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FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM OF ANTI-ALLERGIC DRUG

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ABSTRACT

The aim of present work was the development of fast dissolving oral film of Loratadine to overcome the limitations of current routes of administration, to provide immediate action and increase the patient compliance. To improve the bioavailability of the drug, fast dissolving oral film were formulated using different grades of Hydroxy Propyl Methyl Cellulose(HPMC) and various plasticizers like Polyethylene Glycol(PEG) 400, glycerol, Propylene glycol(PG) by solvent casting method. The formulated films were evaluated for film thickness, surface pH, folding endurance, weight variation, % moisture loss, exvivo permeation study, tensile strength, % elongation, drug content uniformity, in vitro dissolution studies, in vitro disintegration test and in vivo study. The optimized formulation (F9) containing HPMC E5 and glycerol showed minimum disintegration time (10.5 s), highest in vitro dissolution (92.5%) and satisfactory stability. Ex vivo permeation study of optimized formulation showed a drug release of 80.6% within 10 min. The milk induced leucocytosis inrat proved that fast dissolving oral films of Loratadine produced a faster onset of action compared to the conventional tablets. These findings suggest that fast dissolving oral film of Loratadine could be potentially useful for treatment of allergy where quick onset of action is required.

Keywords: *Fast dissolving oral film; Loratadine; Plasticizer; Solvent casting*

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INTRODUCTION

Fast dissolving oral film is a novel dosage form that dissolves or disintegrates quickly in tongue or buccal cavity than conventional dosage form. Fast dissolving oral film is prepared using hydrophilic polymers, which dissolves rapidly in buccal cavity or on tongue. The film overcomes the drawbacks of conventional quick dissolving/ dispersing intraoral tablets like fear of choking. It is easy to handle, alleviates unpleasant taste, easy to manufacture, ensure accurate dose administration, afford a simple and convenient packaging [1].

Fast dissolving films are placed on top or floor of tongue and release rapidly the drug for local and/ or systemic absorption. Disintegrated film rapidly releases the drug from the polymer matrix which are absorbed directly and enter the systemic circulation without undergoing hepatic first pass metabolism and increases the bioavailability of the active ingredient, thereby reduction in dose which can lead to reduced side effects[2].

In case of conventional dosage forms like tablets and capsules, it delays the onset of action due to disintegration and dissolution. Fast dissolving film disintegrates rapidly in the oral cavity, bypass the hepatic first pass metabolism, releases drug immediately to the systemic circulation and produces a rapid onset of action. In situations of sudden allergic attack, faster pharmacological effect is required. Hence, the fast dissolving film is an ideal formulation for quick onset of action compared to conventional dosage forms. It does not require water to swallow, which is convenient for patients who are travelling and have no ready access to water[3].

Allergy is the response of body's immune response to substances such as pollen, house dust mites, food items etc. The allergic manifestations include itching and swelling, sore throat and morning cough, skin rashes,

wheezing and shortness of breath The epidemiological study revealed that 30-35% people are affected by allergy at some stages of their life [4].

Loratadine is a second generation antihistamine drug used to treat allergies and which is marketed for its non-sedating properties. It is a derivative of Azatadine and H_1 receptor antagonist which is used for the symptomatic treatment of allergy such as urticaria, 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. Unlike classical antihistamines it lacks central nervous system depressing effects like drowsiness [5,6].

The objective of this study is to formulate fast dissolving oral film of Loratadine in order to improve the bioavailability of the drug, to provide a quick onset of action and to select the best formulation based on the evaluation parameters.

MATERIALS AND METHODS

Materials

Loratadine was obtained as a gift sample from Vasudhev pharma chem. Limited, Hyderabad, India. HPMC E5, HPMC E15, PG, PEG 400, Glycerin, Tween 80, Saccharin sodium, citric acid were supplied by nice chemicals, kottayam, Kerala, India.

Preformulation Study

Identification of Drug The monograph of Loratadine signified that the substance under examination was dispersed in mineral oil. The spectra of test specimen was recorded over the range from 3800 cm^{-1} to 650 cm^{-1} and compared with the corresponding USP reference standard [6].

Organoleptic Evaluation

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

Determination of melting point

The melting point of drug was determined by capillary method. The drug was filled to capillary which was sealed at one end. The filled capillary was placed in melting point apparatus and the temperature at which drug melted was noted [6].

Determination of solubility of drug

Solubility of Loratadine was checked in various solvents like methanol, dichloromethane, acetone, chloroform and water [6].

Analytical Method In The Determination Of Drug

λmax for Loratadine

Accurately weighed 10 mg of Loratadine into 100 ml volumetric flask and dissolved in 50 ml of methanol. The volume was made up to the mark using phosphate buffer pH 6.8. The standard stock solution (100µg/ml) was further diluted with methanol to get the concentration of 10 µg/ml. This solution was scanned between 400 nm to 200 nm in UV spectrophotometer (Systronics 2202, Gujarat)[7].

Calibration curve for Loratadine

10 mg of Loratadine was accurately weighed and transferred into 100 ml volumetric flask. The drug was dissolved in methanol and made up to the volume with phosphate buffer pH 6.8. It was further diluted with methanol to get concentration of 2, 4, 6, 8, 10 µg/ml. The absorbance of solution was measured spectrophotometrically at 247 nm using methanol as blank. The absorbance values were plotted against concentration to obtain the standard graph [8].

Drug Excipient compatibility studies

The drug excipient compatibility studies were carried out by Fourier Transmission Infrared Spectroscopy (FTIR) method and Differential Scanning Calorimetry (DSC) method.

FTIR Study

The IR spectra were recorded using FTIR spectrophotometer (Bruker, USA). The samples were prepared by mixing the drug and the excipients in 1:1 ratio and stored in closed containers for 1 week. FTIR spectrum of the samples was taken using mull technique. The physical mixtures of Loratadine and excipients were scanned in the wavelength region between 3800 and 650 cm^{-1} and compared to check compatibility of drug with excipients [9].

Differential Scanning Calorimetry

DSC study was carried out using DSC-60 instrument (Shimadzu, Japan) to check the compatibility of ingredients. The samples were prepared by mixing the drug and the excipients in 1:1 ratio. Accurately weighed samples were sealed in aluminium pans and analyzed in an inert atmosphere of nitrogen at flow rate of 25 ml/min. A temperature range of 0°C to 300°C was used, and the heating rate was 10°C/min. DSC thermo grams of pure drugs and physical mixtures of drugs and polymers were studied for their interactions [10].

Preparation of fast dissolving oral film of loratadine

Fast dissolving oral film was prepared by solvent casting method. Different grades of polymer HPMC such as E15, E5 were used to formulate the strip with different plasticizers such as glycerin, PEG 400, PG. Citric acid was used as saliva stimulating agent, Saccharin sodium as sweetening agent and Tween 80 as surfactant. The formulation design of fast dissolving oral film of Loratadine is given in Table 1. The specified amount of HPMC was dissolved in a mixture of methanol and dichloromethane. The required amount of plasticizer was added to film forming solution. Drug, sweetener, saliva stimulating agent and surfactant were added one by one into above solution with continuous stirring to form a clear aqueous solution. The solution was kept undisturbed until the air bubbles were removed. The aqueous solution was poured into the petridish and was dried at 45°C in hot air oven. The film was carefully removed from the petridish and cut into required size suitable for testing. The formulated film was further stored in desiccators for 2 days and wrapped in aluminum foil and packed in self-sealing cover [11].

Table 1: Formulation Design of fast dissolving oral film of Loratadine

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Loratadine (mg)	96	96	96	96	96	96	96	96	96	96	96	96
HPMC E15 (mg)	250	250	250	300	300	300	-	-	-	-	-	-
HPMC E5 (mg)	-	-	-	-	-	-	250	250	250	300	300	300
PEG 400(mg)	-	37.5	-	-	45	-	-	37.5	-	-	45	-
Glycerin(mg)	-	-	37.5	-	-	45	-	-	37.5	-	-	45
PG(mg)	37.5	-	-	45	-	-	37.5	-	-	45	-	-
Citric acid(mg)	10	10	10	10	10	10	10	10	10	10	10	10
Sodium Saccharin (mg)	15	15	15	15	15	15	15	15	15	15	15	15
Tween 80 (mg)	30	30	30	30	30	30	30	30	30	30	30	30
Dichloromethane: methanol	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1

Evaluation of Fast Dissolving Oral Film

Organoleptic evaluation

The formulated fast dissolving oral films were evaluated for organoleptic characteristics like color, odor and shape. All the films were visually inspected for color and shape [12].

Folding endurance

Folding endurance was determined by repeatedly folding the film at the same place till it breaks. The number of times it can be folded without breaking gives the value of folding endurance [13].

Thickness

The thickness of the film was measured using calibrated vernier caliper at different spots of the film. The mean thickness was calculated [14].

Weight variation

Weight variation was determined by individually weighing 10 randomly selected films and average weight was calculated. Weight of each film was measured using digital weighing balance [15].

Surface pH

The films to be tested was moistened with phosphate buffer pH 6.8 in a petridish and kept for 30 s. The pH of the formulation was noted after bringing the electrode of pH meter in contact with the surface and allowed to equilibrate for 1 min [14].

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 applied load at rupture by the cross-stional area which is given by the equation [16].

$$\text{Tensile strength} = \frac{\text{load at breakage}}{\text{strip thickness}} \times \text{strip width}$$

Percentage elongation

% elongation was calculated by dividing the extension at the point of rupture by initial length of the specimen and multiplying by hundred [16].

$$\%\ \text{elongation} = \frac{\text{Increase in length}}{\text{Original length}} \times 100$$

Drug content uniformity

Drug content uniformity was determined by assay of 10 dosage units individually. The film was transferred into a graduated flask, dissolved in 100 ml methanol and the flask was shaken continuously. The solution was filtered after suitable dilutions with methanol, the absorbance was measured at 247 nm and the drug content was calculated[16, 17].

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[13].

$$\%\ \text{moisture loss} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100$$

***In vitro* disintegration test**

Disintegration test was performed to ensure the disintegration of film in phosphate buffer pH 6.8. Film was placed in beaker containing 10 ml of phosphate buffer pH 6.8. Slight agitation was given at every 10 s, the time at which film starts to disintegrate or break is the disintegration time [14].

***In vitro* dissolution study**

The dissolution study of the film was carried out using modified type 5 dissolution apparatus (Electrolab, Mumbai) at 37°C ± 0.5°C using 300 ml of simulated saliva (pH 6.8) as dissolution media. The agitation speed of paddle was 50 rpm. At predetermined time intervals, 5 ml of sample was withdrawn and replaced with fresh

medium. The sample was filtered through Whatmann filter paper and analyzed at 247 nm[15].

Kinetic Study

To analyze the drug release rate kinetics and mechanism of drug release from the fast dissolving films, the *in vitro* drug release studies data was fitted into Zero order, First order, Higuchi model, Hixson-Crowell Cube Root Law model and Korsmeyer peppas models. Best-fit models were selected from these. The quantitative interpretation of the values obtained in the dissolution is facilitated by the usage of a generic equation [18].

***Ex Vivo* Permeation Study**

Permeation study was carried out with buccal mucosa of goat using the Franz diffusion cell. The mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with isotonic phosphate buffer of pH 6.8 maintained at 37± 0.2°C and hydrodynamics were maintained using magnetic stirrer. One film (2 cm×2 cm) previously moistened with a few drops of phosphate buffer pH 6.8 was placed in donor compartment. The donor compartment was filled with 1 ml of pH 6.8 phosphate buffer. From the receptor compartment, samples were withdrawn at suitable time intervals and replaced with an equal amount of phosphate buffer. The % amount of drug in the receptor compartment was determined by measuring the absorbance [13, 14].

Milk-induced leucocytosis in rats

The protocol of the experiment was approved by the Institutional Animal Ethics Committee (IAEC/KMCP/262/2016).Male Wistar rats were divided into three groups (n= 6). Group-1 was the control group and received saline; Group-2 was the test group and received a single dose of the dissolution medium withdrawn at the 1 min. time interval during the dissolution study of fast dissolving oral film. Group-3 was the reference group and received a single dose of the dissolution medium withdrawn at the 1 min. time interval during the dissolution study of reference tablet. All the groups received boiled and cooled milk injection (dose of 4 ml/kg, s.c). The total leucocyte count was done in each group before the induction of leucocytosis and 24 h after milk injection. The drug was administered 24 h. after the induction of leucocytosis, from the sample withdrawn at 1 min. of the dissolution study of fast dissolving oral film of loratadine (1 min. dissolution study). The leucocyte count was done using Neuber's chamber, after 30 and 60 min time intervals of drug administration, and drop in leucocytes was observed [19].

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 6 months using stability chamber at a temperature of 40± 2°C and RH 75± 5%. The samples were analyzed at initial, third and sixth month for various parameters [16].

RESULTS AND DISCUSSIONS

Preformulation Study

Identification of Drug

The sample spectrum was compared with the reference spectrum and there were no significant changes in the frequency of the functional groups (Fig.1,2). The frequency of the observed functional groups C=O, C-H, C-O, C-Cl are within the specified limits. The finger-print area has no change. So, the drug was identified as Loratadine.

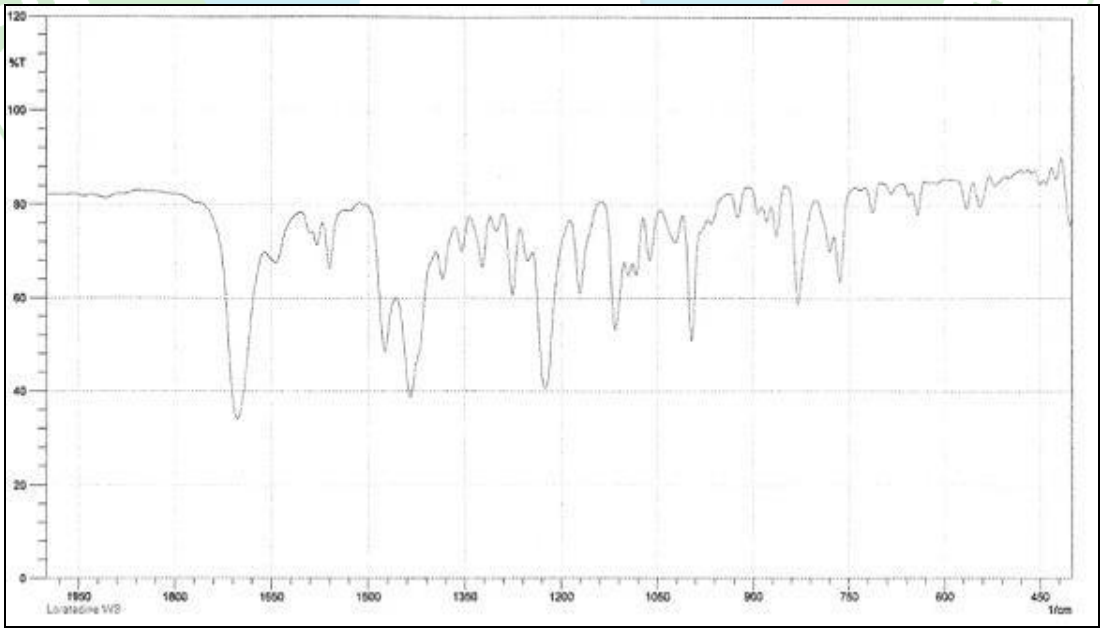

Fig. 1: FTIR spectrum of Loratadine Reference

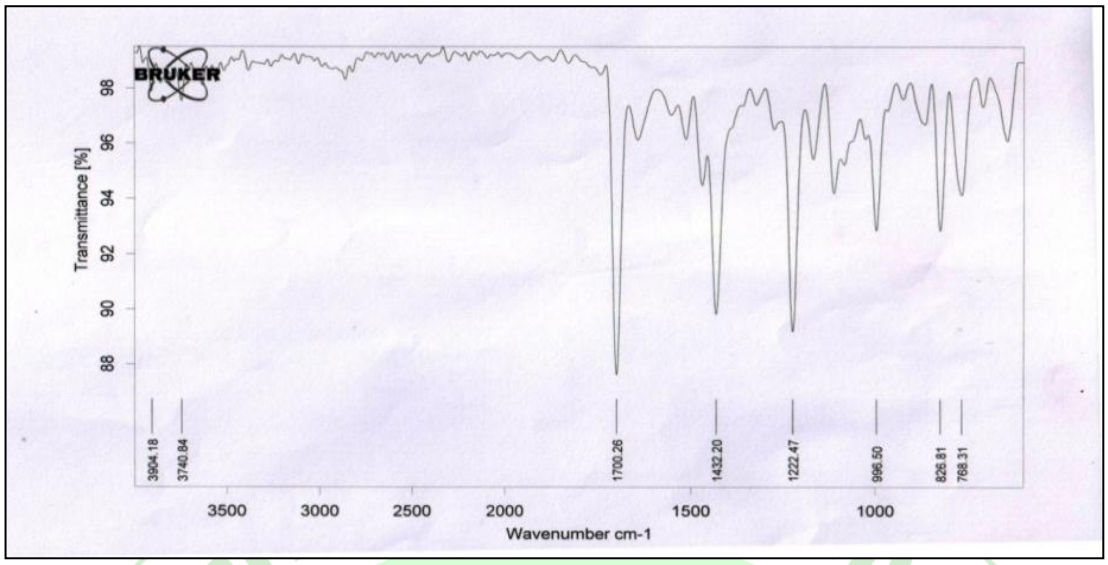

Fig.2: FTIR spectrum of Loratadine Sample

Organoleptic evaluation

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

Determination of melting point

The standard melting point is in the range of 132^{0}C – 137^{0}C. The observed value was 136^{0}C and was within the range as per 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.

Analytical Method for the Determination of Drug

Determination of λ max of Loratadine

The 10 µg/ ml sample was prepared and scanned between 200-400 nm. The drug showed maximum absorption at 247 nm. So, the λ maxof Loratadine was found to be 247nm.

Preparation of calibration curve of Loratadine The various concentrations of drug (2,4,6,8,10 µg/ml) were preparedand the standard graph was plotted (Fig.3). The y- intercept and R^2 values were found to be 0.047, 0.989 respectively.

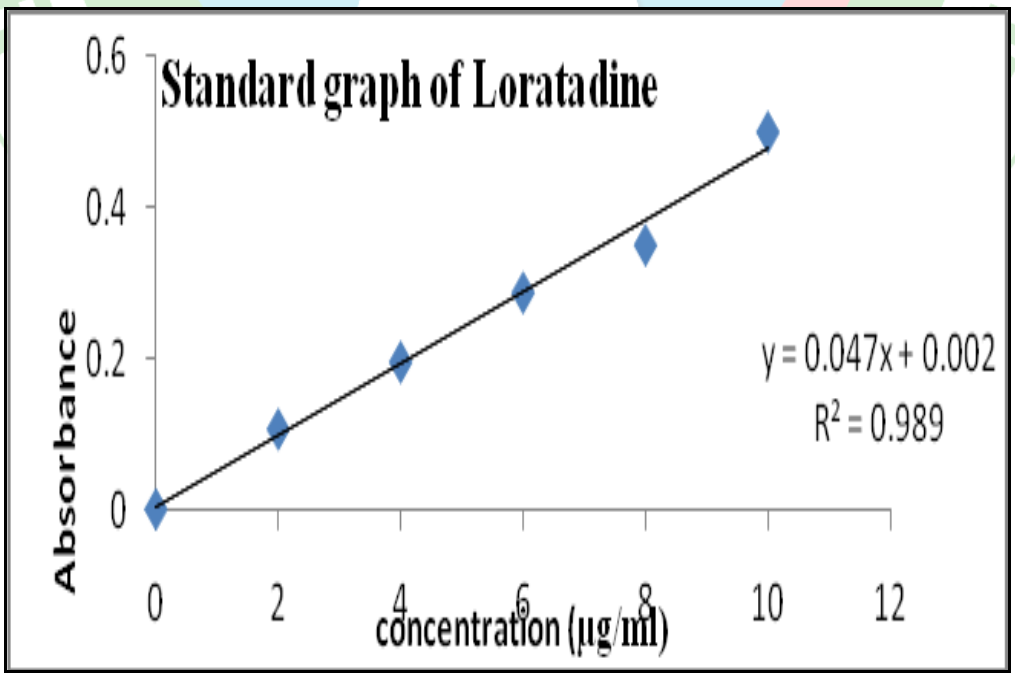

Fig.3: Standard graph of Loratadine at 247 nm

Drug Excipient compatibility studies

FTIR studies

FTIR studies were carried out for Loratadine and Loratadine-polymer physical mixtures. There were no significant changes in the frequency of functional groups of Loratadine in the presence of polymers. So, the drug was compatible with HPMC E5 and HPMC E15.

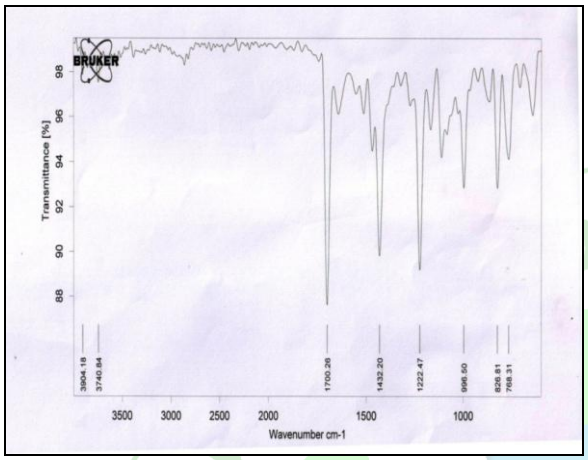

Fig.4: FTIR spectrum of Loratadine

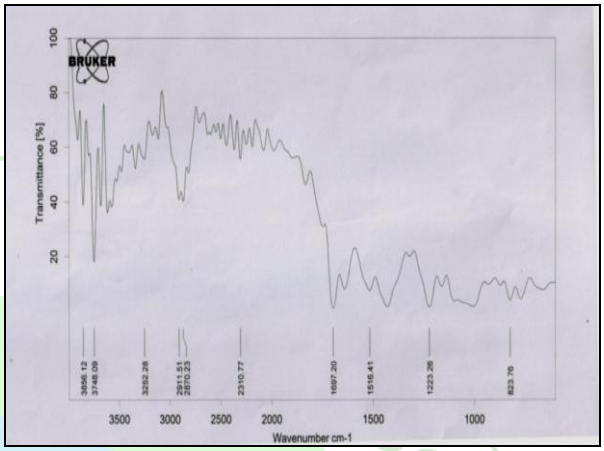

Fig.5: FTIR spectrum of Loratadine with HPMC E5

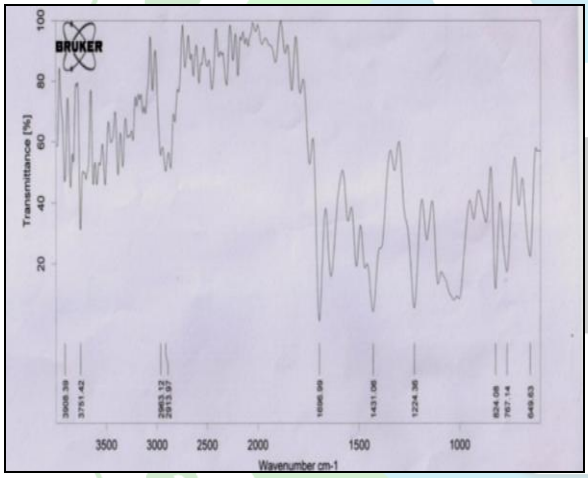

Fig. 6: FTIR spectrum of Loratadine with HPMC E15

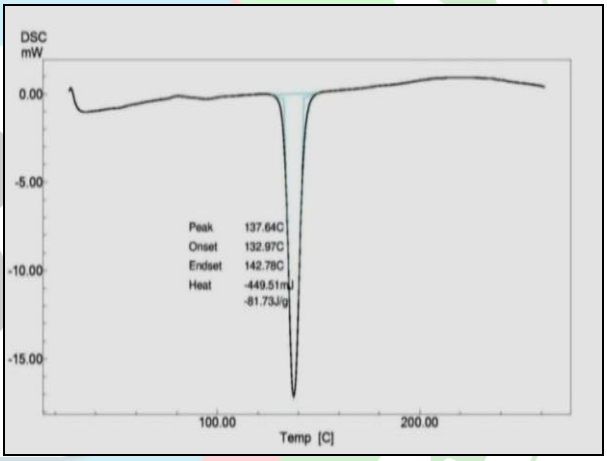

Fig.7: DSC Thermogram of Loratadine

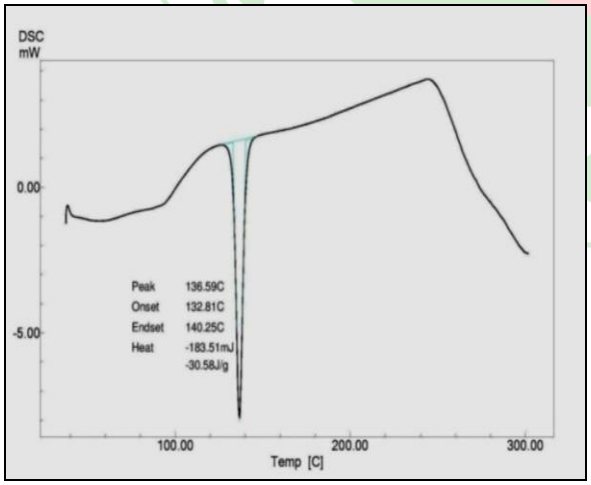

Fig.8: DSC Thermogram of physical mixture of Loratadine and HPMCE5

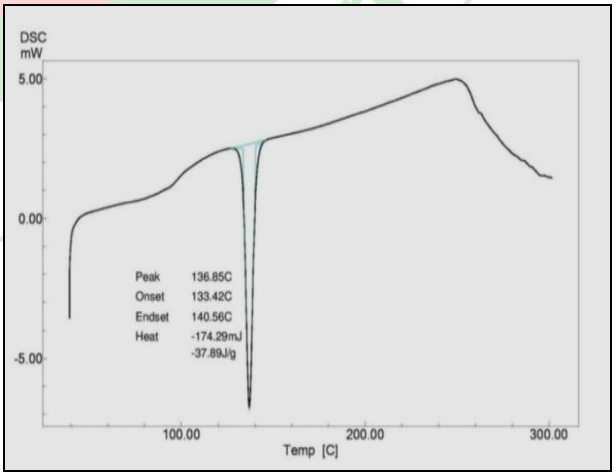

Fig.9: DSC Thermogram of physical mixture of Loratadine and HPMCE15

DSC studies were carried for Loratadine and drug-polymer physical mixtures. The results are given in Fig.7,8,9. The melting point remains almost the same, indicating that the drug and excipients are compatible.

Evaluation of Loratadine Fast Dissolving Oral Films

Organoleptic Evaluation of fast dissolving film

Shape - Circular
Color - Colorless
Odor - Odorless

Fig. 10: Fast dissolving oral film of Loratadine

Folding enduranceof fast dissolving film

The value of folding endurance was in the range of 101± 0.57- 384± 1.52. It was observed that with increase in concentration of polymer and plasticizer, the folding endurance also increased. Higher the value of folding endurance, lower is the chance of film to rupture.

Table 2: Evaluation of fast dissolving oral film

Formulation Code	Folding endurance* (Mean±SD)	Thickness*(mm) (Mean±SD)	Weight variation (mg) *(Mean±SD)	Surface pH (Mean±SD)
F1	313.0±1.52	0.366±0.057	25.3±0.57	6.95±0.01
F2	321.0±1.00	0.433±0.057	28.3±0.50	6.95±0.005
F3	350.3±0.57	0.366±0.057	25.6±0.57	6.96±0.005
F4	384.6±1.52	0.533±0.115	32.8±0.76	6.95±0.011
F5	375.0±1.00	0.433±0.057	38.6±0.76	6.98±0.010
F6	361.3±0.57	0.466±0.057	34.8±0.66	6.98±0.005
F7	139.6±1.52	0.366±0.057	28.0±0.50	6.96±.0208
F8	101.3±0.57	0.466±0.115	30.5±0.50	6.99±0.011
F9	115.0±1.00	0.466±0.152	28.6±0.57	7.006±0.015
F10	150.6±1.15	0.433±0.057	33.5±0.60	6.95±0.010
F11	117.6±1.52	0.466±0.057	40.5±0.50	6.99±0.015
F12	128.6±0.57	0.433±0.057	34.7±0.81	6.926±0.005

*Each reading is an average of 3 determinations

Thickness of fast dissolving film

Thickness of the film was measured with vernier caliper. The uniformity of the film thickness could be attributed to the accuracy of dose in the strip. As the concentration of the polymer and plasticizer increased, the thickness was gradually increased. The film thickness ranged from 0.366 to 0.533 mm (Table 2).

Weight variation of fast dissolving film

The average weights of 10 films were determined and the results are given in the Table 2. The weight variation was in the range of 25.33± 0.57 to 40.5± 0.50 mg. As per USP requirement, the formulations meet the criteria for weight variation.

Surface pH of fast dissolving film

The surface pH was measured to determine the possibility of any *in vivo* side effects, as the acidic or alkaline pH may cause oral mucosal irritation. The surface pH of the strips was ranging from 6.92 to 7.006 as shown in Table 2. The surface pH values of films assured that there will be no irritation to the oral mucosal lining.

Percentage elongation of fast dissolving film

The % elongation of films was determined and the results are as given in Table 3. The % elongation was ranged from 6.12-7.28. The nature of polymer affects the % elongation. It increased with the increase in the concentration of polymer and plasticizer. It gives an indication of elasticity of the film.

Tensile strength of fast dissolving film

The tensile strength was ranging from 1.11-1.27 kg/ mm^2 (TableIII) and wasfound to increase with increase in the concentration of polymer and plasticizer. The tensile strength gives an indication of the film strength which is important to resist the mechanical movements that may occur during the packing, storage and shipping of the films.

Table 3: Tensile strength and % elongation of fast dissolving oral film

Formulation Code	% elongation*(Mean±SD)	Tensile strength(kg/mm^2) (Mean±SD)
F1	6.12±0.196	1.11±0.04
F2	6.23±0.104	1.11±0.03
F3	6.24±0.438	1.12±0.030
F4	6.69±0.494	1.16±0.041
F5	7.28±0.943	1.16±0.0305
F6	6.28±0.612	1.196±0.0152
F7	6.46±0.301	1.136±0.055
F8	6.24±0.402	1.11±0.02
F9	6.758±1.836	1.1905±0.177
F10	6.72±0.193	1.27±0.025
F11	7.12±0.08	1.24±0.066
F12	7.24±1.33	1.22±0.020

*Each reading is an average of 3 determinations

Drug content uniformityof fast dissolving oral film

The % drug content in various formulations ranged from 83.93 % – 98.7 %. As per USP requirement, the drug content was found to be within limit.

***In vitro* disintegration test**

The disintegration time of film was in range of 10.5-28 s as given in Table IV. As the concentration of HPMC and plasticizer increased, the disintegration time also increased.

Table 4: Measurement of % drug content, *in vitro* disintegration and % moisture loss

Formulation Code	%Drug content* (Mean±SD)	Disintegration time*(s)(Mean±SD)	% moisture loss*(Mean±SD)
F1	87.70±0.907	20.6±1.15	2.23±0.152
F2	85.70±0.737	16.3±0.57	1.1±0.1
F3	90.80±0.793	14.3±0.57	3.48±0.076
F4	85.27±0.624	28.0±1.00	2.35±0.05
F5	87.88±0.393	24.0±1.00	1.27±0.025
F6	98.03±0.763	18.5±0.50	2.12±0.105
F7	98.46±0.450	14.5±0.50	1.89±0.036
F8	95.75±0.500	12.6±0.28	1.02±0.064
F9	97.83±0.873	10.5±0.50	1.54±0.04
F10	85.93±0.550	22.5±0.50	2.33±0.032
F11	94.68±0.503	20.8±0.70	1.24±0.041
F12	98.70±0.200	14.0±0.50	2.32±0.046

* Each reading is an average of 3 determinations

Percentage moisture loss

% moisture loss was determined and results are given in Table IV. It was determined to know about the films stability nature and ability of film to withstand its physicochemical properties under normal conditions. % moisture loss varied within the range of 1.1 to 3.48 %.

***In vitro* dissolution study of fast dissolving film**

Fast dissolving oral films formed by higher quantity of polymer and plasticizer had shown slower dissolution rate. It might be due to the increase in the concentration of polymer which results in the formation of high viscous gel layer that is caused by more intimate contact between the particles of polymer. It results in reduced mobility of drug in swollen matrices and hence decreased release rate. Formulations containing HPMC E5 (F7-F12) gave higher dissolution when compared to formulations containing HPMC E15 (F1-F6) and is represented in Fig.11,12. It is because as the viscosity of polymer increases, the drug release rate from the film decreases. The formulations containing glycerin gave superior dissolution profile when compared to formulation containing PEG 400 and PG. The formulation F9 showed a better release of 92. 5 %.

***Ex vivo* permeation studies**

Ex vivo permeation studies were conducted on optimized formulation F9. 80.6% of drug was permeated through oral mucosa within 10 min as given in Table12. The amount of the drug that permeated through oral mucosa can bypass the first pass metabolism so bioavailability of drug may enhance.

Milk-induced leucocytosis

The comparison between fast dissolving oral film and reference tablets was done by milk-induced leucocytosis in rats. Leucocytosis was observed after the parenteral administration of milk. The control group showed a significant ($P < 0.05$) increase in the leucocyte count Table 5. As expected, the fast-dissolving film treated group showed a significant decrease in the number of leucocytes after 30 min. (time interval between 30 and 60 min) as compared to reference drug. There was no drop in leucocytes in the group treated with reference tablets, as the dissolution medium expected to contain either very little drug or no drug. This is because; the reference tablet cannot release the drug within a minute. The value obtained was found to be statistically significant ($P < 0.05$) in animals treated with films. The normal leucocyte count ranged from 8000 ± 100 to 9100 ± 50. After injecting milk, the total leucocyte count was found to range from 10,533 ± 174 to 10,985 ± 196 showing the signs of leucocytosis.

Kinetic study of the film

The results of *in vitro* drug release were plotted in different kinetic models. The release kinetics data indicates that the release of drug from fast dissolving film F9 best fits to first order release kinetics. R^2 values of first order kinetic equations (0.993) were found to be greater than zero order kinetic(0.893) for the optimized formulation F9 indicating that the release from the films was dependent on the concentration of drug present in the formulation.

The data was fitted with Higuchi equation which gave a linear plot with highest R^2 (0.980) indicating the mechanism of drug release was diffusion. To determine whether fickian or non-fickian diffusion existed, the Korsmeyer Peppas equation data was analyzed. Using the Korsmeyer -Peppas model, n= 0.595 (0.45 <n> 0.89) indicates anomalous behavior or non-Fickian transport.

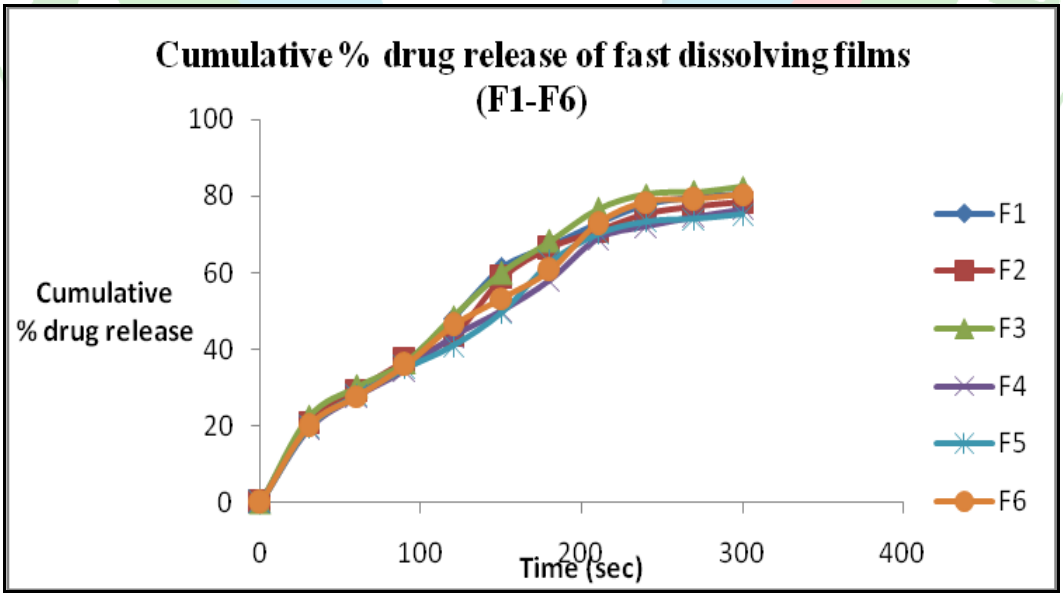

Fig.11: Comparison of cumulative % drug release of films F1-F6

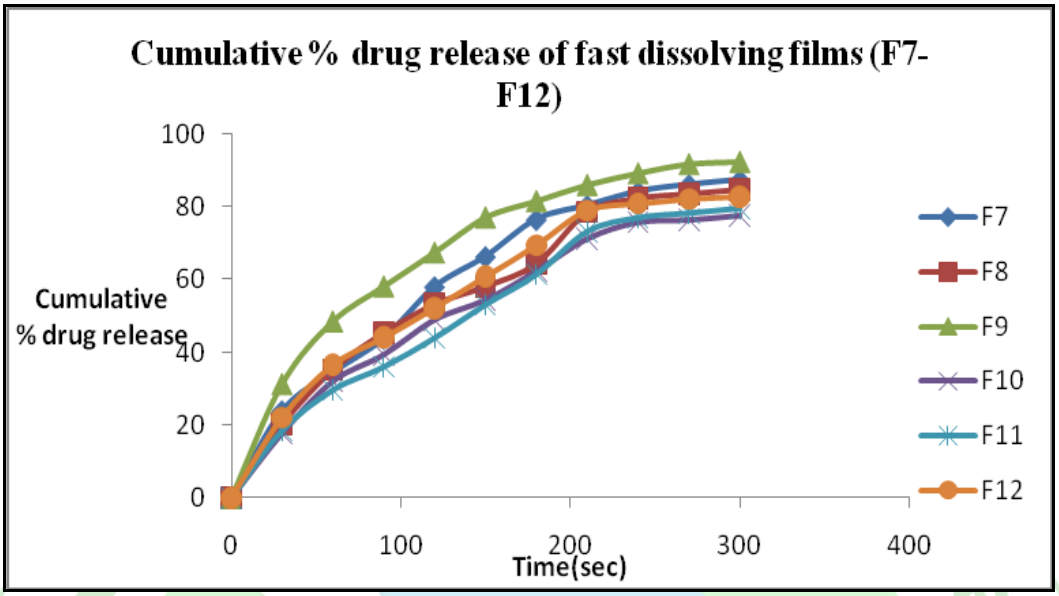

Fig.12: Comparison of cumulative % drug release of films F7-F12

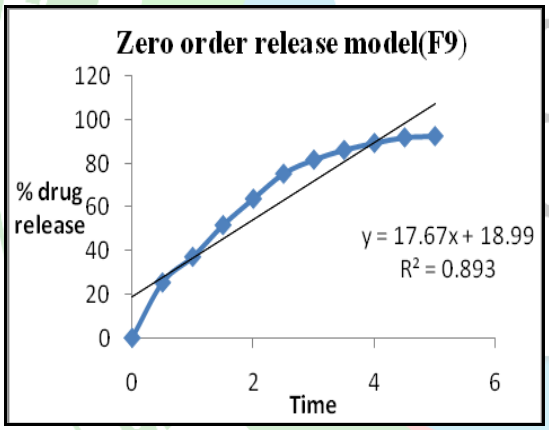

Fig.13: Zero order plot of F9

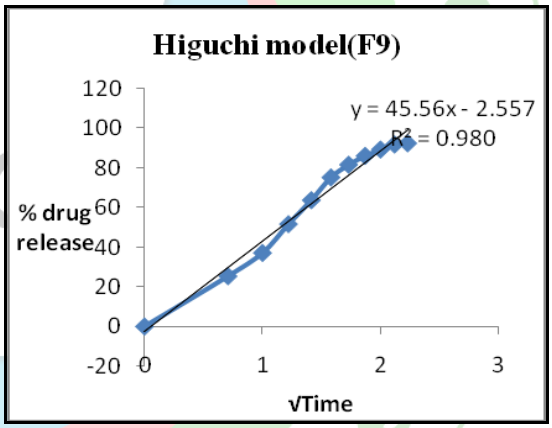

Fig.14: First order plot of F9

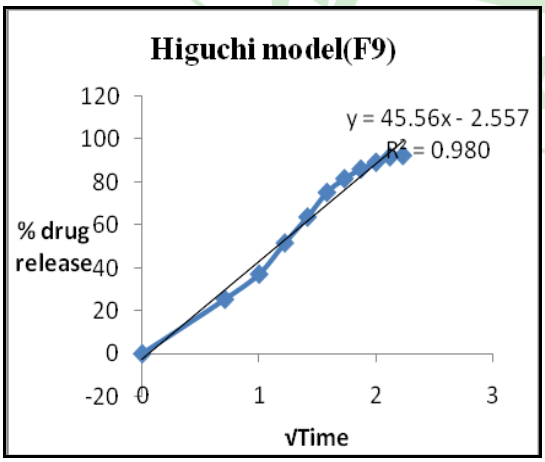

Fig.15: Higuchi plot for F9

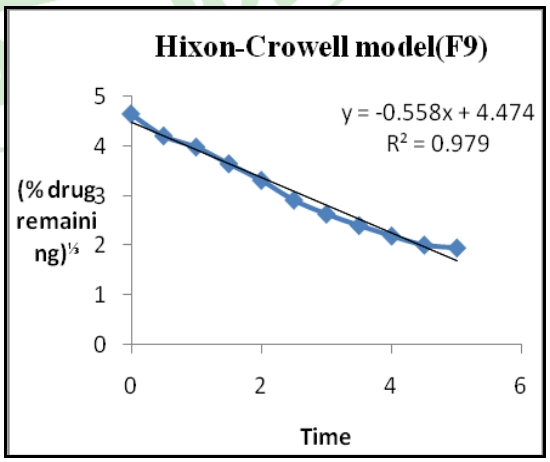

Fig.16: Hixon-Crowell plot for F9

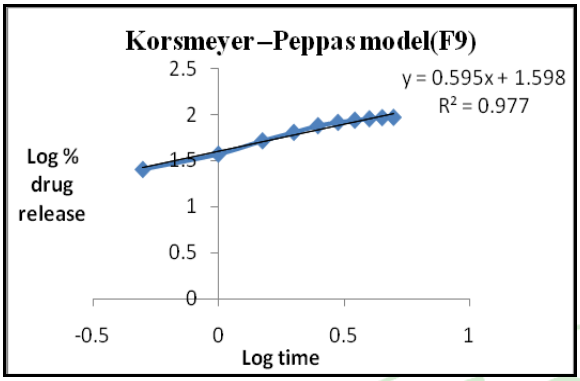

Fig.17: Korsmeyer –Peppas plot for F-9

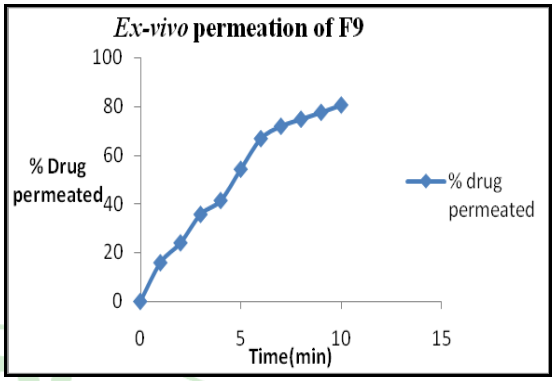

Fig. 18: *Ex vivo* permeation study of formulation F-9

Table 5: Milk induced leucocytosis in rat

S.No	Treatment	No. of leucocyte in mm^3(mean ± SD)		
		Before treatment	After treatment	Difference
1.	Group 1	10,615 ± 208	10, 460 ± 172	155 ± 63^{NS}
2.	Group 2	10,985 ± 196	8,865 ± 127	$2,120 \pm 78^{*}$
3.	Group 3	10,533 ± 174	10,256 ± 136	277 ± 69^{NS}

Values are expressed as mean ± SD, $n = 6$, for each group. $^{*}P < 0.05$ compared to control; NS = Statistically not significant.

Stability studies

The selected formulation F9 was subjected to stability study. Initial and third month studies were carried out and the results were mentioned in the Tables 6. The 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. The stability study will be continued further up to 6 months.

Table 6: Stability study data at 40±2°C / 75% RH

Parameters	Initial	After 90 d 40±2°C / 75±5% RH
Thickness	0.466 mm	0.466 mm
Weight variation	28.6 mg	27.5mg
% Drug content	97.83%	96.85%
Surface pH	7.006	7.0
Disintegration time	10.5s	11s
Folding endurance	115	113

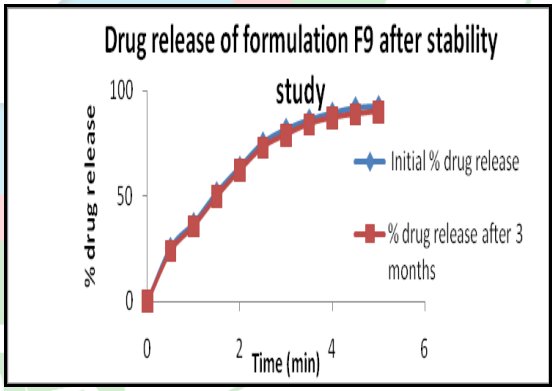

Fig. 19: Drug release profile of formulation F9 after stability study

CONCLUSION

Fast dissolving oral film is an innovative dosage form that is having great importance in emergency situations like allergic attacks where an immediate onset of action is required.

The film prepared with HPMC E5 and glycerol (F9) was selected as the best formulation based on various evaluation parameters. The *ex vivo* permeation study of the optimized formulation showed a permeation of 80.6% within 10 min which exhibit that it would provide an immediate relief from allergic reactions due to its faster absorption in oral cavity and is a better alternative to conventional dosage forms.

It can be concluded that the fast dissolving 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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