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Fast Dissolving Film of Levocetirizine: Solubility Enhancement by forming Inclusion Complex with β-cyclodextrin, Formulation and Evaluation

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ABSTRACT:
Objective: Levocetirizine is a long-acting potent nonsteroidal anti-inflammatory drug (NSAID) which has a very low solubility in Gastrointestinal (GI) fluids results in poor bioavailability after oral administration. The present investigation aimed to formulate and evaluate fast dissolving oral films containing levocetirizine to overcome solubility and bioavailability problems thereby to facilitate the convenience of paediatric and geriatric patients.
Method: The inclusion complexes of levocetirizine with β-cyclodextrin were prepared. In vitro dissolution study was performed to fix the ratio with better dissolution rate. The selected inclusion complex was then utilized for the preparation of fast dissolving oral films by solvent casting method using sodium CMC/ chitosan as film-forming agents, sodium starch glycolate/crospovidone as super disintegrating agents. PEG 400 used as a plasticizer. Formulations (F1-F6) were prepared and evaluated for their physicochemical properties. In vitro disintegration, dissolution and permeation studies were also carried out.

KEY WORDS: Fast dissolving film, Solubility enhancement, Inclusion complex, β-cyclodextrin, Levocetirizine.

I. INTRODUCTION

It is estimated that 25 % of the population finds it difficult to swallow tablets and capsules and therefore do not take their medication as prescribed by their doctors resulting in high incidence of non-compliance and ineffective therapy. Furthermore, 90% of the drugs administered through oral route are subjected to extensive first pass metabolism before reaching to the systemic circulation. In spite of all the cones, the oral route of administration still remains to be the most popular means of drug administration due to its ease of administration, virtually pain free and patient compliance. A new oral dosage form is the oral thin films prepared using hydrophilic polymers which rapidly disintegrates and dissolves on tongue or the buccal cavity. The drug administered via oral mucosa gain access to the systemic circulation through a network of arteries and capillaries. The major artery supplying the blood to the oral cavity is the external carotid artery. The venous backflow goes through branches of capillaries and veins and finally taken up by the jugular vein. [1,2] This novel approach is in great demand for the paediatric and geriatric patients. Various bio-adhesive and mucosal dosage forms have been formulated which includes adhesive tablets, gels, ointments, patches and more recently the mouth disintegrating films.
Levocetirizine is a class of second-generation antihistaminic agent. It is an active enantiomer of cetirizine; its principal effects are mediated via selective inhibition of H1 receptor. It does not prevent actual release of the histamine from the mast cells, but prevents its binding to its receptor. The daily dose of levocetirizine is 10mg per day. It is freely water soluble and very bitter in taste. Many researchers developed and reported the oral films of levocetirizine using different film forming polymers like CMC, Sodium starch glycolate, Citric acid, crospovidone. [5,6,7,8]
The aim of the present study is to prepare and evaluate an oral fast dissolving film of levocetirizine with β-cyclodextrin as taste masking agent, CMC as a film forming polymer and sodium starch glycolate and croscarmellose sodium as superdisintegrant for the fast disintegration and dissolution of the films and quick relief in different allergic conditions.

II. MATERIALS AND METHOD:

Levocetirizine was a gift sample from Yarrow Chemical Pvt Ltd. Sambhajinagar. Croscarmellose Sodium (CMC), Sodium starch glycolate, Crospovidone (Signet chem, Mumbai) All the other chemicals used in analytical grade were procured from Lobacheme Pvt. Ltd, Mumbai.

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III. METHOD OF PREPARATION OF INCLUSION COMPLEX

Method of preparation of inclusion complex. The inclusion complex of drug with β-CD was prepared by wetting the physical mixture of levocetirizine: ß-CD in the 1:1 molar ratio in a mortar with water. The wet mixture is then kneaded thoroughly with pestle to obtain paste like consistency. The paste was then dried under vacuum at room temperature, pulverized by passing through sieve no. 80 and stored in a desiccator till further use. [9]

IV. PREFORMULATION STUDIES

1. Physical appearance:

The parameter was checked simply with a visual inspection of films and evaluation of texture by feel and touch.

2. Solubility:

Solubility of a drug defines as the amount of solute that dissolves into the solvent to obtain the saturated solution of solute at constant temperature and pressure.

3. Melting point:

The melting point of the drug was carried out by the capillary tube method.

Table 1: Preformulation studies

Sr. No.	Test	Specification	Result
1	Description	White powder	White powder
2	Solubility	Solubility in water	Complies
3	Test	Bitter	Complies
4	Odor	Odourless	Complies
5	Melting point	214 ^{0}C	215^{0}C

4. UV spectroscopy:

The UV spectrum of Levocetirizine was obtained by scanning the solution in the 400 to 200 nm range. The maximum absorbance occurred at 230nm.

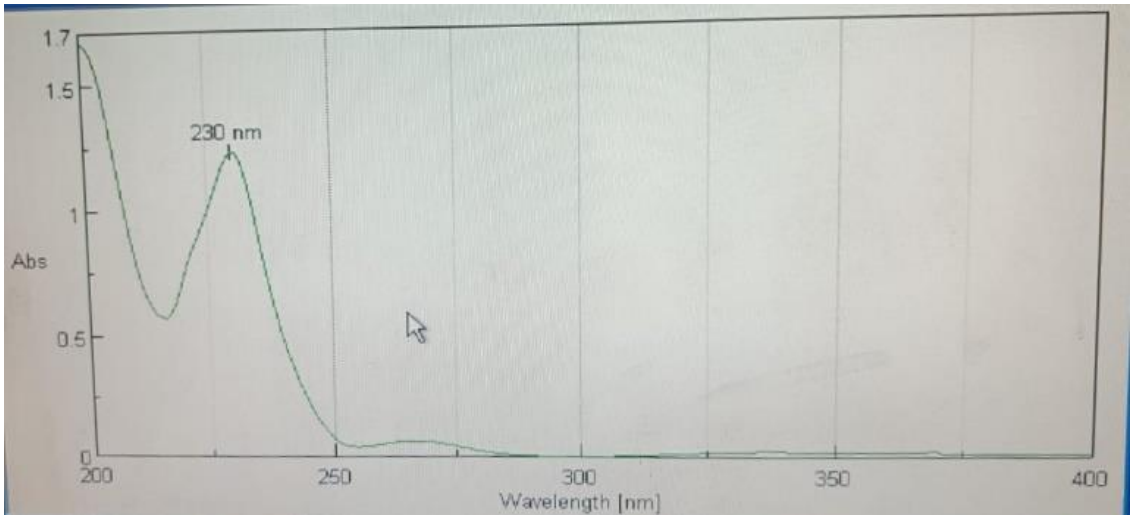

Fig. no.1 Calibration curve of levocetirizine

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Table 2: Absorbance of Levocetirizine

Concentration µg/ml	Absorbance
0	0
2	0.1754
4	0.3765
6	0.5765
8	0.7865
10	0.9876

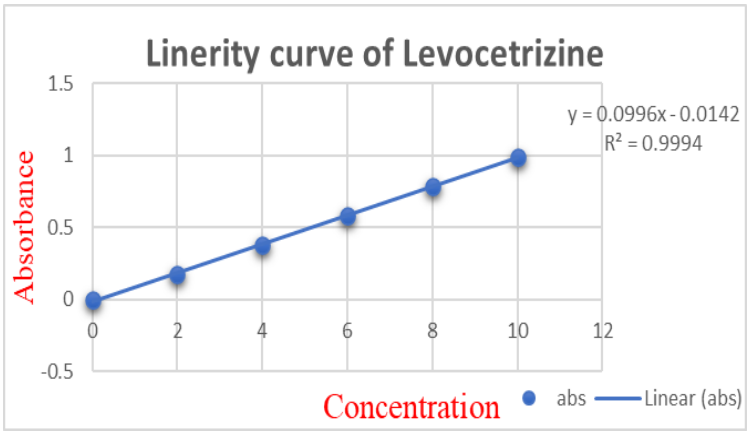

Fig no.2 Fig. Linearity graph of Levocetirizine

V. COMPATIBILITY STUDIES

1. FT-IR:

FTIR study was carried out to check the compatibility of drug with polymers. Infrared spectrum of levocetirizine was determined on Fourier transform Infrared spectrophotometer using KBr dispersion method.

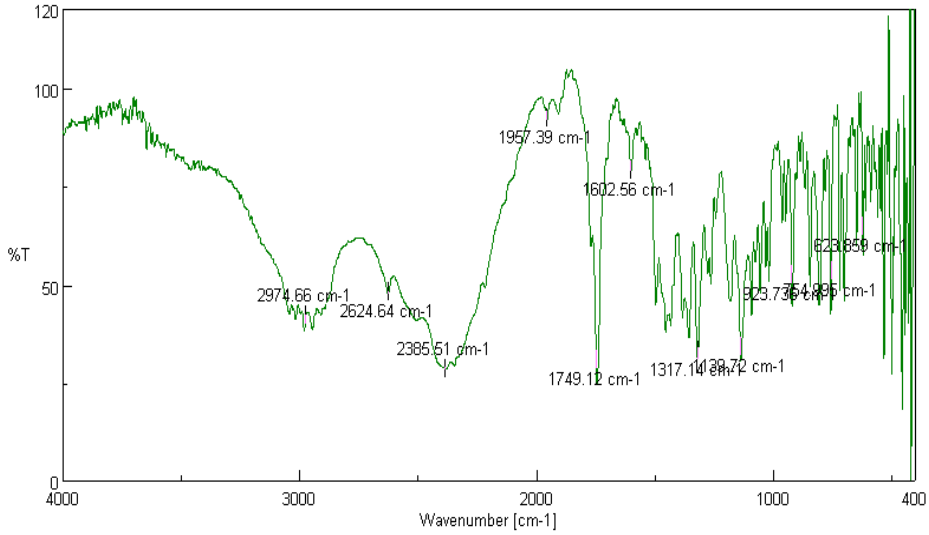

Fig no.3: FTIR spectrum of levocetirizine

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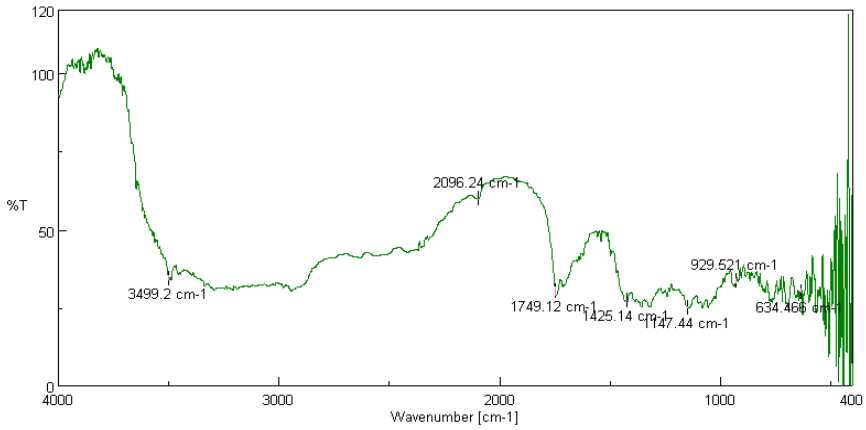

Fig no. 4: FTIR Spectrum mixture of drug with polymer and excipients

2. **Differential Scanning Calorimetry (DSC):**
Drug-Excipients compatibility is being determined by DSC. The DSC study was carried out Differential scanning calorimeter (DSC 60) with thermal analyser. As mixture of drug and mixture of drug and polymer with the excipients were analysed using DSC.

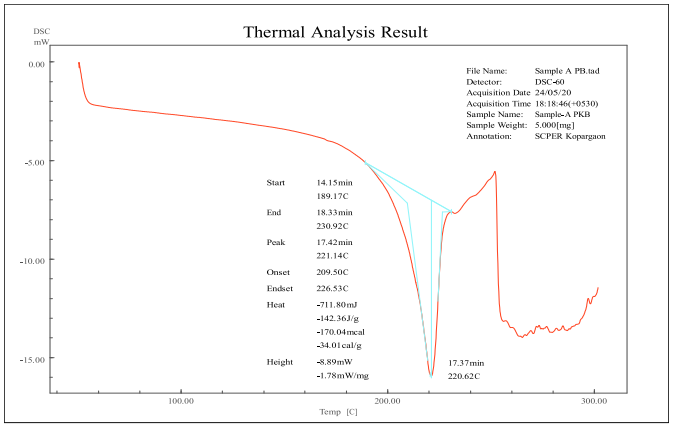

Fig no.5: DSC graph of pure drug – levocetirizine

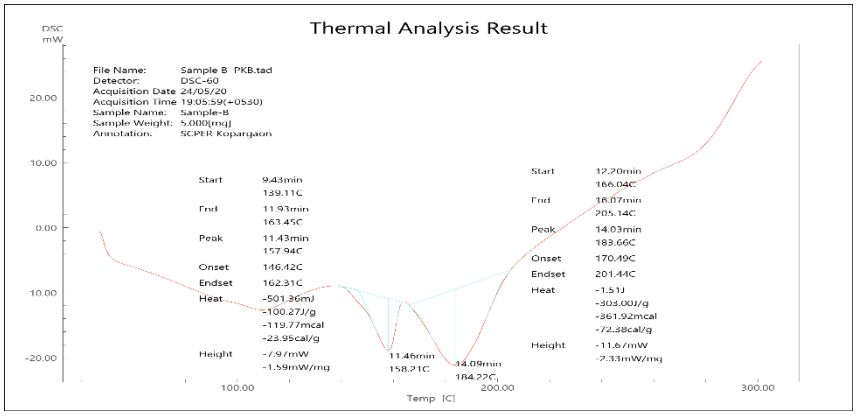

Fig no.6: DSC graph of pure drug and Polymer

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VI. FORMULATION OF FAST DISSOLVING FILMS

Preparation of fast dissolving film of levocetirizine

fast dissolving film was prepared by solvent casting method. Aqueous solution I was prepared by dissolving film forming polymer in specific proportion of distilled water and stirred for 3 hours and kept for 1 hour to remove all the air bubble entrapped. Aqueous solution II was prepared by dissolving the pure drug, sweetener and plasticizer in specific proportion in distilled water. The aqueous solution I and II were mixed and stirred for 1 hour The solutions were cast on to 8cm diameter Petridis and were dried in the oven at 450C for 12 hours. The film was carefully removed from surface of Petridis and cut according to size required for testing (square film 1.cm length, 1cm width). The samples were stored in glass container maintained at a temperature.[10]

Table 2: Formulation table

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
ß-CD +LCTZ (mg)	10	10	10	10	10	10	10	10	10
Sodium CMS (gm)	150	250	350	350	350	350	350	350	350
Sodium starch glycolate (mg)	5s0	100	150	_	_	_	_	_	_
Crospovidone (mg)	_	_	_	50	100	150	50	100	150
Citric acid (mg)	100	100	100	100	100	100	100	100	100
PEG 400(ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Distilled water	15	15	15	15	15	15	15	15	15

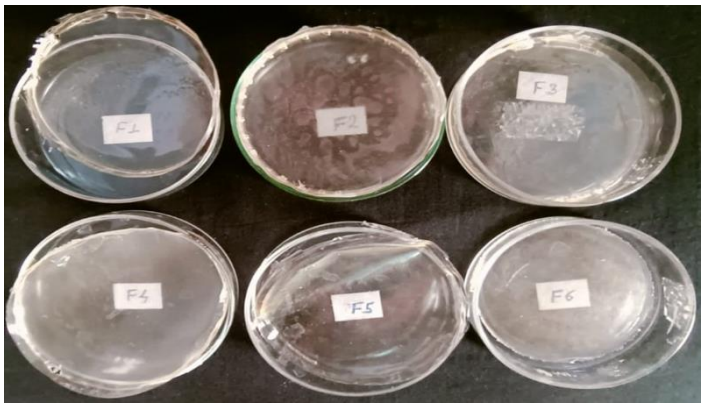

Fig no.7: Formulation of fast dissolving films

VII. EVALUATION OF FAST DISSOLVING FILM

1. **Weight variation:**

From all batches, the patches were cut into small (1 × 1 cm^2) pieces. Three different patches were chosen at random and weighted, with the average weight determined by its standard deviation.

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2. **Thickness:**
The thickness of each films was measured using a screw gauge with a least count of 0.01mm at different positions of the films. The little variation in thickness between different formulations may be due to changes in density for different combinations of polymers.

3. **Folding endurance:**
Evaluation of folding endurance is the study to check the folding capacity of the films when subjected to frequent extreme conditions of folding. The folding endurance of each patch was determined by repeatedly folding the films at the same place till it was broken or folded up to 100times, which is considered satisfactory to reveal good films properties.

4. **Percentage elongation:**
It was calculated by

$$\text{Percentage elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

5. **Tensile strength:**
Tensile strength is the maximum stress applied to a point at which the strip specimen breaks.it is calculated by the formula,

$$\text{Tensile strength} = \frac{\text{Load at failure} \times 100}{\text{Strip thickness strip width}}$$

6. **Drug content uniformity**
Drug content uniformity was calculated by taking 3 films units of each formulation were taken in separate 100ml volumetric flasks, 100ml of Ph 6.8 phosphate buffer was added and continuously stirred. The solutions were filtered, diluted suitably and analysed at 243nm in a UV Spectrophotometer.

Table 3: Drug Content

Concentration	Observation
F1	94 ±0.54
F2	93 ±1.14
F3	97 ±0.55
F4	88 ±0.21
F5	92 ±1.43
F6	98 ± 1.78

7. **Disintegration studies.**
Petri dish method: The time for films to dissolve was recorded using modified disintegration method. In this disintegration test petri dish filled with 2ml distilled water and the film strip was placed on the water surface carefully and recorded until the oral film is completely submerged & time was noted as disintegration time.

Table 4: Formulation disintegration studies

Batches	Weight variation (mg)	Thickness (mm)	Folding Endurance	Drug content
F1	22.8±1.21	0.96±0.10	208 ±1.14	94 ±0.54
F2	28.1±1.67	0.97±0.21	250 ± 0.27	93 ±1.14
F3	26.9±0.17	0.96±0.12	284 ± 0.54	97 ±0.55
F4	29.9±0.69	0.95±0.04	180 ± 1.17	88 ±0.21
F5	41.6±1.90	0.98±0.16	197 ± 0.62	92 ±1.43
F6	18.7 ±1.14	0.97±0.03	186 ± 0.85	98 ± 1.78

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8. **In vitro drug release:**

Drug release is usually controlled by diffusion mechanism due to the swelling of polymers after hydration which releases the drug. Among the six formulations, F3 showed a maximum drug release of 78% in 3hrs due to the high wettability of the polymer sodium CMC.

Sodium CMC (F3) showed a fairly fast drug release, in 3hrs all the amount of incorporated drug was released. (F5) showed the lowest release of 70% in 5hrs.

Table 5: In vitro drug release

Time (min)	Average % Drug Release of Formulation F1-F6					
0	F1	F2	F3	F4	F5	F6
5	9.54	8.56	9	10	8.25	7
10	14	16	18	15	12	11
15	26	25	27	22.8	20	24.7
30	31	33	36	31	29	30
45	37	39	41	38	39.7	37
60	44	46	46	41	45	45
90	54.27	53	52	50	52.8	51
120	63	59	61	58	60	59
150	68	65	67	64	66	65
180	76	71	78	73	70.4	74

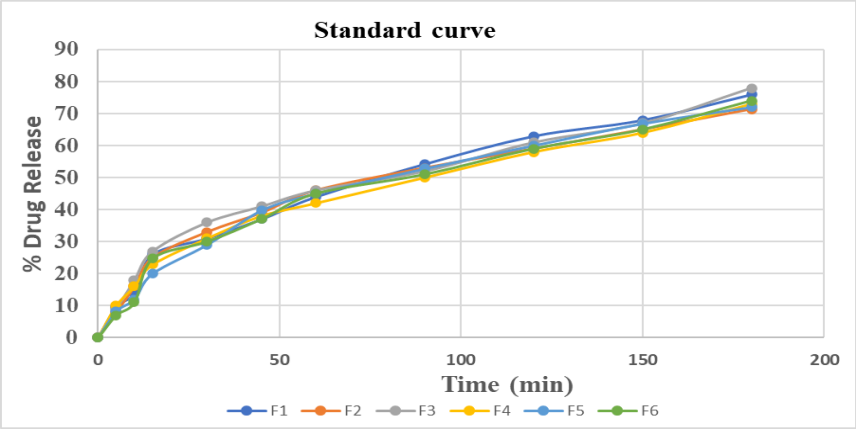

Fig no.8: Drug Release Profile

9. Stability study:

To determine the change in performance of dosage form on storage, a stability study of optimized formulations (F3) was carried out at 40 ± 2 °C and 75 ± 5% Rh fo3 months. Samples were withdrawn after each month and evaluated for physicochemical properties. It was concluded that formulation F3 was stable and retained its original properties with minor differences. There was no physical change in appearance and flexibility. Moreover, there were no major changes in weight variation, folding endurance, drug content and *in vitro* drug release. Hence, the formulations were found to be stable.

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Table 6: Stability studies

Sampling time interval	Weight variation	Folding endurance	Drug content
Initial	22.8±1.21	284 ± 8.5	95.89±1.78
30 days	22.8±1.21	284 ± 7.5	95.70±1.12
60 days	21.8±1.21	283 ± 1.5	95.55±1.46
90 days	20.8±1.21	282 ± 2.5	95.40±078

DISCUSSION

The IR peaks obtained in the spectra of each physical mixture correlated with the peaks of the drug spectrum. Hence, it was concluded that all the polymers used were compatible with the drug and did not lead to a stability problem when used in the formulation. levocetirizine inclusion complexes with β-CD were prepared by kneading method to enhance the solubility of the drug.22 All three prepared inclusion complexes showed the uniform distribution of the drug. The dissolution rate of the complexes was found to be increased compared to pure drug probably due to the formation of water-soluble inclusion complexes of the drug with the β-CD.23,24 Among the inclusion complexes prepared, formulation IC2, i.e., the inclusion complex of levocetirizine with β-CD (1:1 ratio) prepared by the kneading method showed a faster dissolution rate (Figure 2). Therefore for the formulation of fast dissolving films polymers such as Sodium CMC and Chitosan and super disintegrants like sodium starch glycolate and crospovidone were selected as an excipient by solvent casting technique. All the formulations were evaluated for their physicochemical parameters. The Thickness of fast dissolving film depends on the concentration of the polymer. Here the concentration of polymer is kept constant. Hence, the thickness of fast dissolving film depends on vary in concentration of the super disintegrating agent.25 Low concentration of the super disintegrating agent in F1 (2 % w/v of sodium starch glycolate) may be the reason for the lowest thickness of the film and high concentration of the super disintegrating agent in F6(6 % w/v of sodium starch glycolate) may be the reason for the highest thickness of the film.26 Content uniformity study results confirmed the uniform distribution of the drug in all the formulations. All the films passed the weight variation test as the standard deviation of % weight variation of individual formulations was found to be within the pharmacopoeia limit, i.e., ±7.5 %. Low concentration the super disintegrating agent in F1 (2 % w/v of sodium starch glycolate) may be the reason for the lowest weight of the film and high concentration of the super disintegrating agent in F6 (6 % w/v of sodium starch glycolate) may be the reason for the highest weight of the film.27 The surface pH, tensile strength, percentage elongation, folding endurance and % moisture content of all formulations were found to be within the satisfactory range. Moisture loss is the quantity of moisture transmitted through the unit area of film in unit time indicates films ability to withstand its physicochemical properties under normal conditions.28 All the formulated films (F1-F6) were disintegrated rapidly which is a very important property of fast dissolving films.29 In vitro, drug release studies confirmed the fast release of the drug from formulations and F6 formulation released the drug faster compared to all other formulations. It was observed that levocetirizine easily permeated across the membrane since it belongs to the BCS class II.30 So, the result of in vitro permeation study indicates the easy solubilization and absorption of levocetirizine from fast dissolving film.

CONCLUSION

A successful attempt was made to developed an oral fast dissolving film of levocetirizine with β-cyclodextrin as taste masking agent and sodium starch glycolate and croscarmellose sodium as super disintegrants. F3 with 2% croscarmellose sodium was found to be the best formulation.

The fast-dissolving oral films of Levocetirizine inclusion complexes were developed successfully via solvent casting technique with the intention of obtaining better therapeutic efficiency with patient compliance.

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