving films).

Table 14: Blood histamine level data

Treatment	Serum histamine (ng/ml)
Normal Control (Saline)	21±0.5774
Control (Toxic)	72±0.8165
Standard (10 mg/kg)	69±0.9574 NS
Formulation A1(3 mg/kg)	37±0.7560*
Formulation B1(3 mg/kg)	29±0.7742*
Formulation C3(3 mg/kg)	32±0.8216*
Formulation D3(3 mg/kg)	39±0.5000*

Values are mean± SD, n=4 for each group, *P<0.05 significant compared to control; NS: non significant

CONCLUSIONS:

The main objective of the study was to Design and evaluate fast dissolving film containing loratadine. The fast dissolving films can be easily formulated by solvent casting method by using polymers such as hydroxypropyl methylcellulose (HPMC K4M), polyvinyl pyrrolidone-K30 (PVP-K30), and poly vinyl alcohol (PVA). In different ratios with suitable plasticizer like propylene glycol and sweetener like aspartame. Compatibility of loratadine with polymers was confirmed by FT-IR studies. It was observed that the physicochemical characteristics such as uniformity of weight, thickness, folding endurance, surface pH and uniformity of drug content of all film sample showed satisfactory results with respect to variation of these parameters between films of same formulation. Tensile strength and percentage elongation of the films were increased with increase in the concentration of HPMC polymer. Disintegration time of the films was found to be decreased with increase in the concentration of HPMC 15 cps polymer. Based on the physicochemical parameters and *in vitro* drug release studies, formulation FA1, FB1, FC3, and FD3 were considered as the best formulations which exhibited the drug release of 95.52%, 95.97%, 94.90%, and 93.46%, respectively at the end of 30 sec. From *in vivo* blood histamine level study, it was concluded that, fast dissolving films have the potential reducing blood histamine level at relatively faster rate compared to marketed tablet formulation and hence can open a new horizon in sublingual drug delivery system. Present study reveals that all the twelve formulated films showed satisfactory film parameters. From the present investigation it can be conclude that fast dissolving film formulation can be a potential novel drug dosage form for paediatric, geriatric and also for general population.

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