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Original Article

FORMULATION AND EVALUATION OF MOUTH-DISSOLVING FILM OF AN H1 ANTIHISTAMINE DRUG

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ABSTRACT

Objective: The objective of present work was to develop a Mouth dissolving film of Levocetirizine dihydrochloride drug by Solvent casting method using different natural polymers. The best polymer was selected on the basis of the release of the drug and disintegration time.

Methods: Sodium alginate and Guar gum are used as a natural polymers. Starch is used as a disintegrant. Glycerol is used as a plasticizer. Citric acid is usedas a saliva-stimulating agent. Mannitol is used as a sweetener. Peppermint oil as a flavoring agent. Mouth-dissolving films were prepared by using the solvent casting method.

Results: The compatibility study of the drug with different natural polymers was carried out. The IR spectral studies showed no interaction between drug and polymers. Obtained satisfactory results for Preformulation and post-formulation tests. Formulation F6 containing sodium alginate, F9 containing guar gum and F14 containing a combination ratio of (Sodium alginate: guar gum) showed good results throughout the study. The stability studies on the formulations F6, F9 and F14 indicates that there is no significant change in physical appearance, disintegration time and drug content release study.

Conclusion: From the results, it was concluded that the Mouth dissolving films of Levocetirizine dihydrochloride containing natural polymer sodium alginate (F6) showed the least disintegration time (14.28 sec), highest dissolution rate (98.24%) than the formulation containing natural polymer guar gum and combination ratio of (Sodium alginate: guar gum).

Keywords: Mouth dissolving films, Sodium alginate, Guar-gum, Disintegration, Drug content, Dissolution and solvent casting method

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INTRODUCTION

Rhinitis allergic

Rhinitis is characterized by nasal congestion, rhinorrhea, sneezing, itchy nose, and/or postnasal drainage. Rhinitis is described as inflammation of the membranes lining the nose [1].

Levocetirizine dihydrochloride is active R-enantiomer of cetirizine, is a second-generation histamine H1 antagonist with outstanding benefit-risk characteristics for the treatment of allergic rhinitis and urticaria. The chemical name is(R)-[2-[4-[(4-chlorophenyl)phenylmethyl]-1piperazinyl]ethoxy]acetic acid dihydrochloride. It has a molecular weight of461.82 and $C_{21}H_{25}ClN_2O_3$•2HCl is the empirical formula for levocetirizine dihydrochloride [2]. It does not Prevent actual release of the histamine from the mast cells, but prevents its binding to its receptor. In comparison to several other second-generation antihistamines, levocetirizine dihydrochloride has a reduced volume of distribution (Vd), is extensively absorbed, slightly metabolized, and has a favorable pharmacokinetic profile. As a result, it relieves the normal hay fever symptoms, reducing nasal congestion and other symptoms of both seasonal and chronic allergic rhinitis [3].

Oral route of administration is the most convenient and recommended route of drug administration among the various other delivery systems. More than 60% of drugs are available in the market in the form of solid dosage form. Due to its stability, affordability and ease of administration, the solid dosage form is the most popular dosage form, which results in a high level of patient's compliance.

A quick-dissolving medicine delivery system was formulated in the 1970s to help elderly and paediatric patients who had trouble swallowing tablets and capsules. Drug administration through the oral mucosa is essential. There are many bioadhesive oral mucosal dosage forms that have been developed, including mucoadhesive tablets, gel, ointments, patches and the use of films for buccal distribution, often known as oral thin strips [4].

The easiest and most affordable technique of making MDFs is through the solvent casting method. While other dosage forms, such tablets, need different granulation, punching and coating processes. In order to avoid the drawbacks related to the aforementioned solid and liquid preparation, liquid preparations like syrup should retain the stability of the product. Mouth-dissolving films (MDFS) were formulated [5].

Because of their special qualities, oral dissolving dosage forms have gained importance. They dissolve and disintegrate quickly, can be administered without water, and are best suited for geriatric and paediatric patients. In addition to breath strips, mouth-dissolving films (MDFs) have become more common in the personal care, food and pharmaceutical industries [6].

MDFs are a well-established and widely used technique today for the systemic distribution of pharmacological active components. MDFs can be used for a wide range of medications, including those for repeated emesis, heart attacks, motion sickness, paralysis, anti-asthmatic, anti-hypertensive and mental illnesses [7].

MATERIALS AND METHODS

Drug is Levocetirizine dihydrochloride and the polymers are (Sodium alginate, Guar gum), plasticizer (Glycerol), disintegrant (Starch), sweetening agent (Mannitol), flavouring agent (Peppermint oil), saliva stimulating agent (Citric Acid), Levocetirizine dihydrochloride was obtained by Intra life Private Limited as gift samples. All the other excipients were of laboratory grade. Double distilled water was used throughout the study.

Preformulation studies

The Preformulation is the first step in the rational development of a dosage form of a drug substance alone and combined with the excipient. The overall objective of the Preformulation is to generate useful information to design an optimum drug delivery system.

Organoleptic properties of the drug

The sample of levocetirizine dihydrochloride was evaluated for its organoleptic properties such as color, odor, and appearance.

Determination of solubility

The solubility of levocetirizine dihydrochloride was determined in different solvent systems. Solubility was estimated by keeping the amount of drug constant (1.0g.) and gradually increasing the amount of solvent (ml). The solubility of the drug was determined in various solvents like distilled water, methanol, ethanol, hydrochloric acid, acetone, and methylene chloride.

Determination of melting point

Melting point of levocetirizine dihydrochloride was determined by using a digital auto melting point apparatus. A capillary fused at one end was taken and a small quantity of levocetirizine dihydrochloride was pushed in through the free end of the capillary. The capillary was then placed in a digital melting point apparatus. The temperature at which the drug started to melt was noted.

Analytical methods

Determination of λ max of levocetirizine dihydrochloride in phosphate buffer pH 6.8

The solution of levocetirizine dihydrochloride containing a concentration 10µg/ml was prepared using phosphate buffer pH 6.8 and UV spectrum was taken using Elico spectrophotometer. The solution was scanned in the range of 200-300. The absorption maximum was found to be 230.1 nm.

Preparation of standard stock solution of levocetirizine dihydrochloride

Standard calibration curve of levocetirizine dihydrochloride was prepared by dissolving accurately Weighed 100 mg of levocetirizine dihydrochloride in 100 ml volumetric flask and the volume was made up to 100 ml by using phosphate buffer pH 6.8 solution to obtain a stock solution of 1000 µg/ml (SS-I). From this stock solution, 1 ml withdrawn and diluted with 100 ml by using phosphate buffer pH 6.8 to obtain a stock solution of 10µg/ml (SS-II). Different aliquots of levocetirizine dihydrochloride in the range 1-10 ml were pipetted into different 10 ml volumetric flasks and volumes were made up to 10 ml with phosphate buffer pH 6.8 to get the concentration of 4, 8, 12, 16 and 20µg/ml. The absorbance of these drug solutions were measured at 230.1 nm. The calibration curve was plotted as concentration v/s absorbance.

Fourier transform infrared (FTIR) spectroscopy

Compatibility studies of the drug and the polymers were carried out using an FTIR spectrometer. Part of the sample is mixed thoroughly with 3 parts of dried potassium bromide and it was compressed into thin pellets. The pellets are then scanned under the region from 4000 cm-1 to 400 cm-1.

Method

Preparation of mouth-dissolving films

Water-soluble natural Polymers (sodium alginate and guar gum) and disintegrants were weighed accurately and dispersed in water. Then plasticizers were added for different formulations, mixed well till a clear solution was obtained. Then the drug was added to the polymeric solution. Remaining ingredients citric acid, mannitol and peppermint oil were added and stir continuously for 15 min using a glass rod. After the solution was placed on ultra-sonication for 30 min (to remove the air bubble). 15 ml of prepared solution was cast on a glass plate which can be covered in 11×20.2 Cm=222.2Cm^2 area i.e. 11 cm width of film and 20.2 cm length of the film. Casting solvent was then allowed to evaporate for 24h to obtain dry film. After 24 h, the dried patches were taken out packed in self-sealing covers and stored in a desiccator for further studies. The dose of levocetirizine hydrochloride is 2.5 mg in 2 cm ×2 cm film i.e. 4 Cm^2 area.

138.87 mg of drug

222.2 cm^2 area of the film

Each film 2×2=4 Cm^2

Each 4 cm^2 film contains 138.87×4/222.2= 2.5 mg of the drug

Table 1: Composition of mouth-dissolving film of levocetirizine dihydrochloride

	Batch	Drug (%)	Polymer (%)	Starch (%)	Glycerol (%)	Citric acid (%)	Mannitol (%)	Peppermint oil (ml)	Water (ml)
Sodium alginate	F1	1.38	4.36	9.57	0.60	3.49	3.49	0.5	10
	F2	1.38	5.24	9.57	0.60	3.49	3.49	0.5	10
	F3	1.38	6.11	9.57	0.60	3.49	3.49	0.5	10
	F4	1.38	6.98	9.57	0.60	3.49	3.49	0.5	10
	F5	1.38	8.73	9.57	0.60	3.49	3.49	0.5	10
	F6	1.38	10.4	9.57	0.60	3.49	3.49	0.5	10
	F7	1.38	12.23	9.57	0.60	3.49	3.49	0.5	10
	F8	1.38	13.97	9.57	0.60	3.49	3.49	0.5	10
Guar gum	F9	1.38	2.18	9.57	0.60	3.49	3.49	0.5	10
	F10	1.38	4.36	9.57	0.60	3.49	3.49	0.5	10
	F11	1.38	6.55	9.57	0.60	3.49	3.49	0.5	10
	F12	1.38	9.57	9.57	0.60	3.49	3.49	0.5	10
SA: GG 1:1	F13	1.38	2.5:2.5	9.57	0.60	3.49	3.49	0.5	10
2:1	F14	1.38	5:2.5	9.57	0.60	3.49	3.49	0.5	10
3:1	F15	1.38	7.5:2.5	9.57	0.60	3.49	3.49	0.5	10

SA: Sodium alginate GG: Guar gum

Evaluation of mouth-dissolving film of levocetirizine dihydrochloride

Physical appearance

All the prepared films were visually inspected for color, flexibility and smoothness [1, 2]

Drug content

Drug content for all batches were determined by UV Spectrophotometric method. For this 2×2 cm^2 strip from each batch was cut and dissolved in 50 ml of phosphate buffer pH 6.8. The solution was filtered through whatman filter paper and diluted by pipetting 1 ml of this solution to a 25 ml volumetric flask with phosphate buffer pH 6.8. The resulting solution was measured spectrometrically at 230.1 nm by using an ELICO spectrophotometer [3, 8].

Thickness

Thickness of the film was measured using a screw gauge with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the film and the average was taken by using the following formula [9, 10].

Least count = pitch/Total number of division of the circular scale

= 1 mm/100

= 0.01 mm

Fig. 1: Formulation placed on ultra-sonication to remove air bubble

Fig. 2: After the drying film removed from the film former

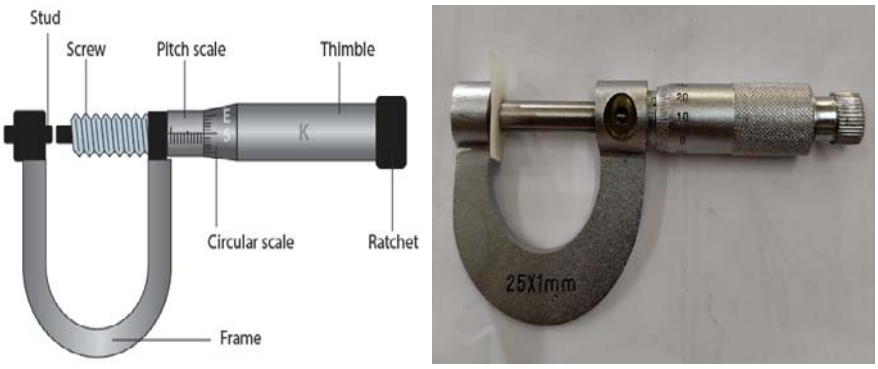

Fig. 3: Screw gauge measuring thickness of the film

Folding endurance

The films were folded at an angle of 180 ° at the same place more than 100 times without cracking and was noted as folding endurance. The studies were performed in trice and the average mean was calculated [9, 10].

Disintegration

Disintegration time was determined visually in a petri dish containing a pH 6.8 phosphate buffer with swirling every 10 seconds. The disintegration time reported was the time when the film started to break (Petri dish method) [11, 12].

Fig. 4: Film placed in petri plate for disintegration

Weight variation

All prepared Films were calculated for weight variation. Randomly selected ten Films were weighed individually and together in a single pan balance. The average weight was noted and the standard deviation was calculated [13, 14].

% weight variation = difference in weight/average weight x 100

Moisture loss studies

The percentage moisture loss study was carried out to check the physical stability and integrity of the films. In the present study, the moisture loss capacity of the film was determined by the Known weight and predetermined by placing size of the film in a desiccator containing anhydrous calcium chloride for three days. The films were removed and reweight and the percentage moisture loss of the film was measured placing by using the following formula [15, 16].

Percentage moisture loss = initial weight–final weight/final weight × 100

Percentage of moisture uptake

The prepared films were weighed and kept in desiccators containing anhydrous silica at Room temperature for 24 h. It was then taken out from the desiccators, weighed and exposed to relative humidity of 75% (saturated solution of sodium chloride) in desiccators. The film was weighed until it showed a constant weight. Percent moisture uptake was determined using the formula [17, 18].

Percentage moisture uptake = final weight–initial weight/initial weight × 100

Surface pH

An acidic alkaline pH may cause irritation to the oral mucosa. It is determined to keep the surface pH is as close to neutral as possible. The film is slightly wet with the help of water. The pH is measured by using a digital pH meter. The procedure was performed in triplicate and the average with the standard deviation was calculated [19, 20]

Tensile strength

Tensile strength is the maximum tensile force applied until the thin-film specimen breaks. It is obtained by dividing the applied force by the cross-sectional area of the film and multiplying by a hundred [21, 22]

% Tensile Strength = Load at Failure/Film Thickness × Film Width × 100

Fig. 5: pH meter measuring surface pH of the film

Dispersion test

A film equivalent of 25 mg of Levocetirizine dihydrochloride was placed in 200 ml of 6.8 pH phosphate buffer and was stirred for 3 min. then the resulting solution was passed through sieve number 22. No residue was left; hence the film passed the dispersion test [23, 24].

Percentage elongation

The increase in the length of a film when it is pulled under standard conditions of stress just before the point of break is known as percent elongation. Randomly 3 films were selected from each formulation and the initial length was measured. Films were pulled manually until it was broken. Then final length was observed and the average percentage elongation was determined. Percentage elongation was calculated from the formula mentioned below [25, 26]

% elongation = increase in length/initial length × 100

Water vapour permeability

Water vapour transmission rate (WVTR) of the film was measured by the modified ASTM E96 method. The film was sealed on the top of a glass vial (4 ml) containing 2.5 ml of distilled water (100% RH; 3169 Pa vapour pressure at 25 °C), which was placed in a desiccator at 25 °C and 0% RH containing fused calcium chloride (0 Pa water vapour pressure). The vials are weighed every 24 h for 1 w. The amount of water vapour permeated through the films was determined from the weight loss. WVTR and water vapour permeability (WVP) were calculated using the formula

$$\text{WVTR} = \Delta w/\Delta t \times A$$

$$\text{WVP} = \text{WVTR} \cdot L/\Delta,$$

Where WVTR is in g/h m2, $\Delta w/\Delta t$ is rate of water gain in g/h, A is the exposed area of the film in m^2, L is the mean thickness of film specimens in m, and Δp is the difference in partial water vapour pressure between the two sides of film specimens in Pa. The water vapour pressure on the high-stream side of the film was 3.169 kPa (i.e., saturated water vapour pressure at 25 °C), while the low-stream side is assumed to be zero. Three replicates of the determinations were done [27, 28]

Procedure

In vitro drug release was studied using Lab India Dissolution Apparatus (LABINDIA DS 8000, India), in 300 ml phosphate buffer pH 6.8, maintained at 37±5 C for 5 min, at 50 rpm. 1 ml of sample

was withdrawn after specified time from the dissolution medium. Collected samples were analyzed spectrophotometrically at a measured wavelength of 230.1 nm, and cumulative percent drug release was calculated. Drug release profile was studied using percentage drug release versus time (Sec) plot [30-32].

Table 2: *In vitro* dissolution studies

Apparatus	USP dissolution apparatus type II
Dissolution Medium.	Phosphate buffer pH (6.8)
Temperature.	37±5 °C
RPM.	50 rpm
Vol. withdrawn and replaced.	1 ml every 30 sec
Λmax	230.1 nm
Blank Solution.	Phosphate buffer pH (6.8)
Duration of study.	5 min
Volume of dissolution media.	300 ml

Stability studies

The purpose of stability testing is to provide evidence on how the quality of drug substance or drug product varies with time under the influence of a variety of factors like temperature, humidity, light to establish the period for drug substance or shelf life for the drug product and storage condition. The nature of stress testing will depend upon the individual drug substance and the type of drug product involved. The stability study should be conducted on the drug substance packed in a container closure system that is the same as or simulates the packing proposed for storage and distribution. Stability studies for selected formulations were carried out by storing in an amber color bottle tightly plugged with cotton and capped at (40 °c/75% RH) for 3 mo. The formulations were evaluated for physical appearance, disintegration time and drug content at each and every month interval of time [33-35].

RESULTS AND DISCUSSION

Preformulation studies

Preformulation studies of levocetirizine dihydrochloride was carried based on the following parameters

Identification studies

Organoleptic properties of the drug

The drug Levocetirizine dihydrochloride was evaluated for its physical properties and it was observed that it is a free-flowing white or almost white powder with unpleasant odour. The physical properties were found to be similar as given in literature I. P.

Solubility of drug

Levocetirizine Dihydrochloride was freely soluble in water, soluble in ethanol, methanol and Hydrochloric acid, 0.1N HCL, phosphate buffer pH6.8 and insoluble in methylene chloride and acetone.

Melting point of drug

The melting point of Levocetirizine dihydrochloride sample was found to be 218.5 °C. The normal range of the melting point of Levocetirizine dihydrochloride is 210-230 °C, which shows that the melting point of the drug was lying between the ranges. The melting point indicates the purity of the drug.

Analytical methods

Determination of λmax of levocetirizine dihydrochloride in phosphate buffer pH6.8

The absorption maximum of the standard solution was scanned between200-300 nm regions on the UV Spectrophotometer. The absorption maximum was found to be 230.1 nm.

Standard calibration curve of levocetirizine dihydrochloride

For the preparation of the standard calibration curve, samples were prepared from a stock solution (4, 8, 12, 16, 20 µg/ml). The absorbance of the sample was taken at 230.1 nm.

Table 3: Absorbance data for the standard calibration curve of Levocetirizine dihydrochloride

S. No.	**Concentration (µg/ml)**	**Absorbance**
1.	0	0
2.	4	0.3021
3.	8	0.5891
4.	10	0.6961
5.	12	0.8164
6.	18	1.1263
7.	20	1.2454

Table 4: Statistical data for the calibration curve

S. No.	**Parameters**	**Value**
1.	λmax (nm)	230.1
2.	Beer law limits.	4-24
3.	Slope	0.061
4.	Constant	0.0551
5.	R^2	0.9925

Fourier transform infrared (FTIR) interaction studies

Compatibility studies of the drug and the polymers were carried out using Shimadzu–FTIR spectrometer. The infrared (IR) spectra of Levocetirizine dihydrochloride and physical mixtures with Levocetirizine dihydrochloride and natural polymers (sodium alginate and guar gum) were recorded by FTIR spectrometer.

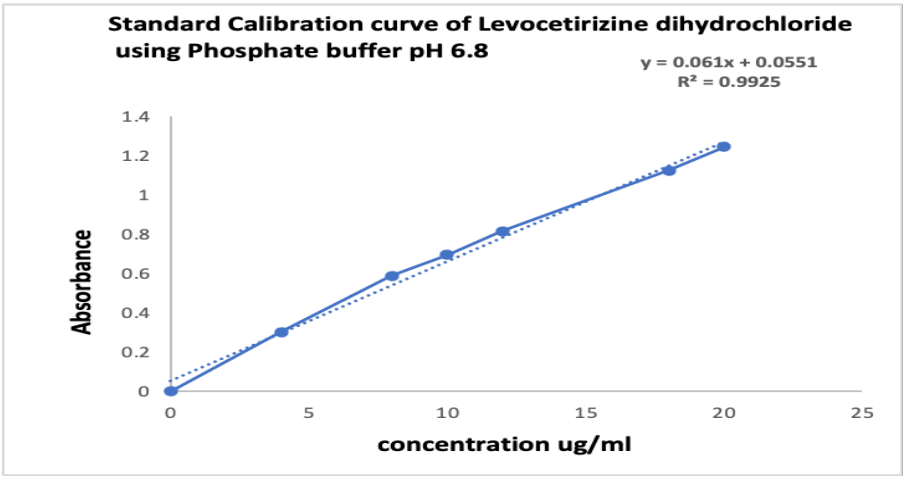

Fig. 6: Calibration curve of levocetirizine dihydrochloride in phosphate buffer pH6.8 at 230.1 nm

Table 5: Interpretation of FTIR spectrum

Functional group	Observed frequency (cm^{-1}) pure sample	Observed frequency (cm^{-1}) with drug+sodium alginate	Observed frequency (cm^{-1}) with guar gum	Observed frequency (cm^{-1}) with polymer ratio
O-H Stretching	2354	2358	2355	2357
C-N Stretching	1319	1319	1319	1319
COOH Stretching	1745	1745	1745	1745
C=O Stretching	1456	1456	1456	1456
C-Cl Stretching	758	758	758	758
N-H Stretching	919	919	919	919
C-H Stretching	758	758	758	758

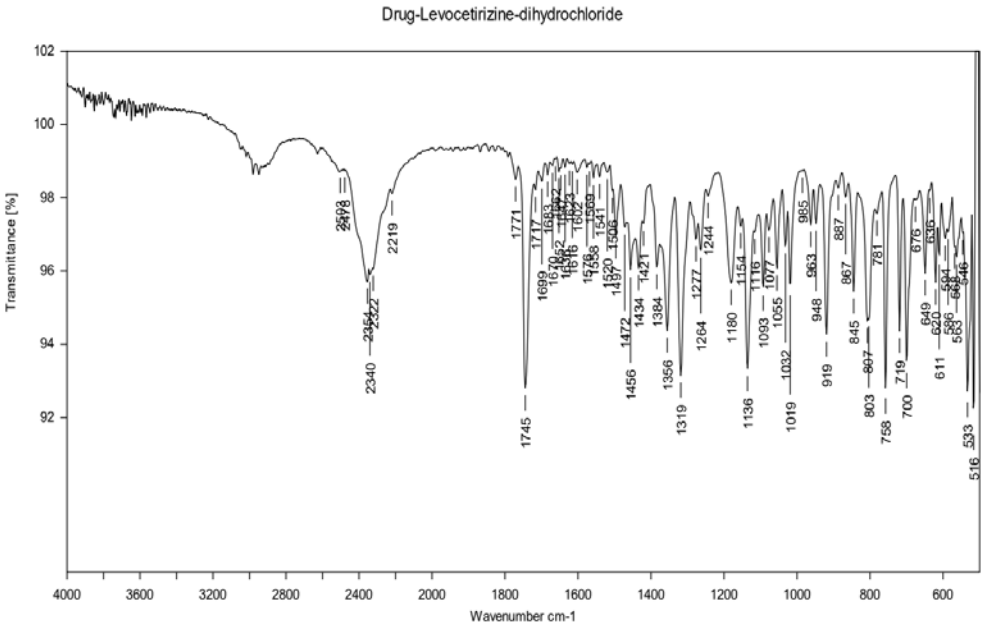

Fig. 7: FTIR Spectrum of levocetirizine dihydrochloride pure drug

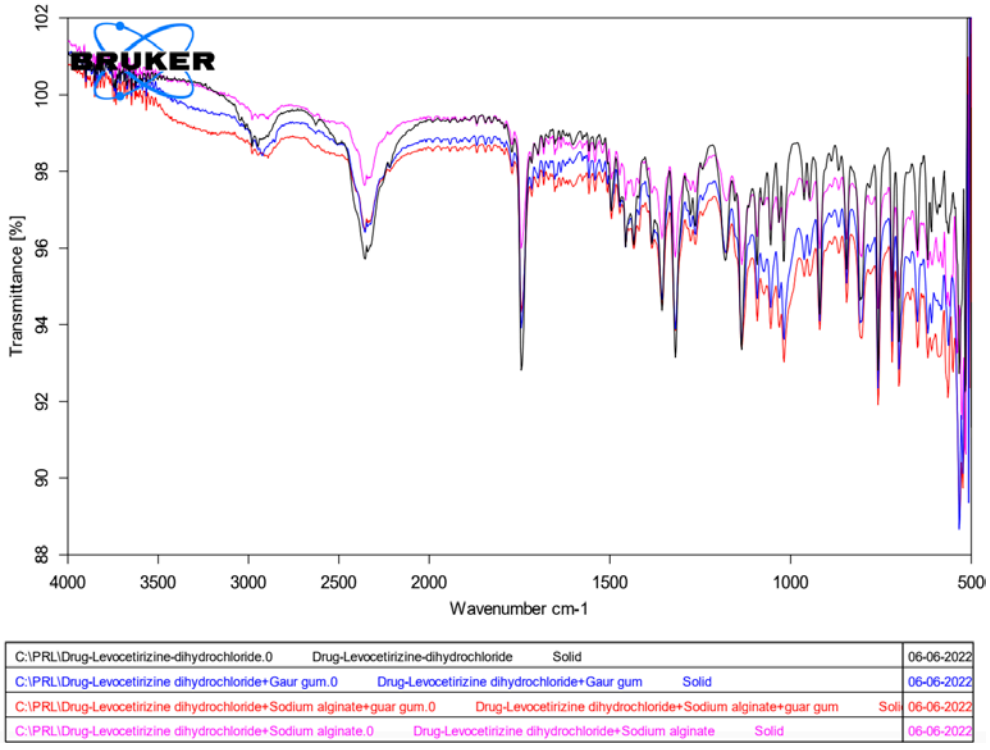

Fig. 8: Comparison study of FTIR spectrum with drug and polymers

Evaluation of mouth-dissolving films

Table 6: Physical appearance and drug content of the formulated films

S. No.	Formulation	Physical appearance	Drug content (%)
1.	F1	white, smooth, uniform and flexible	88.40±0.027
2.	F2	white, smooth, uniform and flexible	90±0.025
3.	F3	white, smooth, uniform and flexible	84.80±0.027
4.	F4	white, smooth, uniform and flexible	89.20±0.043
5.	F5	white, smooth, uniform and flexible	88.80±0.032
6.	F6	white, smooth, uniform and flexible	97.60±0.021
7.	F7	white, smooth, uniform and flexible	91.51±0.015
8.	F8	white, smooth, uniform and flexible	90.40±0.041
9.	F9	semi-transparent, uniform and flexible	95.60±0.015
10.	F10	semi-transparent, uniform and flexible	86.40±0.034
11	F11	semi-transparent, uniform and flexible	90.40±0.045
12	F12	semi-transparent, uniform and flexible	91.60±0.014
13	F13	semi-transparent, uniform and flexible	93.60±0.034
14	F14	semi-transparent, uniform and flexible	96.92±0.018
15	F15	semi-transparent, uniform and flexible	96.80±0.028

All value are mean of three reading±standard deviation, All formulated films were White, smooth, Uniform and Flexible

Table 7: Evaluated for thickness, folding endurance, disintegration time, weight variation, surface pH and water-vapour permeability

Formulation code	Film thickness (mm)	Folding endurance	Disintegration time (sec)	Weight variation (mg)	Surface pH	Water-vapour permeability (gm/Pa hm^2)x10$^-$[10]
F1	0.15±0.001	52±5	15.57±2.08	66.80±0.10	6.24±0.50	4.39
F2	0.18±0.003	58±5	16.86±2.64	65.06±0.09	6.60±0.10	5.52
F3	0.22±0.004	61±5	15.28±1.52	64.83±0.06	6.44±0.51	5.84
F4	0.25±0.012	66±5	15.93±1.73	69.60±0.15	6.62±0.52	9.08
F5	0.26±0.005	69±5	16.32±0.57	67.40±0.12	6.29±0.17	11.26
F6	0.28±0.01	92±5	14.28±1.52	61.60±0.16	6.78±0.10	11.75
F7	0.28±0.009	99±5	31.30±1.52	70.43±0.15	6.75±0.15	13.98
F8	0.29±0.008	98±5	30.28±2.08	89.43±0.06	6.32±0.14	11.84
F9	0.13±0.002	100±5	29.32±0.57	87.60±0.10	6.66±0.15	2.46
F10	0.17±0.003	192±5	35.31±1.52	92.63±0.15	6.23±0.05	3.58
F11	0.24±0.005	278±5	31.30±1.52	95.53±0.12	6.90±0.13	4.55
F12	0.25±0.008	391±5	35.21±3.51	94.45±0.13	6.81±0.51	8.37
F13	0.15±0.005	184±5	34.31±1.52	68.27±0.15	6.64±0.17	9.57
F14	0.19±0.01	283±5	25.26±2.51	69.43±0.18	6.81±0.13	13.2
F15	0.24±0.014	304±5	36.49±0.70	78.57±0.20	6.54±0.19	13.4

All value are mean of three reading±standard deviation

Table 8: Evaluated for moisture content, Moisture uptake, tensile strength, dispersion test and percentage elongation

Formulation code	Moisture content (%)	Moisture uptake (%)	Tensile strength (kg/mm^2)	Dispersion test	Percentage elongation
F1	2.81±0.014	2.15±0.025	1.11±0.03	Passed	6.12±0.18
F2	1.80±0.031	2.30±0.031	1.12±0.04	Passed	6.23±0.13
F3	2.72±0.021	3.52±0.021	1.13±0.30	Passed	6.24±0.29
F4	2.50±0.008	3.70±0.008	1.13±0.04	Passed	6.69±0.51
F5	2.07±0.051	3.08±0.051	1.14±0.03	Passed	6.28±0.43
F6	1.75±0.025	1.44±0.032	1.15±0.01	Passed	7.28±0.12
F7	2.70±0.025	3.20±0.025	1.18±0.05	Passed	6.47±0.13
F8	2.54±0.032	2.89±0.014	1.13±0.09	Passed	6.23±0.09
F9	2.61±0.016	3.61±0.016	1.17±0.04	Passed	6.73±0.13
F10	2.42±0.009	3.72±0.009	1.25±0.06	Passed	6.71±0.22
F11	2.51±0.014	3.31±0.014	1.23±0.02	Passed	6.11±0.17
F12	2.80±0.025	3.50±0.025	1.20±0.06	Passed	6.23±0.21
F13	2.14±0.032	3.84±0.032	1.26±0.01	Passed	6.22±0.36
F14	2.31±0.016	3.31±0.016	1.21±0.03	Passed	6.25±0.16
F15	2.52±0.009	3.82±0.009	1.28±0.05	Passed	6.70±0.24

All value are mean of three reading±standard deviation

Table 9: Dissolution study of the formulation

Time (sec)	30	60	90	120	150	180	210	240	270	300
FR code										
F1	7.67	18.09	28.71	40.41	53.21	66.37	79.65	83.23	89.42	93.23
F2	6.22	14.40	23.51	33.55	44.22	55.34	68.46	81.75	88.37	95.28
F3	2.75	9.32	18.03	27.38	40.63	51.15	71.79	83.34	89.55	91.99
F4	4.12	9.47	16.12	25.07	34.44	37.06	61.94	78.00	85.32	95.37
F5	2.61	8.47	15.32	22.58	32.46	47.35	62.64	78.35	86.38	94.33
F6	3.30	9.67	17.67	26.31	35.76	49.62	63.84	79.99	87.58	98.24
F7	2.11	6.66	15.57	27.81	42.42	56.91	73.28	81.44	88.75	90.95
F8	3.20	8.30	15.43	25.19	36.60	50.19	66.37	69.62	72.12	85.78
F9	4.99	12.55	21.13	30.72	41.59	53.60	66.29	80.31	86.84	96.15
F10	2.08	6.68	11.89	18.21	25.17	33.60	43.24	55.67	79.68	93.97
F11	1.69	4.96	8.48	14.55	21.58	29.81	39.14	60.34	75.09	91.07
F12	1.63	5.04	9.18	15.03	29.66	38.19	49.62	61.53	73.99	87.36
F13	3.24	6.76	12.37	18.98	27.98	49.92	63.68	78.80	86.44	94.49
F14	2.82	6.37	11.33	16.78	23.59	33.05	46.64	62.28	78.77	96.11
F15	2.19	5.92	10.92	17.01	25.05	35.91	47.47	60.03	76.92	94.98

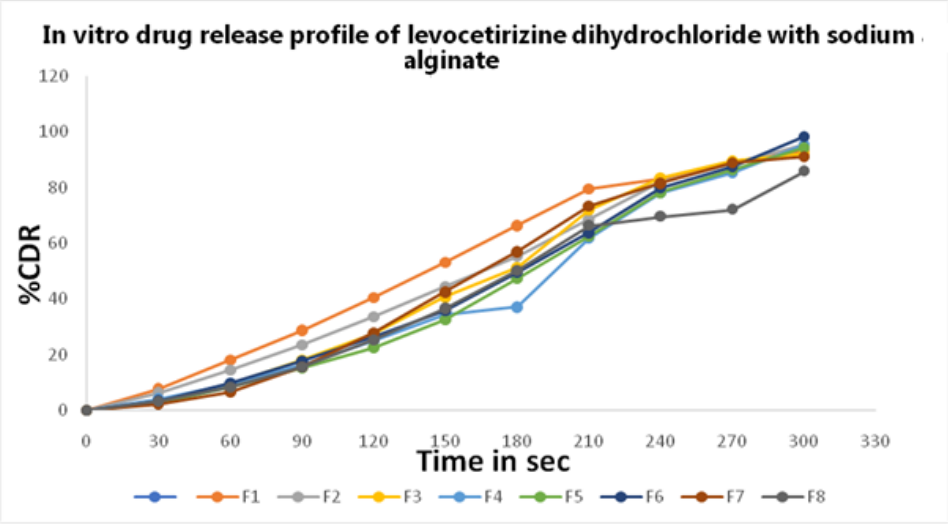

Fig. 9: Cumulative percentage drug release Vs time of F1 to F8

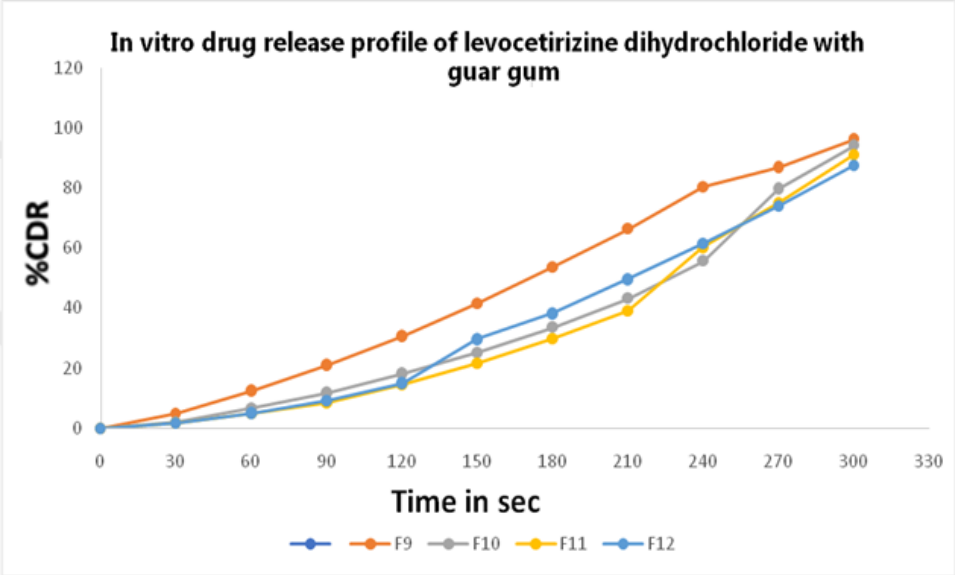

Fig. 10: Cumulative percentage drug release Vs Time of F9 to F12

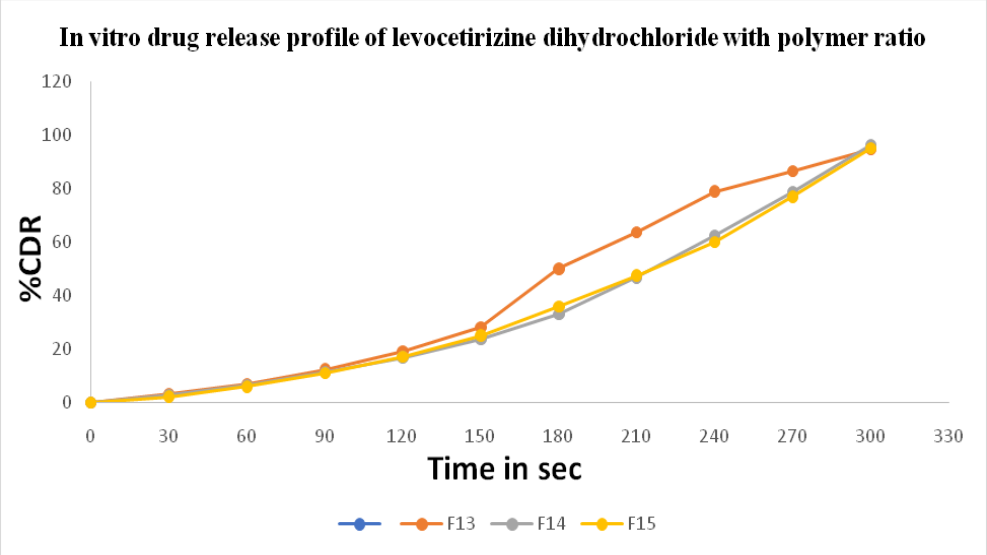

Fig. 11: Cumulative percentage drug release Vs time of F13 to F15

Table 10: Stability studies data of the selected oral film formulations

Formulation stored at (40 °C/75%RH)	Time in days	Physical appearance	*In vitro* disintegration time (sec)	% drug content
F6	0	Good	14	98.24
	30	Good	16	95.81
	60	Good	18	95.28
	120	Good	16	94.02
F9	0	Good	29	96.15
	30	Good	35	95.32
	60	Good	33	94.67
	120	Good	34	94.22
F14	0	Good	25	96.11
	30	Good	28	95.76
	60	Good	30	95.12
	120	Good	28	94.83

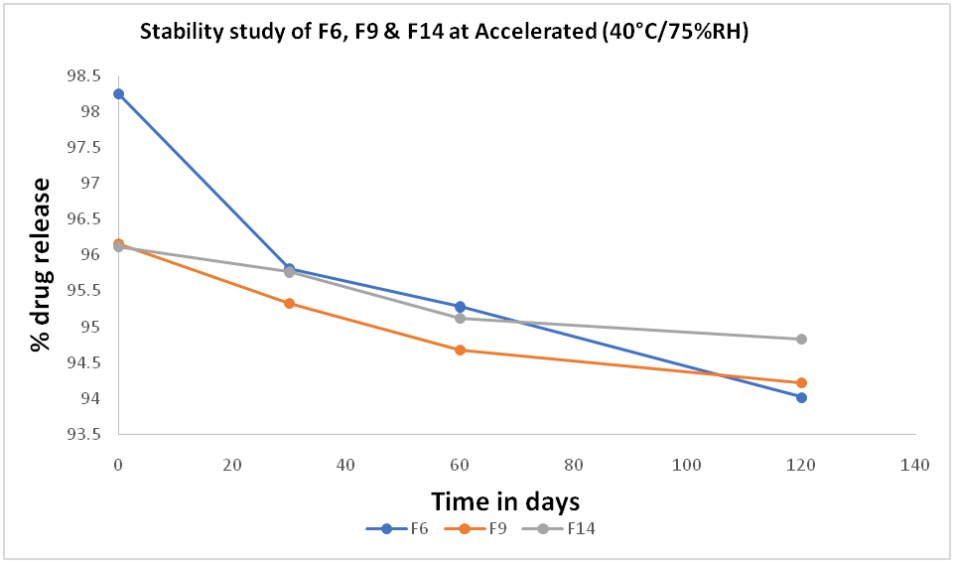

Fig. 12: Stability study of F6, F9 and F14 at accelerated (40 °C/75%RH)

Kinetics / release pattern of selected formulation f6 [36 - 39]

For analyzing the mechanism of drug release kinetics of the film F6, the data obtained were fitted to various kinetic equations of zero order, first order, Higuchi model and Korsmeyer-Peppas model. The regression coefficient was calculated. Graphs of kinetic models were plotted with suitable data are shown in Fig. 13 to 16 and the n value is used to characterize different release mechanisms in Table 11. The regression coefficients are summarized in Table 12.

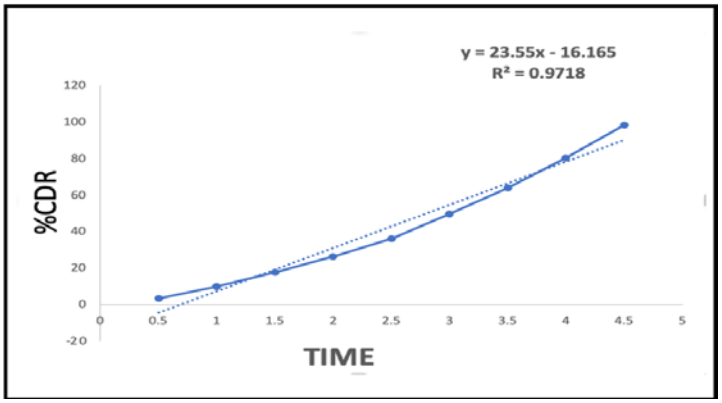

Fig. 13: Zero-order release of oral thin film, F6

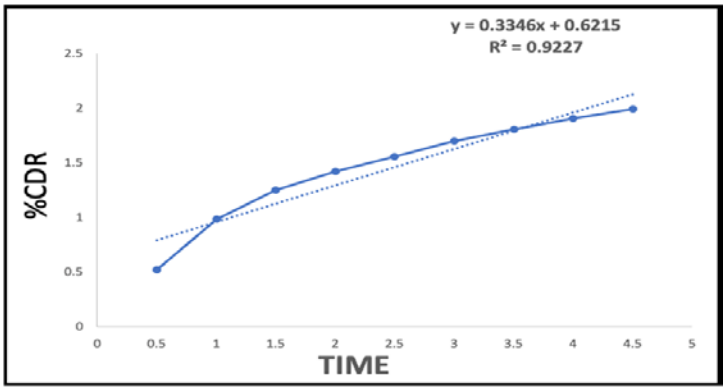

Fig. 14: First order release of oral thin film, F6

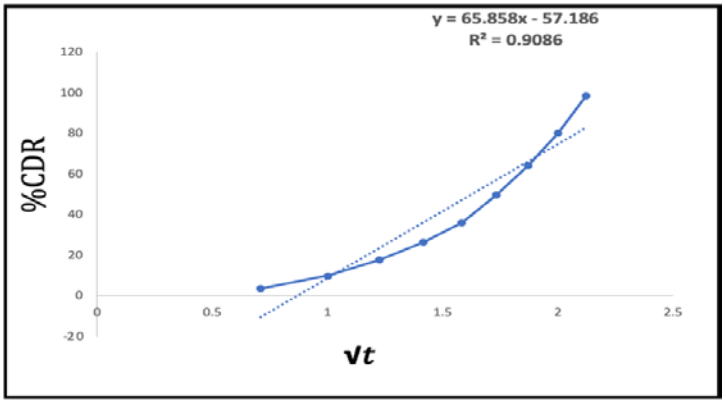

Fig. 15: Higuchi release model of oral thin film, F6

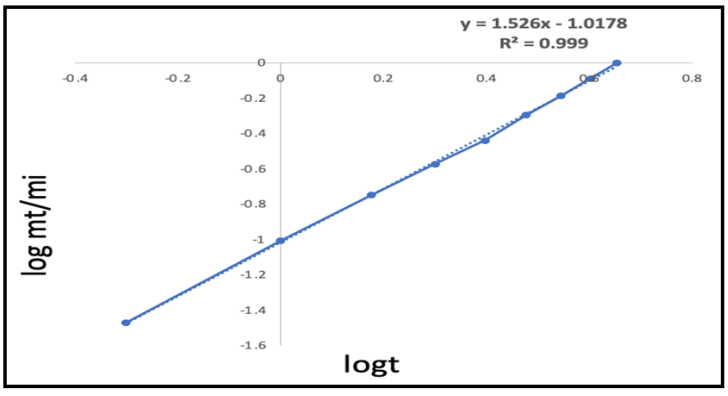

Fig. 16: Korsmeyer-peppas release profile of oral thin film, F6

Table 11: 'n' value to characterize different release mechanisms

Release exponent (n)	Drug transport mechanism	Rate as a function of time	Drug release mechanism
n<0.5	Quasi-Fickian diffusion	t^{n}	non swellable matrix-diffusion
0.5	Fickian diffusion	$t^{0,5}$	non swellable matrix-diffusion
0.5<n<1. 0	Anomalous (Non-fickian transport)	t^{n-1}	for both diffusion and relaxation (erosion)
1.0	Case II transport	(time-independent)	Zero order release
Higher than 1.0	Super case II transport	t^{n-1}	(relaxation/erosion)

Table 12: Data of regression coefficient of different kinetic models

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsmeyer-Peppas (R^2)
F6	0.9718	0.9227	0.9086	0.999

From the evaluation of the selected films, formulation F6 which was prepared from sodium alginate and its release was found to be 98.24% at the end of 5 minute. The results obtained from the study indicates that the natural polymer sodium alginate (F6) showed least disintegration time and best *In vitro* drug release than the formulation containing other natural polymers.

Data analysis (Curve fitting analysis)

The linear regression coefficient of each kinetic model was calculated and the pattern of drug release from the dose was predicted. It was found that the optimized formulation F6 follows a zero order kinetic model as it has the highest R^2value with the Korsmeyer–Peppas mechanism. The "n" exponent value of the optimized batch was found to be 1.526.

CONCLUSION

Mouth dissolving films of Levocetirizine dihydrochloride were successfully formulated by employing Solvent casting method, using different natural polymers. The characterization of drug was done and the physicochemical parameters evaluation were performed as per pharmacopeia standards and compatibility study was done by FTIR method.

Based on the above studies, following conclusions can be drawn The FTIR studies indicated that there was no interaction between the drug and the polymers and their used in the dosage form. Hence, they are compatible with each other and thus suitable for the formulation. Sodium alginate and guar gum as polymers to obtain desired film properties. Starch is used as disintegrant. Citric Acid was used as a Saliva stimulating agent to increase the rate of production of saliva that would aid in the faster disintegration. Mannitol was used as a Sweetener. Glycerol was used as plasticizer for enhancing mechanical property i.e., tensile strength. Based on the *in vitro* disintegration time and dissolution studies formulation F6 containing (10.4%) polymer concentration were found to be promising and showed a disintegration time 14.28±1.52 sec and drug release profile 98.24% respective, when compared to the other formulations. Finally, it was concluded that the MDFs of Levocetirizine dihydrochloride formulation containing natural polymer sodium alginate showed less disintegration time and *in vitro* drug release study faster than the other formulations. Formulations were found to be complying with all the properties of films and the formulations were satisfactory.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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