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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE AND CONTROLLED RELEASE ORAL FILM OF ANTI-HISTAMINE AGENT: LORATADINE

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ABSTRACT

Innovations in oral drug delivery systems have made important contributions to medical practice by providing advances in the delivery of treatment with existing and novel drugs. The rate and extent of drug release and route of drug administration are vital parameters of any formulation. As Buccal delivery has more advantages over other routes of administration, such as providing immediate and prolonged and steadier drug levels, and less frequent dosing is required. It also has the ability to interrupt treatment by removing the film. Oral film of Loratadine which is antihistamine drug with immediate release and controlled release properties is prepared by solvent casting method, with the help of polymers such as HPMC E15, and PEG 400, Glycerin as a plasticize, SLS as a surfactant, Mannitol as sweetening agent, and citric acid as a saliva stimulating agent. The formulated oral film shows good Folding endurance, Swelling index, Surface pH, Weight variation, and Tensile strength.

KEYWORDS: Buccal drug delivery systems, Immediate release, controlled release, antihistamine.

INTRODUCTION

An oral film is a dosage form containing the active pharmaceutical ingredient (API) which disperse quickly, usually within a seconds, when placed in the oral cavity. Oral films can be administered without water, anywhere, at any time. These films have Minimum disintegration time and faster dissolution rate giving quick onset of action. Oral films are generally preferred by patients having dysphasia, motion sickness, repeated emesis, and mental disorders. Also, they exhibit enhanced bioavailability as they bypass the hepatic first-pass

metabolism. They are composed basically of the active pharmaceutical ingredient (API), hydrophilic polymers, plasticizers, sweeteners, flavors, colors, surfactants, saliva stimulating agents. The main disadvantages are the difficulty in attaining uniform dosage and achieving high drug loadings in the films.[1]

Anti-histamine is categories of a drug in which chemical substance which can inhibit the physiological effect of histamine in the human body.[2] The drug used is loratadine, which is a histamine H1 antagonist. Loratadine has non- sedating properties hence it is used commonly for the treatment of dermatoses and pruritus and hypersensitivity reactions such as allergic rhinitis, sneezing, running nose, itching and watering eyes. The adult dose of Loratadine for allergic rhinitis and urticaria is 10 mg orally once a day.[3]

HPMC is a polymer used due to its greater disintegration, dissolution, and good film-forming properties. The important step involved during the dissolution of a hydrophilic polymer includes absorption of water on a polymer, breaking of polymer bonds with simultaneous creation of water polymer bonds, separation of polymer chains, swelling, and finally dispersion of polymer chains in a medium. Dextrose as sweeting agent, citric acid as saliva stimulant, Polyethylene glycol as plasticizer, Sodium lauryl sulfate as surfactant.[4]

Drug profile

Name:- Loratadine (H1antihistaminics)

IUPAC Name:- 1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo [5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-, ethyl ester.

Chemical structure

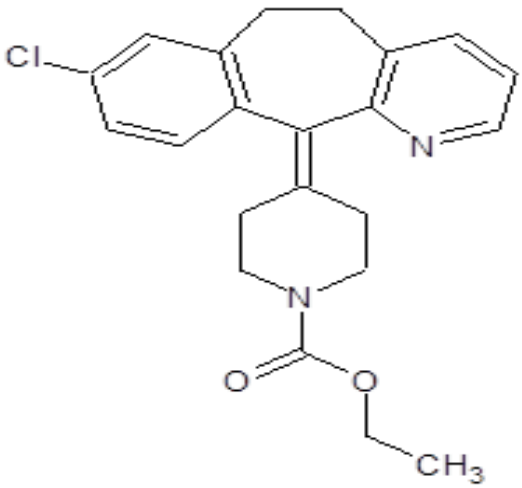

Figure 01: Chemical structure of Loratadine.

Molecular Formula: - $C_{22}H_{23}ClN_2O_2$

Formula Weight: - 382.88

Melting range: - between 132°and 137°.

MATERIALS AND METHODS

Loratadine Drug was obtained as a gift sample from Aarti Chemicals Ltd, Mumbai, Maharashtra. HPMC E15, PEG400, Mannitol, Citric acid and Sodium Lauryl Sulfate used were of analytical grade, purchased from Loba Chemicals Pvt Ltd, Mumbai, Maharashtra.

Preformulation study

❖ **Identification of drug**

Different identification parameters have been checked with references standers from USP, some as are following

- **Organoleptic properties**

Organoleptic properties of the drug-like color, odor was observed and recorded.

➢ **Determination of melting point**

The melting point of active pharmaceutical ingredients was determined by the capillary ethod of melting point detection. The active pharmaceutical ingredient was filled into capillary which was sealed at one end with the help of flame. The filled capillary was placed in melting point apparatus filled with liquid paraffin and the temperature at which drug melted was recorded.

➢ **Determination of solubility of the drug**

The solubility of Loratadine was determined in different solvents like methanol, dichloromethane, acetone, chloroform, and water.

- **Analytical method in the determination of drug**

➢ **λmax of loratadine**

Accurately weighed 10 mg of Loratadine in 100 ml volumetric flask and solubilized in 50 ml of methanol then the volume was made up to the mark using phosphate buffer pH 6.8. The standard stock solution of concentration 100µg/ml was further diluted with methanol to get a concentration of 10µg/ml. This solution was analyzed under a range of 400 nm to 200 nm in UV spectrophotometer (Lab India 3000).[5]

➢ **FT-IR study**

The IR spectra were recorded using FTIR spectrophotometer (Bruker, USA). Loratadine is an active pharmaceutical ingredient was scanned in the wavelength region between 3800 and 650 cm-1 and compared with reference from USP.[3]

➢ **Calibration curve of loratadine**

10 mg of Loratadine was accurately weighed and kept in a 100 ml volumetric flask. The active pharmaceutical ingredient was dissolved in methanol and made up to the volume with phosphate buffer pH 6.8. It was again diluted with methanol to get a concentration of 2, 4, 6, 8, 10µg/ml. The absorbance of the solution was measured spectrophotometrically at 254 nm using methanol as blank. The absorbance values were plotted against concentration.[6]

❖ **Preparation of oral thin films**

- **Solvent casting method**

Oral films were prepared by dissolving the excipients (HPMC) in the solvent mixture (methanol and dichloromethane.). an active pharmaceutical ingredient, sweetener, saliva stimulating agent and surfactant were added one by one into above solution and stirred for 15 minutes or continuous stirring to form a clear aqueous solution stir properly that no entrapment of air should happen if an air bubble is formed that must be removed by the help bath sonicator. Here Mannitol is used as a sweeting agent, citric acid as a saliva stimulant, PEG 400 as plasticizer, Sodium lauryl sulfate as a surfactant. Then The solutions were cast slowly on to a glass plate of diameter 5cm without any air entrapment. These plates were dried at not more than 50°C in hot air .dried films are carefully separated from the plate and stored in desiccators for 48 hours and evaluated. Different formulations were prepared as per the following table.[7]

Table I: Formulation design.

Formulation code	API Loratadine	HPMC E15	HPMC E5	PEG400	Glycerine	Citric acid	Mannitol	SLS	Dichloromethane: methanol
01	10mg	250mg	-	15mg	-	10mg	0.5ml	10mg	1:1
02	10mg	275mg	-	20mg	-	10mg	0.5ml	10mg	1:1
03	10mg	300mg	-	25mg	-	10mg	0.5ml	10mg	1:1
04	10mg	325 mg	-	30mg	-	10mg	0.5ml	10mg	1:1
05	10mg	350mg	-	35mg	-	10mg	0.5ml	10mg	1:1
06	10mg	375mg	-	40mg	-	10mg	0.5ml	10mg	1:1
07	10mg	-	250mg	-	15mg	10mg	0.5ml	10mg	1:1
08	10mg	-	275mg	-	20mg	10mg	0.5ml	10mg	1:1
09	10mg	-	300mg	-	25mg	10mg	0.5ml	10mg	1:1
10	10mg	-	325mg	-	30mg	10mg	0.5ml	10mg	1:1
11	10mg	-	350mg	-	35mg	10mg	0.5ml	10mg	1:1
12	10mg	-	375mg	-	40mg	10mg	0.5ml	10mg	1:1

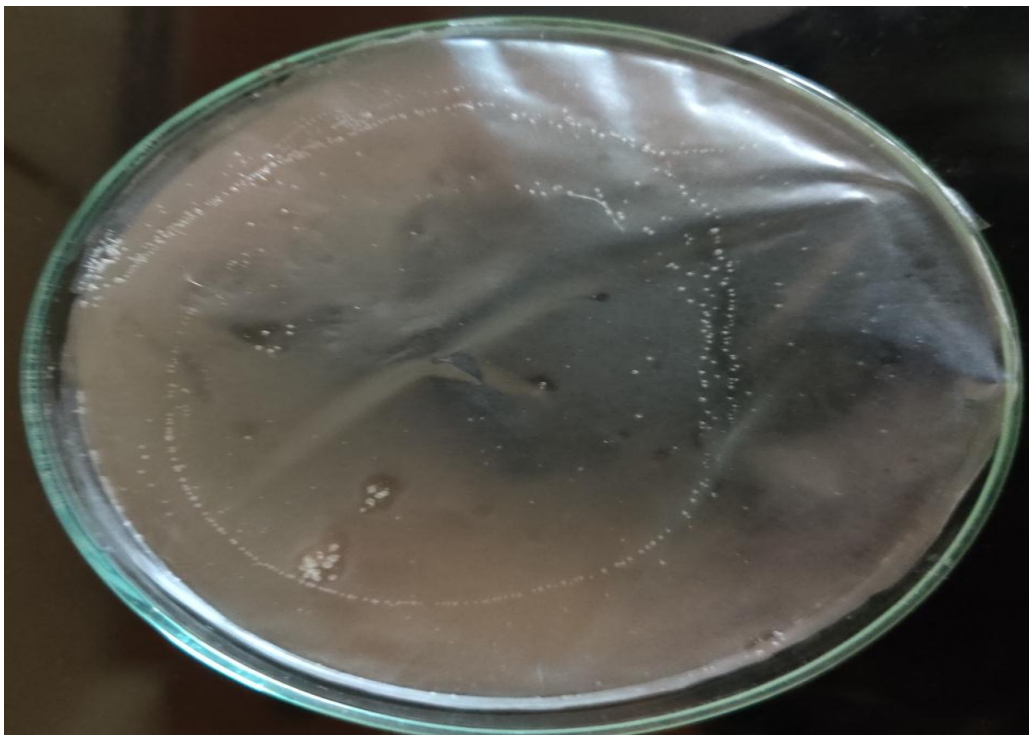

Figure 02: Formulated oral film of loratadine.

Evaluation

- **Organoleptic evaluation**

The prepared oral films were evaluated for organoleptic properties. All the films were visually inspected for color and shape.[2]

- **Thickness**

The thickness of the prepared films was measured at five different points on film using calibrated vernier caliper to ensure the uniformity of film thickness. The mean thickness is calculated, the patches having thickness variation greater than 5% were excluded from analysis.[5]

- **Folding endurance**

Folding endurance of film was determined by repeatedly folding the films of the uniform cross-sectional area until it breaks and The number of times it can be folded without breaking gives the value of folding endurance.[5]

- **Swelling index**

Swelling index is performed to analyze the swelling of the film due to polymer (Gelatin and HPMC E-15).[5]

- **Weight variation**

Weight variation was determined by separately weighing 10 randomly selected films and the average weight was calculated. Weight of each film was measured using digital weighing balance.[3]

- **Surface pH**

The surface pH of the film was determined by using a digital pH meter. The film was slightly wet with the help of water. The pH was measured by bringing electrode in contact with the surface of the film and allowed to equilibrate for 1 min. It is necessary to maintain the pH of the film, as an acidic or alkaline pH may irritate the oral mucosa; it was determined to keep the surface pH as close as to neutral as possible.[8]

- **Tensile strength**

Tensile strength was determined using a TA.XT plus Texture Analyzer. It is the maximum stress applied to a point at which film breaks and is measured by dividing the applied load at rupture by the cross-sectional area which is given by the equation.[5]

$$tensile\ strength = lode\ at\ breakage \div strip\ thickness \times strip\ width$$

➢ **Drug content**

Drug content is calculated by taking the film and dissolved in 100ml of phosphate buffer of 6.8pH. Then the solution is suitably diluted and the absorbance was recorded at 254nm.[5]

➢ **Percentage moisture loss**

Accurately weighed three films of area 2 cmx2 cm and kept in desiccators for 3 consecutive days, films were removed and reweighed. The % moisture loss was calculated using the formula.[3]

$$\%moisture\ loss = (initial\ weight - final\ weight) \div initial\ weight \times 100$$

➢ **In vitro disintegration time**

There are two simple methods in the first method; one drop of dissolution medium that is phosphate buffer pH 6.8 was dropped from a 10ml pipette onto the tightly clamped film. The time taken for the water to make a hole through the film was measured as disintegration time (DT). In the second method, 2 ml of water was placed on a Petri plate with a film on the surface of the water; the time taken for the disintegration of the film was measured. This test was done in triplicates and the average value was taken as disintegration time.[3,5]

➢ **In vitro dissolution study**

In-vitro dissolution test was carried out in USP II paddle dissolution apparatus with 900ml of phosphate buffer as dissolution media. Temperature was maintained at 37±0.5°C and set to a 100rpm. A film of 4cm2 was cut and stick to the basket sidewall. 5ml aliquots of samples were taken for every 30sec and followed by a replacement of 5ml fresh phosphate buffer. The withdrawn samples were analyzed spectrophotometrically at a wavelength of 254nm.[5]

➢ **Stability studies**

The stability study of the formulation was carried out as per ICH guidelines. It was subjected to accelerated stability study for a period of 3 months using a stability chamber at a temperature of 40± 2°C and RH 75± 5%. The samples were analyzed after 3 months for their stability.[9]

❖ **RESULTS AND DISCUSSIONS**

- **Preformulation study**

➢ **Organoleptic evaluation**

Loratadine appears as a white to off- white powder and odorless.

➢ **Identification of drug**

Frequency of the observed functional groups C=O, C-H, C-O, C-Cl is within the specified limits. The finger-print area has no change. So, the drug was identified as Loratadine.

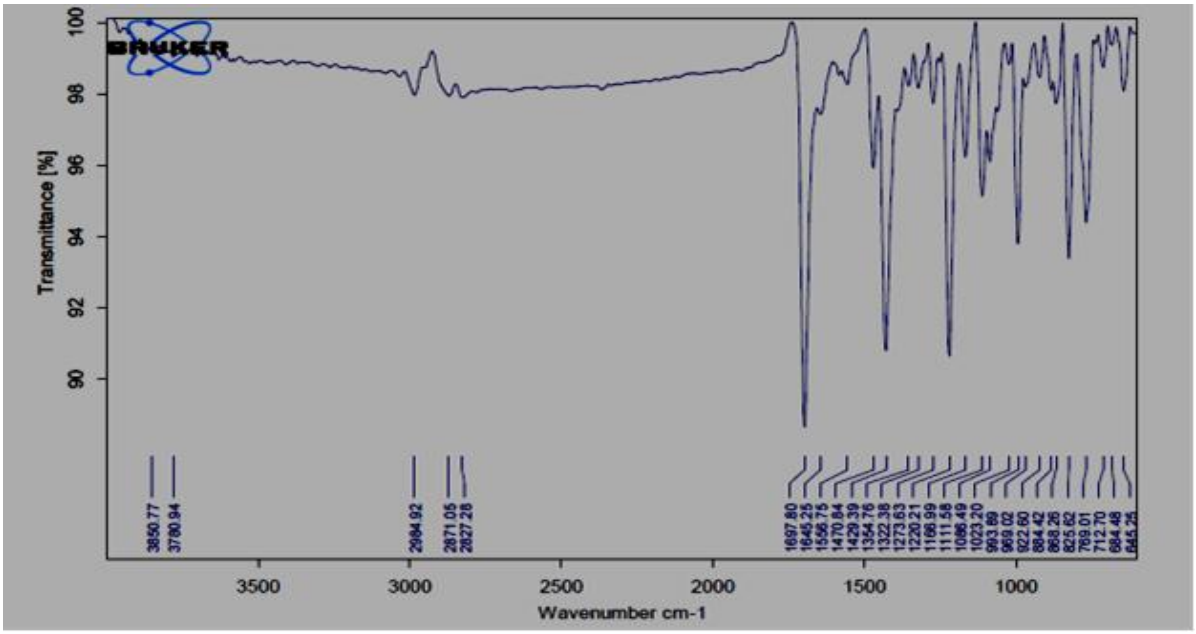

Figure 03: IR spectrum of loratadine.

➢ **λmax of loratadin**

The 10µg/ ml sample was prepared and scanned between 200-400 nm. The maximum absorbance was shown at 254nm hence the λmax of Loratadine is 254nm.

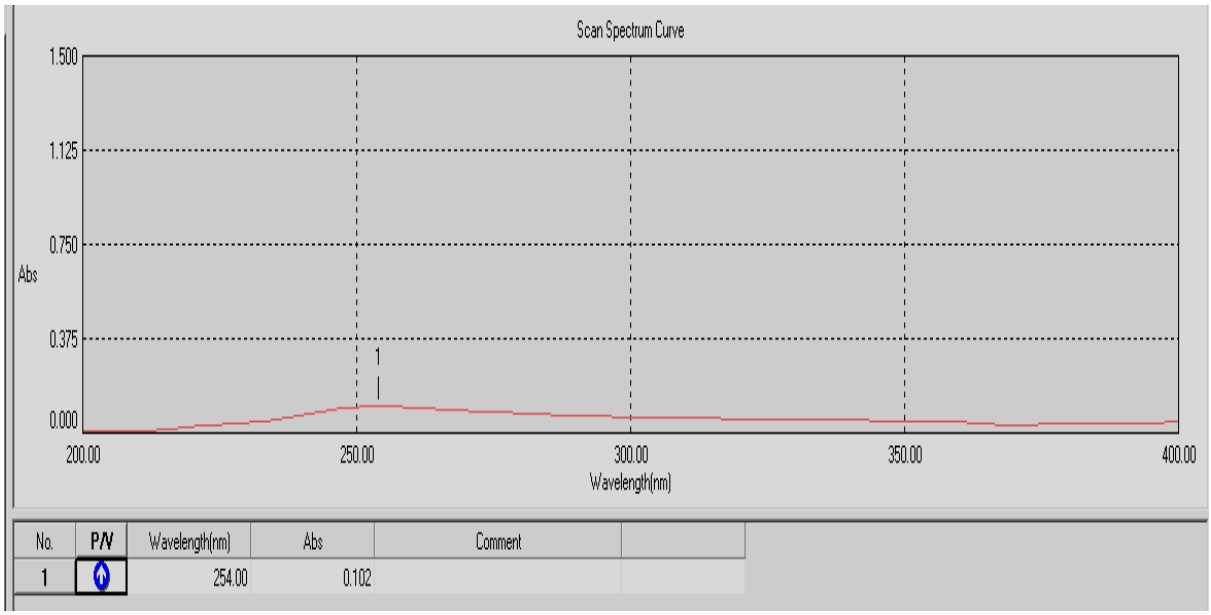

Figure 04: λmax of Loratadine.

➢ **Determination of melting point**

The standard melting point is in the range of 132^{0}C – 137^{0}C. The observed value was 134^{0}C and was within the range as per the official standard.

➢ **Determination of solubility of drug**

The solubility was determined by dissolving the drug in different solvents like methanol, acetone, dichloromethane, chloroform, and water. It was freely soluble in methanol, very slightly soluble in water, soluble in acetone, dichloromethane, and chloroform.

➢ **Preparation of calibration curve of loratadine**

The various concentrations of active pharmaceutical ingredients such as 2,4,6,8 and 10 µg/ml were prepared and the standard graph was plotted.

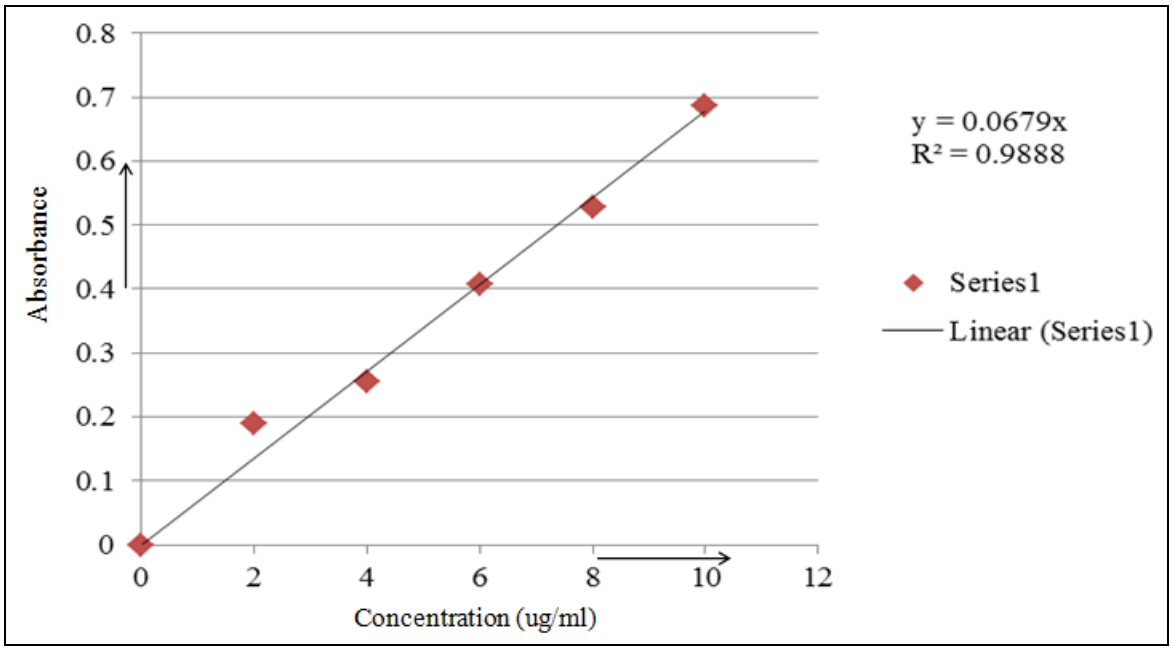

Figure 05: Calibration curve of loratadine.

❖ **Evaluation of dosage form**

Organoleptic Evaluation of oral film

Table II: Organoleptic evaluation.

Colour	White transparent
Odor	Odorless
Shape	Circular

- **Weight variation**

The average weights of 10 films were determined and the results are given determined in the table. The weight variation was in the range of 25.3 to 35.2 mg. As per USP requirement, the formulations meet the criteria for weight variation.

- **Thickness**

The thickness of the prepared films was measured at five different points on film using calibrated vernier caliper to ensure the uniformity of film thickness, as the concentration of the polymer and plasticizer increased, the thickness was gradually increased. The film thickness ranged from 0.261 to 0.551mm.

- **Surface pH**

The surface pH of the film was found to be in the range of 6.8 - 7.2 which is in the range of saliva pH.

- **Swelling index**

The swelling index of the oral thin films was found to be in the range 93-157. A polymer of HPMC E5 and HPMC E15 of weight 150mg showed a better swelling property.

- **Percentage moisture loss**

It was determined to know about the film's stability nature and ability of film to withstand its physicochemical properties under normal conditions. % moisture loss varied within the range of 0.98 to 2.98%.

Table III: Evaluation of oral film of loratadine.

Formulation Code	Weight variation (mg)	Thickness(mm)	Surface pH	% moisture loss	Tensile strength (kg/mm2)	Folding endurance	%Drug content	Disintegration time
F1	25.3	0.270	6.95	1.81	0.90	280.0	89.60	20.6
F2	27.5	0.321	6.96	2.01	1.10	305.0	84.70	26.3
F3	28.7	0.365	6.82	2.28	1.10	353.3	85.54	29.3
F4	30.2	0.422	6.95	2.70	1.12	371.6	86.24	31.0
F5	31.9	0.473	6.95	2.84	1.16	395.0	90.83	39.0
F6	33.4	0.551	6.99	2.98	1.19	405.3	95.67	44.5
F7	25.5	0.261	6.99	0.98	0.99	89.2	94.41	11.8
F8	28.1	0.302	6.99	1.22	1.10	110.3	98.78	16.9
F9	29.4	0.397	7.20	1.57	1.14	123.0	96.64	21.1
F10	32.2	0.412	6.95	1.74	1.20	145.7	97.77	24.6
F11	33.8	0.410	6.99	1.94	1.26	162.2	96.78	29.7
F12	35.2	0.440	6.96	2.20	1.34	170.5	98.20	33.4

- **Tensile strength**

The tensile strength was ranging in between 0.900-1.34 kg/ mm2 and was found to increase with an increase in the concentration of polymer and plasticizer. It indicates the film's strength which is important to resist the mechanical movements that may occur during the packing, storage, and shipping of the films.

- **Folding endurance**

The value of folding endurance was in the range of 89- 405. It was observed that with an increase in the concentration of polymer and plasticizer, the folding endurance also increased. Higher the value of folding endurance, lower is the chance of film to rupture.

- **Percentage drug content**

The % drug content in various formulations ranged from 84.70% – 98.20%. As per USP requirement, the drug content was found to be within the limit of 85-115%.

- **In vitro Disintegration time**

The disintegration time of the film was in the range of 12-44 sec as given in. As the concentration of HPMC and plasticizer increased, the disintegration time also increased.

- **In vitro dissolution study**

Oral films prepared by a higher quantity of polymer and plasticizer had shown a slower dissolution rate and controlled dissolution rate. It might be due to the increase in the concentration of polymer which results in the formation of a highly viscous layer that is due

to more intimate contact between the particles of a polymer. It results in reduced mobility of drugs in swollen matrices and hence controlled release rate. Formulations containing HPMC E5 (F7-F12) gave higher dissolution when compared to formulations containing HPMC E15 (F1-F6). It is because as the viscosity of polymer increases, the drug release rate from the film decreases.

➢ **Stability studies**

The selected formulation F6 was subjected to stability study. Initial and third-month studies were carried out. results showed that there were no significant changes for thickness, weight variation, % drug content, surface pH, disintegration time, folding endurance, and *in vitro* drug release. So, the drug product was found to be stable.

Table IV: Evolution of stability studies.

Parameters	Initial	After 90 d 40±2°C / 75±5% RH
Weight variation	33.4 mg	33.9mg
Folding endurance	405.00	410.00
% Drug content	95.60%	95.78%
Thickness	0.551 mm	0.559 mm
Disintegration time	44.00sec	46.00sec
Surface pH	6.99	7.0

❖ **CONCLUSION**

The oral film is a novel dosage form, which has great importance in life-threatening situations like allergic attacks where an immediate onset of action is required along with controlled-release action. Loratadine oral films that were successfully prepared and evaluated by the solvent casting method using the different polymers such as following HPMC E5: HPMC E15. 1:1 ratio of drug and polymer ratio was optimized along with the ratio of plasticizer PEG400 and Glycerin. Among all formulations, Films prepared using HPMC E15 with PEG 400 showed the best results. Dissolution study shows the better results which may effect on bioavailability and contribute to provide immediate relief from allergic reactions. Stability study also gave good results of stable formulation. It can be concluded that the oral film of Loratadine could be a promising approach for the treatment of allergy by overcoming the drawbacks associated with conventional dosage forms.

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