RESEARCH ARTICLE

Formulation development of fast releasing oral thin films of levocetrizine dihydrochloride with Eudragit® Epo and optimization through Taguchi orthogonal experimental design

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The aim of this study was to develop a fast releasing oral polymeric film, prepared using the solvent casting method, with good mechanical properties, instant disintegration and dissolution, an acceptable taste in the oral cavity. Levocetirizine dihydrochloride, an antihistamine, was incorporated to relieve the symptoms of allergic rhinitis. Four batches of films with drug were prepared using different combinations of polymers and plasticizers Eudragit® EPO, HPMC E 5 LV, and PVA were the selected polymers. Glycerin, dibutyl phthalate, propylene glycol, and PEG 400 were the selected plasticizers. The resultant films were evaluated for weight variation, assay, content uniformity, folding endurance, thickness, tensile strength, percent elongation, surface pH, *in vitro* disintegration and *in vitro* dissolution. The formulations from the preliminary trial were analyzed using Taguchi OA experimental design, which was applied to optimize the type of polymers, concentration of polymers, plasticizer, and sweetener based on their disintegration data at three different levels. The optimized films disintegrated in less than 30s, releasing 70-90% of drug within 2 mins. The percentage release varied with the type of polymer and concentration of polymer. The films made with EPO released 96% of drug in 2 mins, which was the best release among all.

Key words: *Antihistamine, fast disintegrating films, levocetirizine, oral thin films*

INTRODUCTION

Currently, there is a high level of interest in the use of the oral cavity as a portal for drug entry to the systemic circulation. As a site for drug delivery, the oral cavity offers advantages over the conventional gastrointestinal, the parenteral and alternative routes of drug administration. Oral thin films are postage stamp-sized rectangular shape polymeric films which instantaneously disintegrate and dissolve within seconds when placed on the tongue. Oral films are preferred by patients suffering from dysphasia, motion sickness, repeated emesis and mental disorders since they are unable to swallow large amounts of water. The advantages of convenient dosing and portability of oral strips have led to a wide applicability of this dosage form in pediatric as well as geriatric patients.

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The advantages of sublingual delivery of drugs via oral films include larger surface area, enhanced safety, high precision during dose administration compared to liquid forms, high levels of patient compliance, and quicker relief.[1] Additionally, other oral formulations can be subject to poor absorption, or delayed onset due to degradation by the gastrointestinal tract, as well as first pass metabolism by the liver. Also, although oral disintegrating tablets disintegrate quickly, their disintegrated materials remain insoluble until swallowing. Buccal, or sublingual delivery through thin films therefore provides a way to circumvent swallowing through rapid dissolution in the oral cavity, thereby causing quick onsets of action at a lower dosage. As the oral film releases the drug instantly, this dosage

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form can be formulated for to treat diseases, such as pain, allergies, sleep disturbances, anxiety and gastric problems, which require a fast onset of action.

Allergic rhinitis is one such disease where a quick relief from the symptoms is needed. Patients with allergic rhinitis, and other pediatric, geriatric and dysphasic patients may have difficulties swallowing the tablet form, and may have poor compliance due to the inherent difficulty of administration. Unlike the tablet dosage form, the disintegration and dissolution of oral films are not the rate-limiting steps for absorption. Oral films disintegrate and release the drug immediately to provide quick relief.[2] Therefore, oral thin films are the best dosage forms for these population types for faster absorption into the systemic circulation.

Levocetirizine dihydrochloride (LCTZ), a crystalline water-soluble drug, is an orally active and selective H1-receptor antagonist used to treat seasonal allergic rhinitis, perennial allergic rhinitis and chronic utricaria.[3] However, since the drug is intensely bitter in taste, the dosage form should be taste masked to yield better patient compliance.[4,5]

The objective of this study was to prepare fast-dissolving oral films of LCTZ for rapid dissolution in the oral cavity. The films were prepared using a solvent casting method which optimized the polymer combinations (Eudragit® EPO, PVA, and HPMC E5 LV) and their concentrations using Taguchi OA experimental design. The drug was incorporated into the polymer network and evaluated for *in vitro* release studies. The prepared films were characterized for other parameters like *in vitro* disintegration, thickness, folding endurance, surface pH, percent elongation and tensile strength.

MATERIALS AND METHODS

Materials

LCTZ was received as a gift sample from Symed labs (India). Eudragits® EPO (EPO), Hydroxy Propyl Methyl Cellulose E5 (HPMC E5) were obtained from SHIN-ETSU (Japan). Polyvinyl alcohol (PVA), hydroxy propyl methyl cellulose - E 15 LV, potassium dihydrogen phosphate, disodium hydrogen phosphate, Tween 20, propylene glycol, glycerol, dibutyl phthalate, polyethylene glycol - 400, mannitol, aspartame and hydrochloric acid (HCl) were purchased from S.D. Fine Chemicals Ltd., India. All the chemicals were of analytical grade. Distilled water was used whenever required.

Methods

LCTZ fast-dissolving films were prepared by the solvent casting method.[6] The polymer Eudragit® EPO was used as it was previously reported to have taste-masking properties. For preliminary trials, drug-free patches were prepared with Eudragit® EPO, PVA, HPMC E 5 LV and HPMC E 15 LV at 2% w/v, 4% w/v, 6% w/v, 8% w/v and 10% w/v concentrations in 0.1N HCl. These solutions were plasticized using 2% w/v glycerin. The solutions were cast on glass plates and dried in an oven at 40°C for 24 hrs. By this preliminary study, concentrations of polymers required for the study were decided based on the thickness, transparency and stickiness; HPMC E 15 LV was excluded from the study as it was taking more time to disintegrate. Further studies were done in four batches with the drug using different combinations of polymers and plasticizers. The amount of drug added was calculated based on the area of plates so that each dosage (4×4 cm^2 area) consisted of 5 mg of LCTZ.[7]

Dose calculations

Diameter of the plate = 6 cm
Area of the plate = 28.6 cm^2
No. of 4-cm^2 films present whole plate = 28.6/4 = 7.065
Each film contains 5 mg of drug.
7.065 no. of films contains mg of drug? = 7.065×5 = 35.325 mg
The amount of drug added in each plate was approximately equal to 36 mg.

Preparation of films with Eudragit® EPO

All the ingredients were weighed accurately according to Table 1. The EPO was dissolved in 5 ml of 0.1 N HCl with continuous stirring. The drug, mannitol and aspartame were added subsequently. The resultant solution was stirred for 15 minutes to produce a clear solution, which was kept aside for 15 mins to get bubble-free solution. These solutions were casted slowly and with continuous flow on a glass plate of diameter 6 cm to prevent the formation of bubbles. The plates were kept in a hot air oven at 40°C for 24 hrs. The dried film was gently separated from the glass plate and evaluated. The same procedure was repeated by using Teflon plates instead of glass plates, and the formed films were evaluated.

Preparation of films using Eudragit® EPO and PVA

In order to investigate the effects of different parameters on the mean and variance of the process performance (what is this "process," it's too generally mentioned here) and to obtain an optimal process that functions well, Taguchi experimental design was selected. In this design, orthogonal arrays arrange the parameters affecting the process of film formation of films and the levels at which they are most likely to affect the process variables. Unlike factorial design, where all the possible combinations are being tested, Taguchi employs few numbers of trials by testing pairs of combinations, thereby saving time and resources. The optimal parameters obtained from these minimal trials are insensitive to environmental changes and other noise factors. Minitab 15 was the software used to carry out the Taguchi design.

Array selector

In the present investigation, four process parameters were studied: concentration of EPO, concentration of PVA, concentration of plasticizer i.e., glycerin (GLY), and concentration of mannitol (MNTL). Each of these parameters is of three different levels, as stated in Table 2.

Table 1: Preparation for first three sets of levocetirizine films

No. of runs	Trial code	LCTZ (mg)	EPO (mg)	PVA (mg)	HPMC (mg)	Glycerin (mg)	Mannitol (mg)	Asparatame (mg)
1	E1	36	200	-	-	50	0	0
2	E2	36	250	-	-	50	0	0
3	E3	36	300	-	-	50	0	0
4	E4	36	200	-	-	50	30	0
5	E5	36	250	-	-	50	30	0
6	E6	36	300	-	-	50	30	0
7	E7	36	200	-	-	50	30	30
8	E8	36	250	-	-	50	30	30
9	E9	36	300	-	-	50	30	30
10	EP1	36	100	50	-	50	20	25
11	EP2	36	200	50	-	150	30	25
12	EP3	36	150	100	-	150	20	25
13	EP4	36	150	50	-	100	40	25
14	EP5	36	200	100	-	50	40	25
15	EP6	36	150	150	-	50	30	25
16	EP7	36	200	150	-	100	20	25
17	EP8	36	100	150	-	150	40	25
18	EP9	36	100	100	-	100	30	25
19	EH1	36	100	-	50	50	20	25
20	EH2	36	200	-	50	150	30	25
21	EH3	36	150	-	100	150	20	25
22	EH4	36	150	-	50	100	40	25
23	EH5	36	200	-	100	50	40	25
24	EH6	36	150	-	150	50	30	25
25	EH7	36	200	-	150	100	20	25
26	EH8	36	100	-	150	150	40	25
27	EH9	36	100		100	100	30	25

List and quantity of materials used for the preparation of levocetirizine dihydrochloride films with different combinations of polymers i.e., only with Eudragit® EPO (first set), Eudragit® and PVA (second set), Eudragit® and HPMC (third set). All ingredients were dissolved in 0.5 ml of 0.1 N HCl.; LCTZ: levocetirizine dihydrochloride, PVA: polyvinyl alcohol, HPMC: hydroxy propyl methylcellulose, mg: milligrams, ml: milliliters, N: normality, HCl: hydrochloride, % -percentage

Table 2: Deciding factors and their levels for construction of Taguchi experimental design

Independent variables (Factors)	Levels for the factors		
	1	2	3
Eudragit® EPO	2% w/v	3% w/v	4% w/v
PVA	1% w/v	2% w/v	3% w/v
Glycerin	1% w/v	2% w/v	3% w/v
Mannitol	0.4% w/v	0.6% w/v	0.8% w/v

Deciding factors or independent variables used are Eudragit® EPO, PVA, glycerin, mannitol with three levels. Percentages were calculated for 5 ml of solvent used i.e., 0.1 N HCl.; PVA: polyvinyl alcohol, % w/v- percentage weight by volume, ml: milliliter, N: normality, HCl: hydrochloride

From the array selector, $L^{[9]}$ orthogonal array was selected and the sequence of the experimental runs was altered to prevent any bias. The nine experiments are listed in Table 3.

All the ingredients were weighed according to Table 4. Eudragit® EPO was dissolved in 5 ml of 0.1 N HCl with continuous stirring. Then PVA was added to the above solution and was stirred for about 15-20 mins. The remaining procedure was carried out in the same way as the preparation of films using Eudragit® EPO alone.

Table 3: Randomized runs according to Taguchi experimental design

Runs	Independent variable (Factors)			
	Eudragit® EPO	PVA	Glycerin	Mannitol
1	1	1	1	1
2	3	1	3	2
3	2	2	3	1
4	2	1	2	3
5	3	2	1	3
6	2	3	1	2
7	3	3	2	1
8	1	3	3	3
9	1	2	2	2

Total nine runs using four different factors. 1, 2 and 3 are lower, medium and higher levels, respectively, for the factors used.; PVA: polyvinyl alcohol

Preparation of films using Eudragit® EPO and HPMC E5LV

All the ingredients were weighed accurately according to Table 4. First, the EPO was dissolved in 5 ml of 0.1 N HCl with continuous stirring. HPMC was subsequently added to the above solution and was stirred for about 15-20 mins. The remaining procedure was carried out in the same way as the preparation of films using Eudragit® EPO alone.

Preparation of films using different plasticizers

The highest polymer concentration was taken and films were prepared with the same procedure as with the glycerin, but by using plasticizers other than glycerin, as in the Table 5. Different plasticizers used were polyethylene glycol 400, propylene glycol and dibutyl phthalate. As the dibutyl phthalate is nonaqueous in nature, two drops of Tween 20 were added in the formulations where ever this plasticizer was used.

Table 4: Formulation of oral films using different plasticizers

No. of runs	Trial code	EPO (mg)	PVA (mg)	HPMC (mg)	Glycerin (mg)	PG (mg)	DBP (mg)	PEG 400 (mg)
1	Eg	300	-	-	50	-	-	-
2	Ep	300	-	-	-	50	-	-
3	Ed	300	-	-	-	-	50	-
4	Epg	300	-	-	-	-	-	50
5	EPg	200	100	-	50	-	-	-
6	EPp	200	100	-	-	50	-	-
7	EPd	200	100	-	-	-	50	-
8	EPpg	200	100	-	-	-	-	50
9	EHg	200	-	100	50	-	-	-
10	EHp	200	-	100	-	50	-	-
11	EHd	200	-	100	-	-	50	-
12	EHpg	200	-	100	-	-	-	50

List and quantity of materials used for the preparation of levocetirizine dihydrochloride films using different plasticizers and different polymers. Plasticizers used were PG, PEG 400, DBP and glycerin and polymers used were Eudragit® EPO, PVA, HPMC. All formulations contain LCTZ 36 mg, aspartame 25 mg and mannitol 25 mg in their preparations. All ingredients were dissolved in 0.5 ml of 0.1 N HCl.; LCTZ: levocetirizine dihydrochloride, PVA: polyvinyl alcohol, HPMC: hydroxy propyl methylcellulose, PG: propylene glycol, DBP: dibutyl phthalate, PEG: polyethylene glycol, mg: milligrams, ml: milliliters, N: normality, HCl: hydrochloride, % -percentage

Table 5: *In vitro* evaluation parameters of levocetirizine films

Formulation code	Disintegration time (secs) Mean±Std dev	Weight (mg) Mean±Std dev	Thickness (mm) Mean±Std dev	Content uniformity (mg) Mean±Std dev
E1	13.66±1.53	39.66±1.52	74±5.48	4.84±0.12
E2	15.66±2.52	45.66±1.52	76±5.48	4.84±0.13
E3	16.33±0.57	52.66±1.53	124±5.48	4.81±0.12
E4	14.66±0.57	43.33±1.16	84±5.48	4.93±0.02
E5	14.33±1.15	51.0±2.0	88±4.48	4.92±0.03
E6	17.0±2.0	57.33±2.08	114±5.48	4.85±0.14
E7	18.33±1.15	49.66±2.08	92±4.48	5.03±0.08
E8	12.66±1.15	55.66±2.51	76±5.48	4.93±0.11
E9	19.66±1.53	63.0±3.0	124±5.48	4.92±0.06
EP1	20.0±1.0	39.33±1.53	68±4.47	4.88±0.21
EP2	33.67±0.58	69.0±3.0	74±5.47	5.01±0.07
EP3	29.0±6.08	65.33±2.51	82±4.47	5.01±0.10
EP4	23.33±1.53	57.33±2.51	78±4.47	4.88±0.10
EP5	32.67±1.52	61.33±2.51	126±5.47	4.99±0.08
EP6	26.0±3.60	60.66±3.21	128±4.47	4.97±0.14
EP7	31.0±1.0	74.66±2.51	136±5.47	4.92±0.07
EP8	27.67±1.15	70.66±1.53	82±4.47	4.96±0.05
EP9	23.33±0.57	55.33±2.52	74±5.47	4.92±0.11
EH1	25.66±2.51	39.33±3.51	84±5.48	4.68±0.05
EH2	35.61±3.05	69.33±2.51	72±4.48	4.94±0.03
EH3	34.0±2.64	66.33±2.08	76±8.95	4.89±0.03
EH4	33.33±1.52	57.0±2.0	86±8.95	4.99±0.06
EH5	34.33±1.15	63.0±2.64	130±0	4.80±0.10
EH6	38.33±1.15	62.66±3.05	130±7.07	4.86±0.14
EH7	41.33±1.53	72.33±2.31	124±5.48	4.87±0.06
EH8	34.33±1.15	69.33±1.53	84±5.48	4.89±0.09
EH9	26.33±1.15	54.0±2.64	72±4.48	4.95±0.01

In vitro parameters were disintegration time in mins, weight variation in mg, thickness in cm, content uniformity of drug in mg. no of films used, N=3. Mean was the average of three films.; PVA: polyvinyl alcohol, HPMC: hydroxy propyl methylcellulose, secs: seconds, mg: milligrams, mm: millimeters, std dev: standard deviation

Characterization of LCTZ oral films

Weight variation

This test ensures the uniformity of the formed film. Three small pieces were cut randomly, each of 1 cm^2 (1 × 1 cm) area, and were weighed individually.

Thickness

The film thickness was measured using a micrometer screw gauge at five points (center and four corners) on the film to ensure the uniformity of the film thickness. The mean thickness was calculated from the five points. Samples with air bubbles, nicks or tears, and those having mean thickness variations greater than 5% were excluded from analysis.

Assay

The assay was performed to ensure the drug loading onto each film. This test was performed by dissolving a 4 cm^2 area of film in 50 ml of pH 6.8 phosphate buffer with stirring. This solution was filtered using a Wattmann filter paper, and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. This solution was analyzed using a spectrophotometer (Chemito double beam UV-visible spectrophotometer).

Content uniformity

The content uniformity test was used to ensure that every film contains the intended amount of drug substance with little variation among films within a patch. Three pieces, each 1 cm^2 (1 × 1 cm), were cut from the whole patch, and assayed for drug content.[8]

Folding endurance

Folding endurance of the film was determined by repeatedly folding a small strip of film (2 × 2 cm) at the same place until it broke. The number of times that the film could be folded at the same place without breaking gives the value of folding endurance.[9,10]

Tensile strength

The tensile strength of the films was measured using a tensile strength instrument, which consisted of a pulley system. A small patch strip (2×1 cm) was cut on a glass plate with a sharp blade. One end of the film strip was fixed between adhesive tapes to support the film in the holder. Another end of the film was fixed between the adhesive tapes with a small pin sandwiched between them to keep the strip straight while stretching. A small hole was made in the adhesive tape near the pin in which a hook was inserted. A thread was tied to the hook, passed over the pulley, and a small pan was attached to the other end of the pulley to hold the weights. A small pointer was attached to the thread, which traveled over the graph paper affixed on the base plate. Weights were gradually added to the pan to increase the pulling force until the patch was broken. The elongation was determined by recording the distance traveled by the pointer on the graph paper before the patch broke. The weight required to break the patch was noted as the break force. This study was conducted to be optimized for film formulations only. Tensile strength was calculated using formula no.1.[11,12]

$$\text{Tensile strength} = \text{Break force} / ab[1 + (\Delta L/L)] \quad (1)$$

Where a, b, and L are width, thickness, and length of strip, respectively, and ΔL is the elongation at break.[13]

Percent elongation at break

This study was conducted only for the optimized film formulations.[14,15]

% Elongation at break was calculated using formula no. 2:

$$\% \text{ Elongation at break} = I_B - I_O / I_O \times 100 \quad (2)$$

Where I_O = Original length of patch I_B = length of patch at break when stress is applied.[16]

Surface pH

1 cm^2 film of each formulation was taken and was placed in a petri dish containing 1 ml of water. After complete wetting of the film, the pH at the surface of film was checked using pH paper.[17]

In vitro disintegration

Two simple methods were used wherein, a small amount of disintegration medium was used. In the first method, one drop of water was dropped from a 10-ml pipette onto the tightly clamped film. The time taken for the water to make a hole through the film was measured as disintegration time (DT). In the second method, 2 ml of water was placed in a petri plate with a film on the surface of water; the time taken for the disintegration of the film was measured. This test was done in triplicates and the average value was taken as DT.[18]

In vitro dissolution

According to previous studies, dissolution studies were performed using USP 23 apparatus 5, paddle over disc method. As the paddle over disc apparatus was not available, USP apparatus 1 (basket) (Electrolab TDT-08L) was used for this study. Nine hundred milliliters of phosphate buffer (pH 6.8), which is a prescribed media for LCTZ according to Indian pharmacopoeia, was used, and was maintained at 37±5°C while the basket was set at 100 rpm. A film sample of 4 cm^2 (2×2 cm) was cut and taken into the basket. Five milliliters of samples were taken every 2 min, and the same amount was replaced with fresh buffer. The withdrawn samples were filtered and analyzed using a spectrophotometer at a wavelength of 230 nm. The percentage release was calculated from previously assayed values of the patch. The relationship between time and percentage release was plotted to determine when the maximum amount of drug is released. Dissolution studies were conducted for optimized formulations.[19,20]

Table 6: *In vitro* evaluation parameters of levocetirizine films using different plasticizers

Formulation code	Weight (mg) Mean±Std dev	Content uniformity (mg) Mean±Std dev	Thickness (mm) Mean±Std dev	Disintegration time (secs) Mean±Std dev
Eg	61.33±3.05	4.85±0.06	126±8.94	21.0±1.73
EP	59.33±2.31	4.94±0.14	130±7.07	22.33±1.53
Ed	62.0±1.73	4.75±0.07	126±5.48	35.67±1.15
EPg	63.66±1.53	4.86±0.02	122±4.48	22.67±0.58
EPg	63.33±2.08	4.95±0.06	120±0.0	25.67±1.15
EPp	63.33±1.15	4.83±0.12	140±0.0	24.34±0.57
EPd	62.0±2.0	4.87±0.06	128±4.48	44.34±1.53
EPpg	61.33±2.52	4.94±0.01	144±5.48	27.67±1.53
EHg	63.33±0.58	4.89±0.02	124±5.48	31.34±1.15
EHp	63.0±2.0	5.03±0.07	108±8.36	26.34±1.53
EHd	64.33±0.58	4.94±0.11	134±5.48	49.34±2.08
EHpg	60.33±1.53	5.01±0.09	140±7.07	31.67±1.53

In vitro parameters were disintegration time in mins, weight variation in mg, thickness in cm, content uniformity of drug in mg. no of films used, N=3. Mean was the average of three films.; HPMC: hydroxy propyl methylcellulose, secs: seconds, mg: milligrams, mm: millimeters, std dev: standard deviation

Table 7: Signal to noise ratio values for the responses (DT) given

Experimental run	S/N ratios for DT
1	26.0278
2	30.5449
3	29.3735
4	27.3719
5	30.2884
6	28.3548
7	29.8302
8	28.8442
9	27.3613

DT: disintegration time, S/N: signal to noise ratio

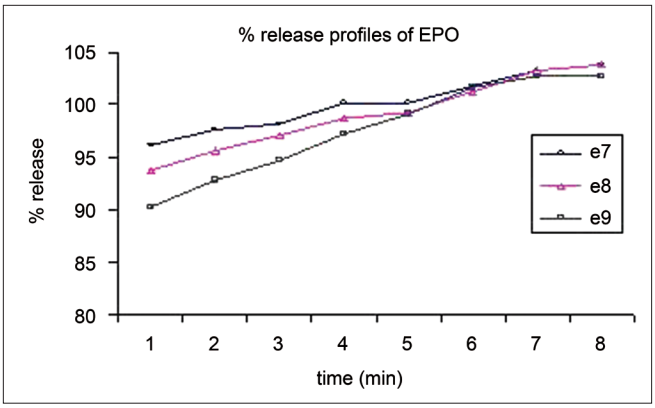

Figure 1: Percentage drug release of films prepared using different concentrations of EPO polymer

RESULTS

Preparation of oral films of levocetirizine di hydrochloride

Films of LCTZ were successfully prepared by gradually increasing the concentration of polymers such as EPO, combination of EPO and PVA, combination of EPO and HPMC in four different batches, and by using different plasticizers.

Evaluation of the prepared oral films [Table 6 and 7]

Weight variation

The films have shown a maximum percent weight variation of less than 5%.

Assay

The assay values for all the films were in the range of 92-02%, which shows that the 5-mg dose was available and nearly maintained compared to the theoretical value.

Folding endurance

Among all the formulations, EP7, EP6, EP5 were the most effective since they displayed a folding endurance of above 300. The formulations prepared using EPO alone had shown folding endurance of about 300. The formulations prepared using a combination of HPMC and EPO were a little brittle compared to the EPO formulations. When the films were folded above 200 times, there were clear distinct strain marks on the film, and the film started to tear.

Content uniformity

The drug was distributed uniformly throughout the film. The percent standard deviation was in the range of 0.5-3%.

In vitro disintegration

The film formulations using only EPO had shown good disintegrating properties. The formulations according to Table 5 were ranked second. The best disintegrating time was reported by EP1. The combination of HPMC and EPO was ranked last, when DT was concerned.

The signal to noise (S/N) ratios were calculated from the Taguchi experimental design. Since the software has assigned ranks based on S/N ratios, the lower the rank assigned, the more the influence of the factor on response, i.e., disintegration time (DT). The concentration of PVA was ranked first, the concentration of plasticizer second, while the concentrations of mannitol and EPO were ranked subsequently lower. The relationship between the data

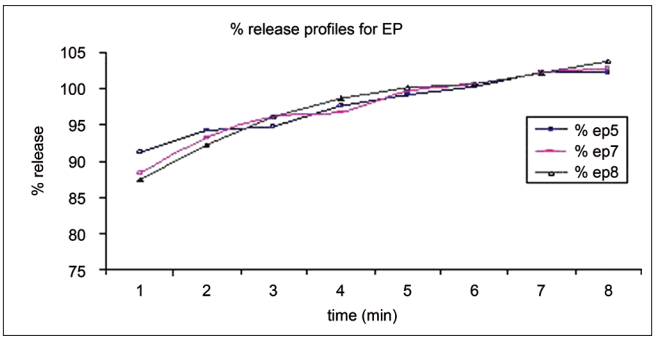

Figure 2: Percentage drug release of films prepared using different concentrations of EPO and PVA

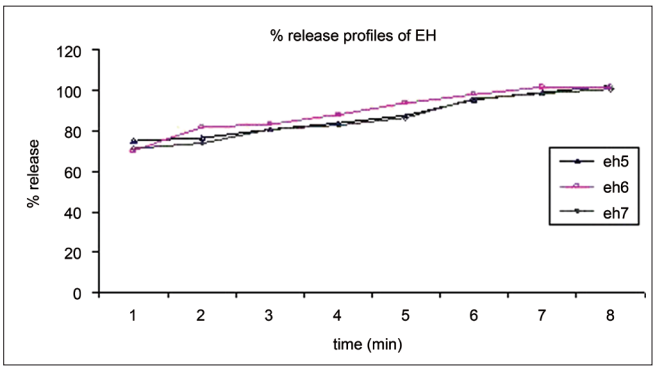

Figure 3: Percentage drug release of films prepared using different concentrations of EPO and HPMC

disintegration time (DT) versus EPO, PVA, Gly, and MNTL, obtained via Taguchi analysis, is represented in Table 7.

Surface pH the pH range was 6-7, which was found to be acceptable.

Tensile strength

The films E7, E8 and E9 showed tensile strength of 160-195 g/cm^2. EP5, EP6, and EP7 showed tensile strength of 190-220 g/cm^2. EH5, EH6, EH7 showed tensile strength of 170-185 g/cm^2.

Percent elongation

The percent elongation range about 19-20% for the first set of films, 17-19% for the second set, and around 18% for the third set. Almost all formulations in the third set showed similar percent elongation. The percentage elongation of the films with glycerin were more varied compared to the results obtained with other plasticizers.

In vitro release studies of optimized LCTZ oral films

Based on the preliminary exclusions, visual inspection, and disintegration time, 12 best films were selected for the dissolution study. The films formed by only EPO were released above 90% of the drug within 2 minutes [Figure 1]. While the films formed by a combination of EPO and PVA were able to release nearly 90% of the drug in 2 minutes, the percentage release was lesser compared to films formed using only EPO [Figure 2]. The films formed by a combination of EPO and HPMC were able to release about 70% of the drug in 2 minutes [Figure 3]. The films cast with plasticizers other than glycerin were not showing much deviation in the percent release compared to formulations where glycerin was used as a plasticizer.

DISCUSSION

Oral disintegrating films, prepared by the solvent casting technique using different polymers like Eudragit® EPO, PVA and HPMC E5 LV, were explored for delivery of LCTZ. Plasticizers, such as glycerin, propylene glycol were used to improve the flexibility, and reduce the brittleness of the strip. We selected the aforementioned plasticizers in particular because of their compatibility with the selected polymers. Plasticizers have been shown to improve polymer strength, and decrease the glass trandition temperature of the polymer.[21]

The films with lower polymer concentration were difficult to remove from the teflon plates. The films cast on teflon plates were easy to separate from the teflon plate surface compared to those on glass plates. Films formulated using both EPO and PVA were successfully formed on both glass and teflon plates. The films formed using only EPO as the film-forming polymer were better films, but there was a little difficulty in separating these films from glass plates. The films formed using both EPO and HPMC were not satisfactory since they were brittle, hazy in appearance, and did not form well on the glass plate.

The thickness of the formulations varied because the polymer concentration differed in almost all the formulations. The polymers were chosen to ensure that the film would not be damaged during handling; therefore, the strength of each film strip was directly dependent on the polymer type, and concentration.[22] However, there was also a need to strike a balance between film durability, and disintegration of the film into the oral or buccal cavity, which was successfully accomplished by ensuring that the polymer % w/w of the oral film strip's dry weight. Other studies have shown success with polymers entailing 45% w/w of the film strip's dry weight.[23] The thickness of the films was varying due to the polymer concentration, which has a direct impact on film thickness.

The percent standard deviation in each film was between 0 and 10%. This could be because of lower sensitivity of the screw gauge (0.01 mm) and due to the teflon plates not having an ideal, flat surface; alternatively, the slant surface of trays in the hot air oven where the plates were kept for drying could have contributed to the standard deviation.

The films prepared using EPO had good tensile strength but was slightly lesser than the films prepared by the combination of EPO and HPMC E5 LV. However, as the films were clearer and transparent with good disintegration time compared to the third set formulation, these were selected as the second

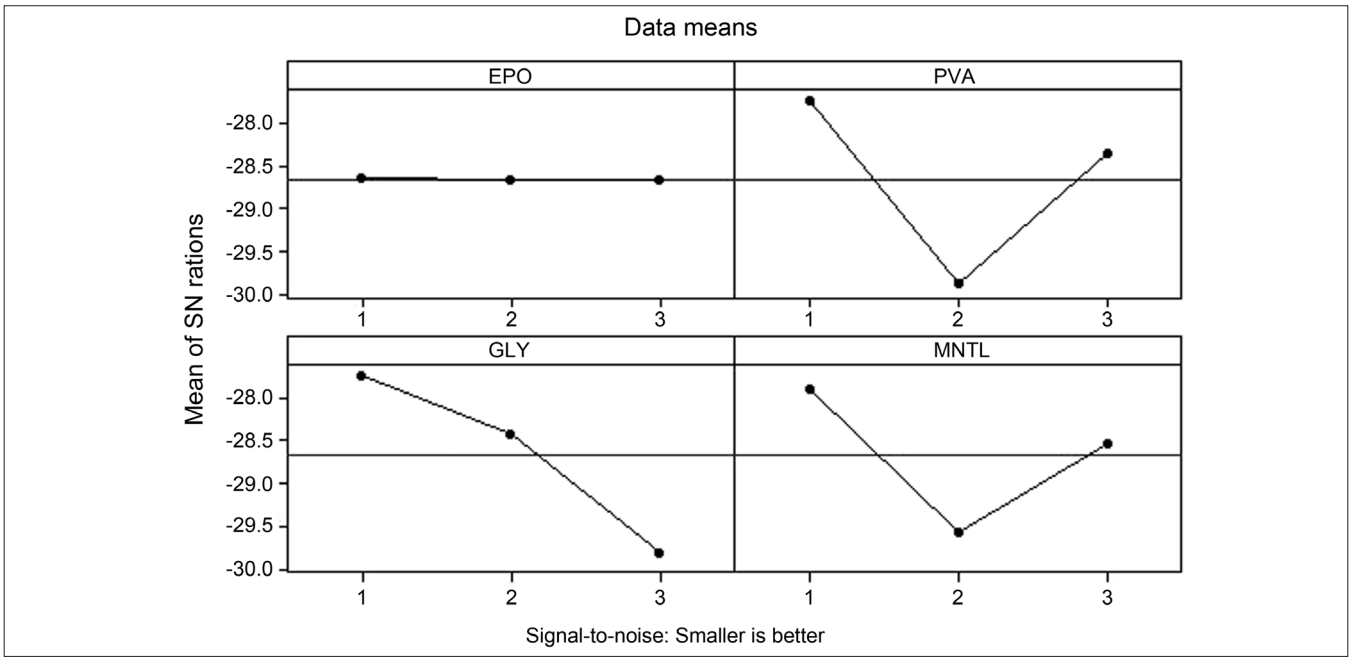

Figure 4: Main effects plot for SN ratios

best formulations after the films prepared by the combination of EPO and PVA. As Eudragit® concentration decreased, the percent elongation also decreased. Percent elongation of the film changes with the change in concentration of mannitol; as mannitol concentration increased. The crystalline nature of the film increased, thereby making the film more brittle.

Taguchi analysis was used to rank the experimental conditions based on S/N ratios [Figure 4]. 'Lower the better' parameter was assigned to determine the influence of the plasticizer and other factors on disintegration time. Based on analysis of the obtained data, concentrations of PVA, plasticizer, mannitol, and EPO were given first, second, third, and fourth rank respectively. Since PVA is a highly water-soluble polymer, it was chosen to be the most important factor for influencing DT. Though the concentration of EPO chosen was the least effecting factor based on DT, its concentration has more influence on the formation of film. Other studies have also shown that EPO, which has taste masking properties to prevent a negative impact on patient compliance, is a major parameter while making an oral formulation.[24,25] Among all the formulations, the second batch consisting of EPO and PVA, EP7, EP6 and EP5 were the best, but the percentage release of combination of polymer films were less compared to films formed using only EPO. The third set of films formed using combination of EPO and HPMC were not satisfactory. The films formed using PG, PEG as plasticizers were clear and transparent, but their consistency was not satisfactory since they were elastic. The combination of EPO, HPMC and DBP took long periods to disintegrate compared to all other film formulations. The films casted with plasticizers other than glycerin were not showing much deviation in the percent release compare to formulations where glycerin was used as plasticizer.

The development of oral formulation is important for controlled drug release, patient compliance, oral drug delivery through oral films provides ease, precision, and is useful for pediatric, and geriatric patients as well as those with dysphagia. Modulating the type of polymers used to build the strip.

CONCLUSIONS

LCTZ oral disintegrating films were successfully prepared by the solvent casting method using the following polymers: Eudragit® EPO, PVA and HPMC E5 LV. The prepared formulations were evaluated for weight variation, content uniformity, thickness, tensile strength, percent elongation, *in vitro* disintegration time and percent drug released. Among all formulations, films prepared using Eudragit® EPO and PVA showed best results. Oral disintegrating films prepared using Eudragit® EPO and PVA would be promising oral delivery systems for LCTZ for quick relief from allergic rhinitis.

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