Research Article

FORMULATION DEVELOPMENT OF FAST RELEASING ORAL THIN FILMS OF LEVOCETRIZINE DIHYDROCHLORIDE WITH EUDRAGIT EPO AND OPTIMISATION THROUGH TAGUCHI ORTHOGONAL EXPERIMENTAL DESIGN

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ABSTRACT

The aim of present research was to develop a fast releasing oral polymeric film, with good mechanical properties, instant disintegration and dissolution, producing an acceptable taste when placed on tongue. Solvent casting method was used to prepare oral films. Levocetirizine dihydrochloride, an antihistaminic was the drug incorporated to relieve the symptoms of allergic rhinitis. The polymers selected were Eudragit EPO, HPMC E 5 LV and PVA. Glycerin, dibutyl phthalate, propylene glycol and PEG 400 were the plasticizers used. Four batches of films with drug were prepared using different combinations of polymers and 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 trail was taken and Taguchi OA experimental design was applied to optimize type of polymers, concentration of polymers, plasticizer, and sweetener based on their disintegration data at their three different levels. The optimized films which disintegrated in less than 30 sec, releasing 70-90% of drug within 2 minutes. The percentage release was varying with type of polymer and concentration of polymer. The films made with EPO released 96 % of drug in 2 min, which was the best release amongst all.

Keywords: Levocetirizine dihydrochloride, Eudragit, plasticizer, oral films, disintegration time.

INTRODUCTION

Currently there is a high level of interest in the use of 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 route, the parenteral and other alternative routes of drug administration.

Oral thin films are postage stamp sized rectangular shape polymeric films which instantaneously disintegrates and dissolves and when placed on tongue within seconds. 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 convenience of dosing and portability of OS have led to wider acceptability of this dosage form by pediatric as well as geriatric population equally. The advantages over other oral dosage like, the larger surface area, high precision in dose administration compare to liquid orals, high level of patient compliance and quicker relief made an oral film a better option[1].

Patient compliance is very important aspect when considering a formulation of NDDS. One of such novel technologies is oral thin film. This dosage form provides a convenient means of administration of drugs. As the dosage form releases the drug instantly, this dosage form can be formulated for those drugs to treat diseases where a quick relief from symptoms is needed, like pain, allergies, sleep disturbances, anxiety, gastric problems, and as a stimulant etc.

Allergic rhinitis is one of the diseases where a quick relief from the symptoms is needed. Levocetirizine dihydrochloride is an orally active and selective H1-receptor antagonist used to treat seasonal allergic rhinitis, perennial allergic rhinitis, and chronic utricaria[2]. Levocetirizine dihydrochloride is a white, crystalline water-soluble drug with a bitter taste[3]. As the drug is intensely bitter in taste, the dosage form should be taste masked to give better patient compliance[4].

Pediatric, geriatric population, dysphasic patients, patients of allergic rhinitis who also suffer from sore throat, where the problem of difficulty in swallowing the tablet dosage arises and the precision of dose administered is less in taking the liquid orals. The oral thin films are the best dosage forms for this type of populations.

All these symptoms related to allergy need quick relief so the drug should be released in a faster manner so that it can be absorbed readily into systemic circulation. Unlike the tablet dosage form the disintegration and dissolution of oral films, are not the rate limiting steps for absorption. It disintegrates and releases the drug immediately and relieves from the symptoms quickly[5].

Having lots of advantages over conventional tablets the oral films of levocetirizine dihydrochloride are better formulations.

The objective of the study was to prepare fast dissolving oral films of levocetirizine dihydrochloride. The films were prepared by optimizing the polymer combinations and their concentrations using Taguchi OA experimental design 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

Levocetirizine dihydrochloride (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). Poly vinyl alcohol (PVA), Hydroxy Propyl Methyl Cellulose – E 15 LV, Potassium di hydrogen phosphate, Di sodium hydrogen phosphate, Tween 20, propylene glycol, glycerol, dibutyl phthalate, poly ethylene glycol - 400, mannitol, aspartame and hydrochloric acid (HCl) were purchased from S.D. fine Chemicals Ltd.(India), all the chemicals used were of analytical grade. Distilled water was used whenever required.

Methods

Levocetirizine dihydrochloride fast dissolving films were prepared by 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 casted on glass plates and dried in an oven at 40 ^{0}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. The further study was done in four batches with drug using different combinations of polymers and plasticizers. The amount of drug added was calculated based on area of plates so that each dosage (4*4 cm^2 area) consists of 5 mg of levocetirizine dihydrochloride[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 = 35.325mg
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. First the EPO was dissolved in 5 ml of 0.1 N HCl with continuous stirring. Then drug, mannitol and aspartame were added subsequently. As plasticizer is in a liquid form it was added to the above solution, by tarring weight of beaker with solution on weighing balance and then required amount of glycerin was added. The resultant solution was stirred for 15 minutes to produce a clear solution. This solution was kept aside for some time to get bubble free solution. These solutions were casted slowly and with a continuous flow on a glass plate of diameter 6 cm to avoid bubble formation and the plates were kept in 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 effect of different parameters on the mean and variance of the process performance 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 and their levels at which they are most likely to affect the process. Unlike factorial design where all the possible combinations are being tested, taguchi employs only few numbers of trials by testing pairs of combinations. This saves both 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 employed to carry out taguchi design.

Array selector

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

From the array selector L^9 orthogonal array was selected and the sequence of carrying out the experimental runs was altered to prevent any bias, conscious or unconscious. The nine experiments are listed in Table 3.

All the ingredients were weighed accurately 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 it was stirred for about 15-20 mins. The remaining procedure was carried out in the similar way as the films prepared by using Eudragit EPO alone.

Preparation of films using Eudragit EPO and HPMC E5LV

All the ingredients were weighed accurately according to Table 5. First the EPO was dissolved in 5 ml of 0.1 N HCl with continuous stirring. Then HPMC was added to the above solution and it was stirred for about 15-20 minutes. The remaining procedure was carried out in the similar way as the films prepared by 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 done with the glycerin, but by using different plasticizers other than glycerin as in the Table 6. Different plasticizers used were polyethylene glycol 400, propylene glycol and dibutyl phthalate. As the dibutyl phthalate is non aqueous in nature, a little amount of tween 20, almost 2 drops was added in the formulations where ever this plasticizer was used.

Table 1: Preparation of Levocetirizine films using Eudragit EPO

No.of runs	Trial code	LCTZ (mg)	Eudragit EPO (%)	Eudragit EPO (mg)	Glycerin (mg)	Mannitol (mg)	Aspartame (mg)
1	E1	36	4%	200	50	0	0
2	E2	36	5%	250	50	0	0
3	E3	36	6%	300	50	0	0
4	E4	36	4%	200	50	30	0
5	E5	36	5%	250	50	30	0
6	E6	36	6%	300	50	30	0
7	E7	36	4%	200	50	30	30
8	E8	36	5%	250	50	30	30
9	E9	36	6%	300	50	30	30

NOTE: All the ingredients were dissolved in 5 ml 0.1N HCl

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

NOTE: The percentages were calculated for 5 ml of solvent i.e. 0.1 N HCl.

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

NOTE: Here 1, 2 and 3 are lower, medium and higher levels respectively for the factors used.

Table 4: Preparation of films using combination of Eudragit EPO and PVA

No. of runs	Trial code	LCTZ (mg)	Eudragit EPO (mg)	PVA (mg)	Glycerin (mg)	Mannitol (mg)	Aspartame (mg)
1	EP1	36	100	50	50	20	25
2	EP2	36	200	50	150	30	25
3	EP3	36	150	100	150	20	25
4	EP4	36	150	50	100	40	25
5	EP5	36	200	100	50	40	25
6	EP6	36	150	150	50	30	25
7	EP7	36	200	150	100	20	25
8	EP8	36	100	150	150	40	25
9	EP9	36	100	100	100	30	25

Note: All the ingredients were dissolved in 0.1N HCl

Table 5: Preparation of oral films using combination of Eudragit EPO and HPMC E 5 LV

No. of runs	Trial code	LCTZ (mg)	Eudragit EPO (mg)	HPMC (mg)	Glycerin (mg)	Mannitol (mg)	Aspartame (mg)
1	EH1	36	100	50	50	20	25
2	EH2	36	200	50	150	30	25
3	EH3	36	150	100	150	20	25
4	EH4	36	150	50	100	40	25
5	EH5	36	200	100	50	40	25
6	EH6	36	150	150	50	30	25
7	EH7	36	200	150	100	20	25
8	EH8	36	100	150	150	40	25
9	EH9	36	100	100	100	30	25

NOTE: All the ingredients were dissolved in 0.1N HCl

Table 6: Formulation of oral films using different plasticizers

No. of Runs	Trail Code	EPO (mg)	PVA (mg)	HPMC (mg)	Glycerin (mg)	PEG (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

NOTE: CTZ 36 mg, Aspartame 25 mg and mannitol 25 mg are common for all preparations. All the ingredients were dissolved in 0.1N HCl solution.

Characterization of levocetrizine dihydrochloride oral films

Weight variation

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

Thickness

The film thickness was measured by using micrometer screw gauge at five points (center and four corners) on the film to make sure that the film thickness is uniform throughout. From the five points mean thickness was calculated. Samples with air bubbles, nicks or tears and having mean thickness variations of greater than 5% were excluded from analysis.

Assay

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

Content uniformity

The content uniformity test was used to ensure that every film contains the amount of drug substance intended with little variation among films within a patch. From the whole patch 3 pieces were cut, each of 1 cm^2 (1 cm*1 cm) and assayed for its drug content[8].

Folding endurance

Folding endurance of the film was determined repeatedly by folding a small strip of film (2 cm x 2 cm) at the same place until it broke. The number of times 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. A small patch strip (2 cm x 1 cm) was cut on a glass plate with a sharp blade. One end of the film strip was fixed between adhesive tapes to give support to the film when placed in the film 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 the small pan attached to the other end to hold the weights. A small pointer was attached to the thread, which traveled over the graph paper affixed on

the base plate. To determine the tensile strength, the film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force until the patch was broken. The elongation was determined by noting the distance traveled by the pointer on the graph paper before the breaking of the patch. The weight required to break the patch was noted as break force. This study was conducted to the optimized film formulations only. Tensile strength was calculated using the following formula[11,12].

$$\text{Tenile strength} = \frac{\text{Break Force}}{ab\left(1+\frac{\Delta L}{L}\right)}$$

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 for the optimized film formulations only[14,15].

% Elongation at break was calculated using the following formula:

% Elongation at break = $I_B - I_O / I_O$ x 100

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 it was placed in a petriplate containing 1 ml of water, after complete wetting of the film, the pH at the surface of film was checked by using pH paper[17].

***In vitro* disintegration**

Two simple methods were used where a small amount of 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 to make a hole through the film was measured as disintegration time (DT). In the second method 2 ml of water was taken in a petri plate and a film was placed on the surface of water and time taken for disintegration of the film was measured as disintegration time. This test was done in triplicates and average value was taken as DT[18].

***In vitro* dissolution**

According to previous studies, the 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-o8L) was used for the study. 900 ml of phosphate buffer pH 6.8 was used as media, which is a prescribed media for levocetirizine dihydrochloride according to Indian pharmacopoeia, the media was maintained at 37 ± 5°C, and basket was set at 100 rpm. A film sample of 4 cm^2 (2 cm*2 cm) was cut and taken into the basket. 5 ml of samples were taken for every 2 min, and the same amount was replaced with fresh buffer. The withdrawn samples were filtered and analyzed by using spectrophotometer at a wavelength of 230 nm. The percentage release was calculated from previously assayed values of the patch. Time vs percentage release plots were drawn to know where maximum amount of drug is released. Dissolution studies were conducted for optimized formulations[19,20].

RESULTS

Preparation of oral films of levocetirizine dihydrochloride

Films of levocetirizine dihydrochloride were successfully prepared by gradual increase in the concentration of the polymers in four different batches using EPO, combination of EPO and PVA, combination of EPO and HPMC and using different plasticizers.

Evaluation of the prepared oral films

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 - 102 %. This shows the dose 5 mg was available and nearly maintained to that of theoretical value.

Folding endurance

Among all the formulations EP7, EP6, EP5 were the best. They were showing a folding endurance of above 300. The formulations prepared using EPO alone had shown folding endurance of about 300. The formulations prepared using combination of HPMC and EPO were little brittle compare to above two. When the films were folded above 200 times there were formation of clear distinct strain marks on the film, and film started tearing.

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.

From the Taguchi experimental design the Signal to noise (S/N) ratios were calculated and given in Table 7. The software has assigned ranks based on S/N ratios. Lower the rank assigned more the influence of the factor on response, i.e. disintegration time (DT). The concentration of PVA was given the first rank, the concentration of plasticizer got second rank, concentration of mannitol and concentration of EPO got the subsequent ranks as given in Table 8. Main effects plot for SN ratios were shown in Figure 1.

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

Table 8: Response table for signal to noise ratios, smaller is better.

LEVEL	EPO	PVA	GLY	MNTL
1	-28.65	-27.74	-27.74	-27.89
2	-28.67	-29.89	-28.43	-29.58
3	-28.68	-28.36	-29.83	-28.53
DELTA	0.03	2.15	2.09	1.68
RANK	4	1	2	3

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 for the first set of films was about 19-20%, second set of films was 17-19 %, third set of films were around 18%, almost all formulations in the third set showed similar percent elongation. The variations in the percentage elongation of films with glycerin were more compared with the results obtained with other plasticizers. Invitro evaluation results of levocetirizine films using EPO, EPO and PVA, EPO and HPMC and different plasticizers were given in Table 9, Table 10, Table 11 and Table 12 respectively.

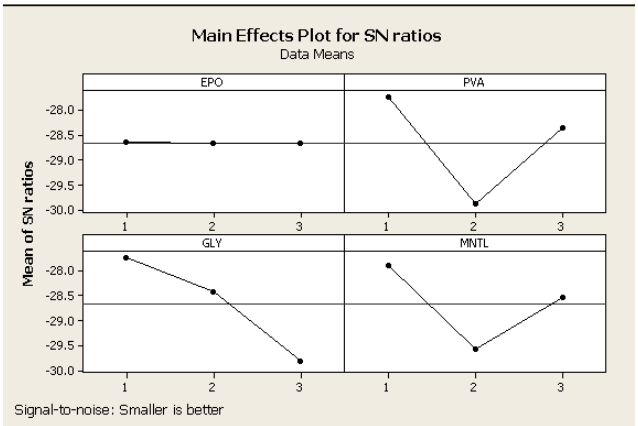

Figure 1: Main effects plot for SN ratios

Table 9: *Invitro* evaluation parameters of levocetirizine films using EPO**.**

Formulation code	Disintegration time Mean ± std dev.	Weight Mean ± Std dev	Thickness Mean ± Std dev	Content uniformity 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

NOTE: Mean – Average of three films; Std. dev – Standard deviation

Table 10: *Invitro* evaluation parameters of levocetirizine oral films using EPO and PVA

Formulation code	Weight Mean ± Std dev.	Content uniformity Mean ± Std dev.	Thickness Mean ± Std dev	Disintegration time Mean ± Std dev.
EP1	39.33±1.53	4.88±0.21	68±4.47	20.0±1.0
EP2	69.0±3.0	5.01±0.07	74±5.47	33.67±0.58
EP3	65.33±2.51	5.01±0.10	82±4.47	29.0±6.08
EP4	57.33±2.51	4.88±0.10	78±4.47	23.33±1.53
EP5	61.33±2.51	4.99±0.08	126±5.47	32.67±1.52
EP6	60.66±3.21	4.97±0.14	128±4.47	26.0±3.60
EP7	74.66±2.51	4.92±0.07	136±5.47	31.0±1.0
EP8	70.66±1.53	4.96±0.05	82±4.47	27.67±1.15
EP9	55.33±2.52	4.92±0.11	74±5.47	23.33±0.57

Table 11: *Invitro* evaluation parameters of levocetirizine films using EPO and HPMC

Formulation code	Weight Mean ± Std dev.	Content uniformity Mean ± Std dev	Invitro disintegration Mean ± Std dev	Thickness Mean ± Std dev.
EH1	39.33±3.51	4.68±0.05	25.66±2.51	84±5.48
EH2	69.33±2.51	4.94±0.03	35.61±3.05	72±4.48
EH3	66.33±2.08	4.89±0.03	34.0±2.64	76±8.95
EH4	57.0±2.0	4.99±0.06	33.33±1.52	86±8.95
EH5	63.0±2.64	4.80±0.10	34.33±1.15	130±0
EH6	62.66±3.05	4.86±0.14	38.33±1.15	130±7.07
EH7	72.33±2.31	4.87±0.06	41.33±1.53	124±5.48
EH8	69.33±1.53	4.89±0.09	34.33±1.15	84±5.48
EH9	54.0±2.64	4.95±0.01	26.33±1.15	72±4.48

Table 12: *Invitro* evaluation parameters of levocetirizine films using different plasticizers

Formulation code	Weight Mean ± Std dev	Content uniformity Mean ± Std dev	Thickness Mean ± Std dev	Disintegration time 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

Table 13: Percent drug release profiles (dissolution) of optimized formulations

Time (mins)	E9	E7	E6	EP5	EP6	EP7	EH5	EH6	EH7
2	96.12	93.71	90.33	91.30	88.40	87.44	71.03	70.06	74.89
4	97.62	95.68	92.76	94.22	93.24	92.27	73.84	81.55	76.76
6	98.16	97.178	94.73	94.74	96.17	96.15	80.52	83.45	80.56
8	100.15	98.67	97.18	97.67	96.69	98.61	82.89	88.25	83.89
10	100.21	99.21	99.16	99.18	99.64	100.12	86.24	94.05	87.25
12	101.72	101.20	101.63	100.19	100.66	100.66	95.88	97.94	95.45
14	103.24	103.19	102.66	102.19	102.17	102.17	98.33	101.85	98.86
16	103.8	103.75	102.73	102.26	102.72	103.69	100.79	101.91	102.29

In vitro release studies of optimized levocetirizine dihydrochloride oral films

Based on the preliminary exclusions, visual inspection and disintegration time, twelve best films were selected for dissolution study and the results were shown in Table 13. The films formed using only EPO were releasing above 90% of the drug within 2 minutes as shown in Figure 2. The films formed using combination of EPO and PVA were able to release nearly 90% of drug in 2 minutes as shown in Figure 3, but the percentage release was lesser compare to films formed using only EPO. The films formed using combination of EPO and HPMC were able to release about 70% of drug in 2 minutes as shown in figure 4. The films casted with different plasticizers instead of glycerin were not showing much deviation in the percent release compare to formulations where glycerin was used as plasticizer.

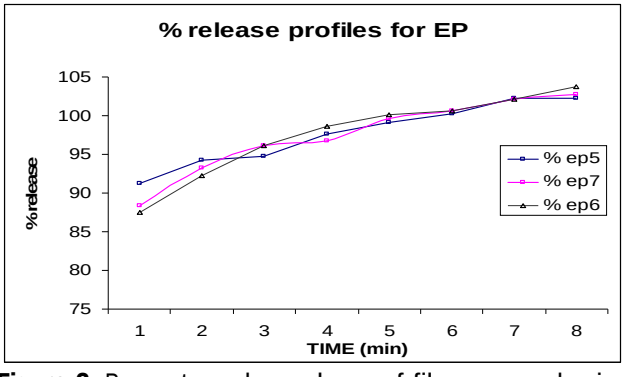

Figure 2: Percentage drug release of film prepared using EPO polymer

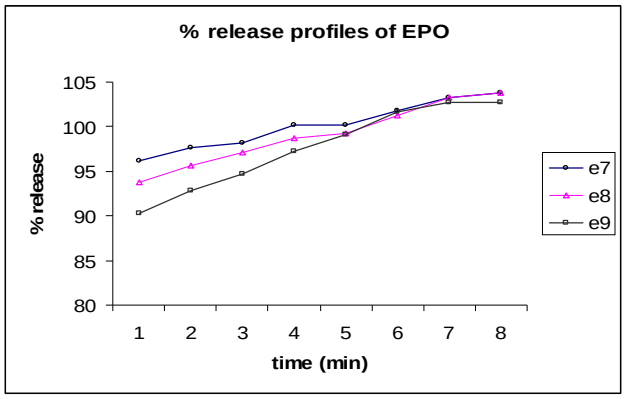

Figure 3: Percentage drug release from the film prepared using EPO and PVA

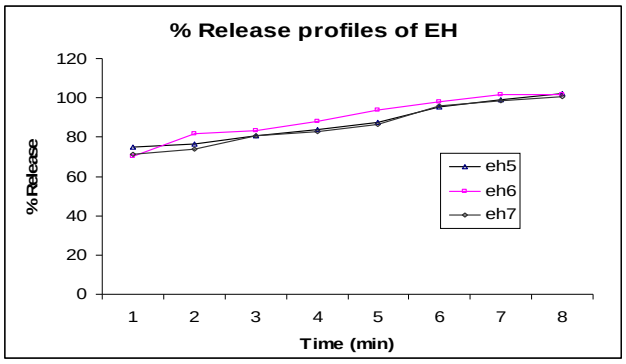

Figure 4: Percentage drug release from the film prepared using both EPO and HPMC

DISCUSSION

Oral disintegrating films were prepared by solvent casting technique using different polymers like Eudragit EPO, PVA, and HPMC E5 LV. The films with lower polymer concentration showed difficulty in removal from plates. The films casted on teflon plates were producing good films and they were very easy to separate from the plate surface compared to that on glass plates. Films formulated using combination of EPO and PVA were successfully formed in both glass and teflon plates. The films formed using only EPO as film forming polymer were good, but there was a little difficulty in separation of film from glass plates. The films formed using combination of EPO and HPMC were not satisfactory. They were brittle, hazy in appearance the film was not forming in glass plate.

The thickness of formulations varied because the polymer concentration was varied in almost all the formulations. As the polymer concentration has direct impact on film thickness, accordingly the thickness was varying. The percent standard deviation in each film was varying from 0-10%. This could be because of lower sensitivity of screw gauge (0.01 mm) and also due to the teflon plates not having ideal flat surface or due to slant surface of trays in hot air oven where the plates were kept for drying.

The films prepared by using EPO had good tensile strength but slightly lesser than the films prepared by the combination of EPO and HPMC E5 LV. But as the films were more clear and transparent with good disintegration time than third set formulation, these were selected as second best formulations next to the films prepared by the combination of EPO and PVA. As Eudragit concentration decreases the percent elongation decreased. Percent elongation of the film changes with the change in concentration of mannitol, as mannitol concentration increases crystallinity of the film increased which makes film more brittle.

From the Taguchi experimental design the S/N ratios were calculated. The software has assigned ranks based on S/N ratios. 'Lower the better' parameter was assigned to find out the influence of the factor on response, i.e. 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. PVA was the highly water soluble polymer, that is why it was chosen as most affecting factor for influencing DT. Though the concentration of EPO was chosen as least effecting factor based on DT, its concentration has more influence on formation of film and the researches have been proven that EPO is having taste masking property, which is a major parameter while making an oral formulation.

Among all the formulations second batch of formulations consisting of EPO and PVA, EP7, EP6 and EP5 were the best, but the percentage release was lesser compare 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 very clear and transparent, but their film consistency was not good. They were very elastic. Combination of EPO, HPMC and DBP took long period to disintegrate compare to all film formulations. The films casted with different plasticizers instead of glycerin were not showing much deviation in the percent release compare to formulations where glycerin was used as plasticizer.

CONCLUSION

Levocetirizine dihydrochloride oral disintegrating films were successfully prepared by solvent casting method using different polymers like Eudragit EPO, PVA, and HPMC E5 LV and evaluated for weight variation, content uniformity, thickness, tensile strength, percent elongation, *Invitro* disintegration time and % drug released. Among all formulations films prepared by using eudragit EPO and PVA showed best results. Oral disintegrating films prepared by using eudragit EPO and PVA would be promising oral delivery systems for Levocetirizine dihydrochloride for quick relief from allergic rhinitis.

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