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Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM OF LEVOCETIRIZINE DIHYDROCHLORID

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ABSTRACT

Preparation of extracts: The fast dissolving oral films were designed using optimal design and numerical optimization technique was applied to find out the best formulation. Film forming agent HPMC, sodium CMC was considered as independent variables. Drug release rate from 45sec to990sec, T50%and release exponent (n) were taken as responses. Decrease the viscosity of film former a specific limit, changes the release from zero order to Hixson-Crowell based release. The optimized formulation F1 was found superior than remaining 8 batches. Amongst all the formulation, formulation F1 releases the complete drug in 360 sec. but other formulation takes more time for complete release. The IR and DSC studies revealed that no physicochemical interaction between excipients and drug. The influence of pH and agitation intensity on the release of drug was studied and the release mechanism was through disintegration. Stability studies revealed that optimized formulation was stable. The observed independent variables were found to be very close to predicted values of most satisfactory formulation which demonstrates the feasibility of the optimization procedure in successful development of fast dissolving oral film containing levocetirizine Dihydrochloride by using HPMC, sodium CMC and PEG-400 as key excipients.

Keywords: Levocetirizine Dihydrochloride, Fast dissolving oral film, Optimal optimization, HPMC, sodium CMC and PEG-400.

INTRODUCTION[1,2]

The fast dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for paediatric and geriatric patients who experienced difficulties in swallowing traditional oral solid-dosage forms. The fast dissolving oral films are used as practical alternative to traditional over the counter medicines because of the various benefit of the film (fast, accurate dosing, safe, efficacy, convenience, portability). As the fast dissolving oral film utilizes sublingual route, rapid absorption of the drug is possible, which finally lead to quick onset of drug action. The HPMC and sodium CMC used as film former as well as PEG400 used a film plasticizer along with sorbitol,Glycerine are also used as sweeting and moisrising agent respectively. A levocetirizine Dihydrochloride was selected for this investigation as modal drug because long-half life, to improve bioavailability by preventing first pass metabolism, no sedative effect, rapid onset of action. Step by step studies were carried out to develop and optimize fast dissolving oral film of Levocetirizine Dihydrochloride using hydrophilic polymers. The fast dissolving oral film were prepared by solvent-casting method.

MATERIALS AND METHODS

Levocetirizine Dihydrochloride was obtained from Khandelwal laboratories Pvt.Ltd.,(Mumbai, India). HPMC and sodium CMC were procured from Loba Chem, Mumbai.PEG400 and Glycerine were obtained from Pure Cham, Mumbai. All other reagent and materials were of analytical or pharmacopoeial grade.

Infrared Spectroscopy (IR):[3]

Physical mixtures of drug and excipients were prepared to study the compatibility. Drug polymer compatibility studies were carried out using IR spectroscopy[3].

UV Spectroscopy:

The UV spectrum of LCZD in PBS (pH 6.8) was scanned in the range 300-200 nm. The spectrum indicated that the observed λ max of LCZD was 230.50 nm which was matched with pharmacopoeial value[4].

Preparation of fast dissolving oral film [5,6]

Oral fast-dissolving film of containing levocetirizine Dihydrochloride was prepared by the solvent-casting method. Film forming polymer i.e. HPMC and CMC sodium was dissolved in about 15ml of distilled water in separate beakers to prevent the excessive air bubbles formation. Then these two solutions were mixed and specified amount of PEG-400 was added to that mixture (know as solution 1). Then solution 1 was allowed to stir for 3 hours. Aqueous solution 2 was prepared by dissolving specified amount of levocetirizine Dihydrochloride, glycerine, sorbitol in about 10ml distilled water. Both aqueous solution 1 and 2 were mixed, stirred for 1 hour and kept for 30min for sonication to remove all air bobbles from final solution. Then the final solution was casted onto a glass slide and it was dried in the oven at 35^{0}C for 12hr. The film was carefully removed from the glass slide, and cut according to the size required for single dose and testing (Dose:1.5x2.5cm).

Table 1: Experimental design for formulations containing various ratios of different polymers

Formulation Code	Trials	Coded Factor Levels	
		X1	X2
F1	1	-1	-1
F2	2	-1	0
F3	3	-1	+1
F4	4	0	-1
F5	5	0	0
F6	6	0	+1
F7	7	+1	-1
F8	8	+1	0
F9	9	+1	+1

1. Evaluation parameters of Films [7,8]

The prepared film was evaluated for following specifications.

Visual Inspection:

Oral fast dissolving films were inspected manually for their transparency and air bubble.

Weight:

Oral fast dissolving films were weighed on analytical balance (Shimadzu AUX-220).

Thickness:

Film thickness was measured by using a micrometer screw gauge. A strip of 1.5 x 2.5cm was placed between the thickness was measured in five different positions.

Folding Endurance:

Folding endurance was measured by manually for the prepared films. A strip of film (4.5 X 2.5 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.

pH:

The pH was determined by dissolving a film in 2 ml of distilled water and then the pH of the obtained solution was measured by pH paper.

Dissolution Time:

Dissolution time was determined by laying down the film (1.5 X 2.5 cm) on the Petri dish and 2 drop of distilled water was added by pipette. The taken for the drop to dissolve the film and form the hole in the film was recorded.

Viscosity of film solution:

Viscosity of the solution was determined by using the Brookfield Viscometer (DV-II + Pro).

2. Content Uniformity [9,10]

Standard solution:

Accurately about 5 mg pure Levocetirizine Dihydrochloride was weighed and transferred it into a 25 ml volumetric flask. Then about 10 ml of PBS (pH 6.8) was added & dissolved it by mechanical shaking then volume was made up to 25 ml with PBS (pH 6.8). The solution was filtered through Whatman filter paper. First few ml of the filtrate was discarded. Then 0.5ml of the filtrate was pippeted out and diluted up to 10 ml with PBS (pH 6.8) in 10 ml volumetric flask so as to get 10 µg/ml final concentrations.

Test Solution:

One film was dropped into the 25 ml volumetric flask. Then about 20 ml of PBS (pH 6.8) was added and dissolved it by mechanical shaking then volume was made up to 25 ml with PBS (pH 6.8). The solution was filtered through Whatman filter paper. First few ml of the filtrate was discarded. Then 0.5ml of the filtrate was pippeted out and diluted up to 10 ml with PBS (pH 6.8) in 10 ml volumetric flask so as to get 10 µg/ml final concentrations. Content uniformity was calculated using following formula –

$$\% \text{ Label claim} = \frac{Abt}{Abs} \times \frac{Ds}{Dt} \times \frac{100}{Lc} \times 100$$

Where,

Abs = Absorption of sample solution,
Lc = Label claim,
Ds = Dilution of standard,
Abs = Absorption of standard solution,
Dt = Dilution of sample

3. Dissolution Studies[10]

The release rate of Levocetirizine Dihydrochloride from fast dissolving film was determined using USP Dissolution Test Apparatus (Type II). The dissolution test was performed using 300 ml of Phosphate Buffer Solution (pH 6.8), at 37 ± 0.5°C with the paddle speed of 50 rpm. Aliquot (7 ml) of the solution was collected from the dissolution apparatus at time interval of 45 seconds and were replaced with same amount of fresh dissolution medium. The aliquots were filtered through Whatman filter paper. Absorbance of the filtrates was measured at 230.5 nm. Aliquots were withdrawn from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall. Cumulative percentage drug release was calculated using an equation obtained from a standard curve. Release studies were performed in triplicate. (IP 2007, b).

RESULT AND DISCUSSION

UV Spectroscopy

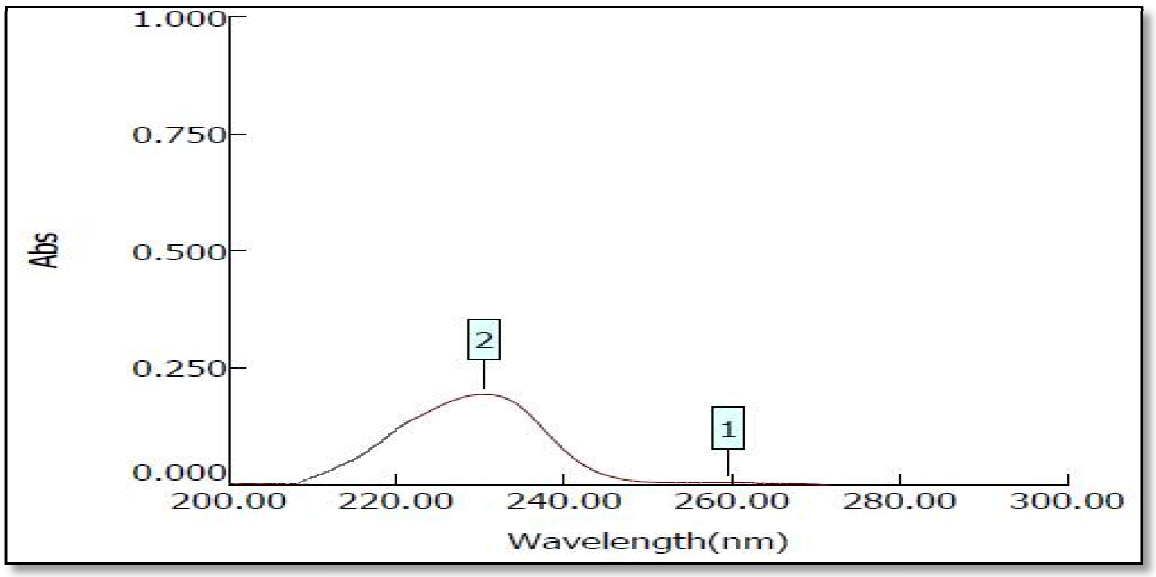


Fig. 1: UV Spectra of LCZD in PBS (pH 6.8)

Table 2: Showing absorbance and λ max

Sr. No.	Peak No.	Wavelength (nm)	Abs
1	1	259.5	0.004
2	2	230.5	0.218

Drug polymer compatibility studies using IR [11,12]

Major functional groups present in LCZD are COOH (carboxylic acid) chlorine (Cl), aliphatic ether (CH_2-O-CH_2).The absorption spectrum shows that presence of aromaticity of structure by the absorption at 2949-2983 cm^{-1}. The presence of the Cl group was indicated by the absorption at 758.02 cm^{-1}. The COOH group was indicated due to presence of absorption at 1720-1740 cm^{-1} and presence of CH_2-O-CH_2 group was indicated by absorption at 1018-1184.From the IR spectrum of mixture of LCZD with all the polymers it was observed that there was no or negligible change in absorption spectrum of the LCZD which indicates there is not any type of interaction between LCZD and all the polymers.

Table 3: Characteristic frequencies in IR spectrum of LCZD

Wave Numbers cm^{-1}	Inference
2949-2983	Presence of aromaticity
758.02	Presence of the Cl group
1720-1740	COOH group
1018-1184	CH_2-O-CH_2 (aliphatic ether)

Table 4: Evaluation of Fast Dissolving Film of LCZD

Formulations	Visual Appearance	Dissolution time#(in sec) (±SD)	Wt. of films*(mg)(±SD)	Thickness of films* (µm)(±SD)	Folding Endurance#	Ph
F1	Transparent	56.33 ±1.52	62.6±1.81	58±1.34	364	6-7
F2	Transparent	72.0±1.72	72.2±1.41	62±1.28	145	6-7
F3	Transparent	83.66±1.52	81.8±1.38	68±1.64	60	6-7
F4	Semi-Transparent	66.6±1.51	82.8±1.92	71±1.73	334	6-7
F5	Semi-Transparent	81.33 ±1.73	84.2±1.64	76±1.25	175	6-7
F6	Non-Transparent	95.66±1.08	85.2±1.48	82±1.19	80	6-7
F7	Non-Transparent	78.33±1.69	86.8±1.92	87±1.68	388	6-7
F8	Non-Transparent	96.66±1.05	89.0±1.59	93±1.61	264	6-7
F9	Non-Transparent	117.33±1.42	92.2±1.26	98±1.34	86	6-7

#n=3, *n=5

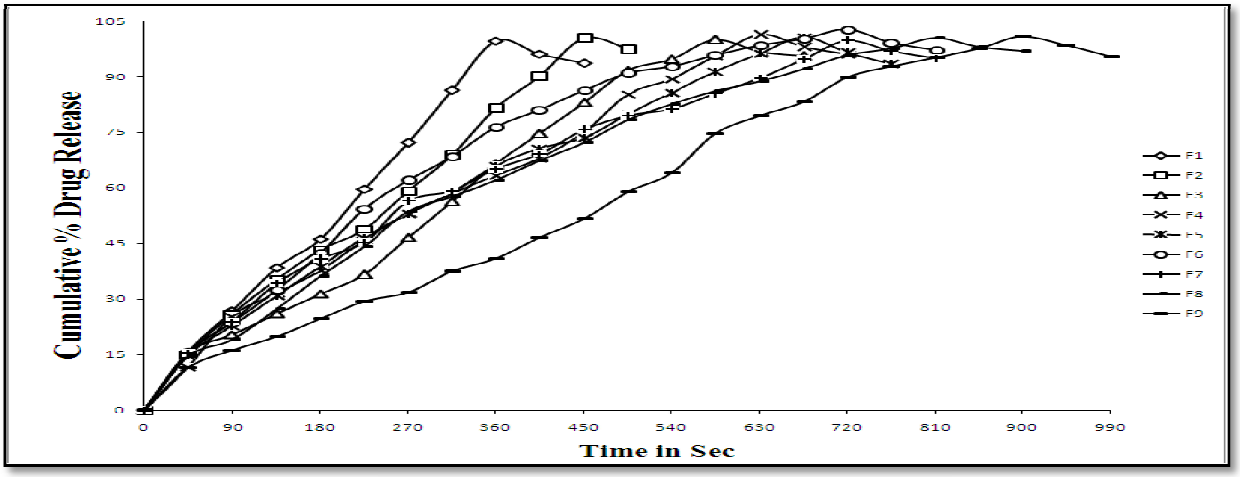
Table 5: Cumulative % Drug Release*(SD) of Oral Fast Dissolving Film of LCZD

Formulation Time (sec)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
45	15.74 ±0.82	15.11 ±1.00	14.49 ±0.63	15.43 ±1.67	14.89 ±1.20	12.36 ±0.87	17.79 ±0.55	14.49 ±1.12	11.49 ±0.68
90	26.61 ±0.65	25.94 ±1.25	20.37 ±0.90	25.40 ±0.79	22.75 ±0.98	23.64 ±0.92	23.95 ±0.26	18.93 ±1.01	16.13 ±0.57
135	38.49 ±0.55	35.32 ±0.66	26.02 ±0.88	31.61 ±1.75	30.93 ±0.57	32.45 ±0.63	34.31 ±0.48	27.34 ±1.15	19.85 ±0.97
180	46.24 ±1.64	43.30 ±1.10	31.44 ±1.01	37.82 ±0.98	38.92 ±0.79	42.44 ±1.03	40.80 ±0.39	36.16 ±0.93	24.66 ±1.02
225	59.64 ±1.18	48.90 ±0.69	36.55 ±0.65	45.91 ±1.08	46.57 ±0.83	54.38 ±1.04	45.34 ±1.26	44.17 ±0.71	29.43 ±1.26
270	72.11 ±1.89	59.23 ±1.67	46.57 ±0.63	53.20 ±1.45	53.02 ±0.97	61.95 ±1.66	56.44 ±1.08	53.54 ±0.56	31.81 ±0.58
315	86.25 ±1.78	68.80 ±0.38	56.25 ±0.63	58.45 ±1.04	58.83 ±1.04	68.55 ±0.82	59.25 ±1.09	57.55 ±0.75	37.44 ±0.59
360	99.59 ±1.06	81.43 ±1.08	66.41 ±1.38	63.44 ±1.45	66.10 ±0.67	76.42 ±0.97	65.16 ±0.39	62.13 ±0.99	40.92 ±0.25
405	96.14 ±0.99	90.00 ±2.63	74.57 ±1.40	68.03 ±0.30	70.62 ±1.33	81.02 ±0.82	69.17 ±0.66	67.44 ±0.95	46.64 ±0.66
450	93.51 ±0.81	100.36 ±1.47	83.08 ±1.11	75.12 ±1.39	73.59 ±1.30	86.30 ±1.00	75.64 ±0.76	72.24 ±1.89	51.77 ±0.68
495	---	97.27 ±1.26	91.72 ±1.33	85.28 ±1.25	79.93 ±1.61	90.89 ±0.73	79.47 ±0.56	78.30 ±0.87	58.90 ±0.99
540	---	---	94.63 ±1.17	89.47 ±1.46	85.75 ±0.74	92.83 ±0.85	81.34 ±0.34	82.57 ±0.77	64.00 ±0.17
585	---	---	99.91 ±0.90	95.59 ±0.85	91.38 ±1.45	95.79 ±0.92	85.50 ±1.06	86.10 ±0.48	74.54 ±0.68
630	---	---	96.63 ±0.54	101.30 ±1.05	96.30 ±1.58	98.56 ±0.77	89.71 ±1.16	88.84 ±0.86	79.38 ±0.99
675	---	---	95.52 ±1.10	97.97 ±0.76	100.72 ±1.84	100.24 ±0.77	94.75 ±1.22	92.03 ±0.36	83.19 ±0.79
720	---	---	---	96.04 ±0.90	96.44 ±2.18	102.63 ±0.65	99.72 ±1.41	95.85 ±0.59	89.91 ±0.43
765	---	---	---	---	93.35 ±0.38	99.22 ±0.95	96.84 ±1.97	97.69 ±0.92	92.69 ±0.54
810	---	---	---	---	---	97.13 ±1.29	94.92 ±1.62	100.42 ±0.70	95.16 ±0.41
855	---	---	---	---	---	---	---	98.12 ±0.29	97.51 ±0.92
900	---	---	---	---	---	---	---	96.98 ±0.76	100.82 ±1.53
945	---	---	---	---	---	---	---	---	98.51 ±0.56
990	---	---	---	---	---	---	---	---	95.45 ±1.53

n=3

Table 6: Kinetic data of all prepared Formulation

Formulation code	Drug Release Kinetics Correlation Coefficients (r^2)					Release Exponent (n)	Kinetics Model
	Zero order	First order	Matrix	Peppas	Hixson-Crowell		
F1	0.9793	0.7840	0.9510	0.9978	0.9147	0.8365	Peppas
F2	0.9890	---	0.9531	0.9969	0.8569	0.8053	---
F3	0.9783	0.8530	0.9462	0.9866	0.9507	0.7911	Peppas
F4	0.9602	0.7763	0.9745	0.9952	0.9443	0.6980	Peppas
F5	0.9460	---	0.9802	0.9966	0.8877	0.6995	---
F6	0.8838	---	0.9777	0.9830	0.8971	0.7196	---
F7	0.9205	0.8520	0.9890	0.9962	0.9678	0.6287	Peppas
F8	0.9283	---	0.9822	0.9914	0.9418	0.7000	---
F9	0.9855	---	0.9395	0.9872	0.8972	0.7875	---



Graph 1: Cumulative % Drug Release of Oral Fast Dissolving Film of LCZD

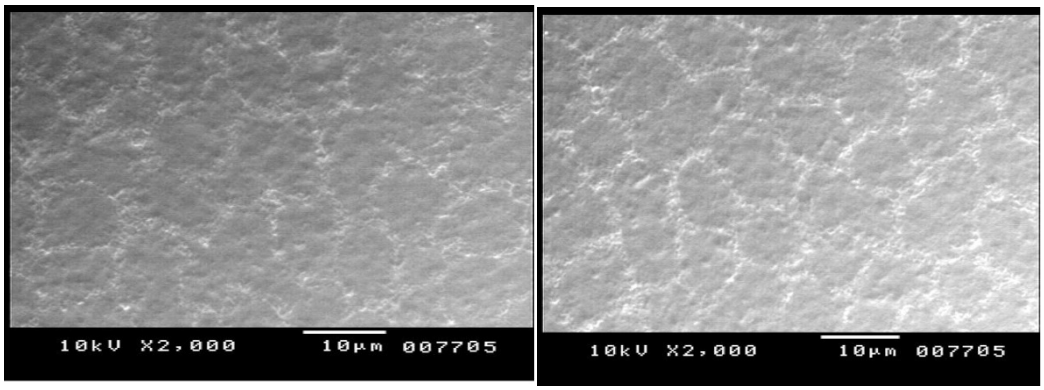


Fig. 2 (a): Lower surface attached to the Fig 2 (b): Upper surface exposed to the Petri dish atmospheric environment[13]

CONCLUSION

Novel developments in the technology have promoted scientists to develop oral fast dissolving films with improved patient compliance and convenience. This system is oral fast-dissolving film that allows children, elderly and the general population to take their medications discretely wherever and whenever needed, satisfying an unmet need. Oral fast dissolving films of Levocetirizine Dihydrochloride are solid unit dosage forms, which dissolve and/or disperse after placement in mouth without chewing and drinking water. Oral fast dissolving films are easy to administer for paediatric, geriatric patients. This is mostly used Over-The-Counter antihistaminic drug to treat Sneezing, Common-cold and allergy. Apart from these this is also helps to reduce asthmatic attack (up to 70%) in children and chronic urticaria. It is beneficial for the patients during travelling who do not have access to water. As the oral fast dissolving films utilizes sublingual route, rapid absorption of drug is possible, which finally leads to quick onset of drug action. Novel oral drug disintegrating dosage forms are also known as fast dissolving, rapid dissolving and quick disintegrating film. In present work, a Levocetirizine Dihydrochloride was selected for this investigation as model drug because long-half live, to improve bioavailability by preventing first pass metabolism, no sedative effect, rapid onset of action. Step by step studies were carried out to develop and optimize Fast Dissolving Oral Film of Levocetirizine Dihydrochloride using hydrophilic polymers.

The Fast Dissolving Oral Films were prepared by Solvent-Casting Method. In the preliminary tests, spectroscopy study (UV and IR) was carried out and no significant drug interaction was observed for Levocetirizine Dihydrochloride with polymers and excipients. UV scan of Levocetirizine Dihydrochloride had shown maximum absorption at wavelength 230.5 nm in PBS (pH 6.8) which is specified in pharmacopoeia, textbooks and in literature survey. Preliminary trials of film forming polymer (HPMC and CMC Sod.) was studied. Results obtained from the preliminary study shows that 3% (w/v) conc. of HPMC (5cps) can form the film but it was very difficult to remove entirely from Petri dish. The results

obtained for CMC sodium also similar to that of HPMC and film of 0.5% (w/v) was unable to remove. Preliminary trials of PEG-400 were studied for their plasticizer effect. The results shows that 38% (w/w) plasticizer completely remove the film from Petri dish. Thus the concentrations of film forming polymer were chosen minimum 3% and maximum 5% for HPMC (5cps) as film forming agent and 0.5% minimum and 1.5% maximum for CMC sodium as gelling and strengthening agent. Evaluation results F1 batch of fast dissolving oral film of Levocetirizine Dihydrochloride was found superior than remaining 8 batches. The results include visual inspection which found more clear than other formulations, weight of the film was found 62.6 mg, thickness of the film was found 58 µm and folding endurance was found 364. The F1 formulation takes least time for dissolution, which was found 56 seconds. Amongst all the formulations, formulation F1 releases the complete drug in 360 seconds but other formulations takes more time for complete release. As per stability studied neither significant change in the evaluation parameter nor drug interaction was found. Thus F1 formulation was selected as optimised formulation of fast dissolving oral film of Levocetirizine Dihydrochloride.

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