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Formulation and evaluation of rapidly disintegrating film of Levocetrizine Hydrochloride

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Abstract

In the present study fast dissolving film of levocetrizine hydrochloride was prepared using sodium alginate as film forming polymer. To decrease the disintegration time of formulations sodium starch glycolate was used as disintegrating agent. A full 3^2 factorial design was applied using concentration of polymer and disintegrant as independent variable and disintegration time and % cumulative drug release as dependent variable. Response surface curves were plotted. Batch F_6 was found to be the optimized batch as its disintegration was completed within the minimum time as compared to all other batches. The formulation (F_6) was also showing sufficient drug release after 6 min. All the nine formulation was showing approximately 70-85% drug release after 6 min.

Keywords: Levocetrizine hydrochloride, fast dissolving film, response surface plot, sodium alginate.

INTRODUCTION

The earliest developed fast dissolving technology existed in the tablet form and the rapid disintegrating properties resulted from special process or formulation modifications. Fast dissolving films are gaining popularity as an alternative to fast dissolving tablets as they eliminates patient's fear of chocking and overcome patient impediments. Fast dissolving films generally consists of plasticized hydrocolloids or blends which can be laminated by using techniques such as hot-melt extrusion and solvent casting. Additionally they also provide easy delivery of drug under emetic condition. Mouth dissolving films, are the new drug delivery system for delivery of drugs through oral cavity and was developed on the basis of technology of the transdermal patch. The delivery system consists of a very thin oral strip, which when placed on the patient's tongue or any oral mucosal tissue gets instantly wet by saliva and rapidly hydrates and adheres onto the site of application. Film then rapidly disintegrates and dissolves to

release the medication for absorption through oromucosal route or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. In contrast to other existing, rapid dissolving dosage forms, which consist of liophylisates, the rapid films can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets [1].

Levocetrizine hydrochloride is a third-generation non-sedative antihistamine, developed from the second-generation antihistamine cetirizine. Chemically it is the L-enantiomer of the cetirizine racemate. Levocetrizine hydrochloride works by blocking histamine receptors. It does not prevent the actual release of histamine from mast cells, but prevents it binding to its receptors. Thus it prevents the release of other allergy chemicals and increased blood supply to the area, and provides relief from the typical symptoms of hay fever [2]. The dose of levocetrizine hydrochloride is 5 mg, which is low enough to be formulated as mouth dissolving tablets.

Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of D-mannuronic acid and L-guluronic acid. Sodium alginate is used in a variety of oral and topical pharmaceutical formulations. In tablet formulations, sodium alginate may be used as both a binder and disintegrant. Sodium alginate is a hygroscopic material, so it will facilitate the water absorption when placed in oral cavity and this will cause faster disintegration of films. [3]

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. [4]

Glycerin is used in a wide variety of pharmaceutical formulations including oral, ophthalmic, topical, and parenteral preparations. It is also frequently used as a plasticizer in film coatings and preparation of soft gelatin capsules. [5]

MATERIALS AND METHODS

Levocetrizine hydrochloride was obtained as a gift sample from Unicure pharma Ltd., Roorkee (India). Sodium alginate, Sodium Starch Glycolate and glycerine were purchased from Central Drug House New Delhi. All other chemicals and reagent were of analytical grade.

Formulation of films

For formulating the film sodium alginate was dissolved in distilled water. Levocetrizine hydrochloride and sodium starch glycolate was added to the polymer solution. When the entire solid material was dissolved in the water, required amount of plasticizer (glycerol) was added to the solution. The solution was then casted on the plastic films and dried in oven at 60 ^{0}C. Dried films were removed and stored in dessicator till further use [6].

Evaluation of films

Thickness: All the batches were evaluated for thickness by using calibrated digital micrometer (Mituotoyo Japan). Three readings from all the batches were taken and mean thickness was evaluated [7].

Table 1: Formulation of fast dissolving film

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sodium alginate (%)	1.25	1.25	1.25	1.5	1.5	1.5	1.75	1.75	1.75
Levocetrizine hydrochloride (mg)	100	100	100	100	100	100	100	100	100
SSG (%)	1.5	2	2.5	1.5	2	2.5	1.5	2	2.5
Glycerine (%)	20	20	20	20	20	20	20	20	20
Distilled water (ml)	20	20	20	20	20	20	20	20	20

Folding endurance: The folding endurance was measured manually for the prepared films. A strip of film was cut 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 value of folding endurance [8].

Drug content: Drug content of all nine batches was determined by UV-spectrophotometric method. For this 1x1 cm^2 strip from the each film was cut and dissolved in 10ml of simulated salivary fluid (pH 6.2). The solution was filtered and absorbance was recorded at 230.5 nm. Drug content was calculated by using standard curve of drug [7].

Uniformity of drug content: For determining the uniformity of drug content in the film at least three strips (1x1 cm^2) were cut from different section of the film and drug content was calculated for all three strips using the same procedure as above. The drug content of all three strips was compared. Same procedure was repeated for all the nine batches [7].

***In vitro* disintegration time**

In vitro disintegration time is determined visually in a glass dish of 25ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates [1].

***In-vitro* dissolution studies:** Dissolution study was carried out in USP basket type apparatus using the stimulated salivary fluid (pH 6.2) as a dissolution medium at 50 rotations per minute. 5ml aliquots were withdrawn at different time intervals and same amount of fresh dissolution medium was added. The aliquots were assayed for drug content at 230.5nm wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated.

RESULTS AND DISCUSSION

Fast dissolving films were prepared using sodium alginate as film forming polymer and sodium starch glycolate as disintegrating agent. The films were evaluated for various properties such as thickness, drug content etc. The result showed that all the films have a smooth surface and good folding endurance. Drug content of all the films was between 4.6 to 5.01mg. The results are shown in table 2. The results of weight and drug content uniformity test showed that the film was uniform and drug was also uniformly distributed in the films. Films were having thickness adequate for handling and use. The disintegration time of the films was evaluated using simulated salivary fluid (pH 6.2). Two times readings for each batch were recorded i.e. time at which disintegration started and time when the film completely disintegrates. The results indicates that disintegration of films initialized in about 30 sec and completes in 142-197 sec.

Batch F_3 and F_6 disintegrates most rapidly. The results of *in-vitro* dissolution of all batches are shown in figure 1.

Table 2: Evaluation of levocetrizine hydrochloride films

Batch	Thickness(mm)	Weight(mg)	Drug content	Disintegration time	
				Start	Complete
F_1	0.221	0.05	4.678	32	197
F_2	0.135	0.03	4.923	28	178
F_3	0.204	0.04	4.812	25	142
F_4	0.201	0.03	4.907	35	202
F_5	0.201	0.04	5.012	38	167
F_6	0.125	0.03	4.827	30	142
F_7	0.158	0.04	4.926	39	200
F_8	0.202	0.03	4.995	35	175
F_9	0.167	0.04	4.988	32	153

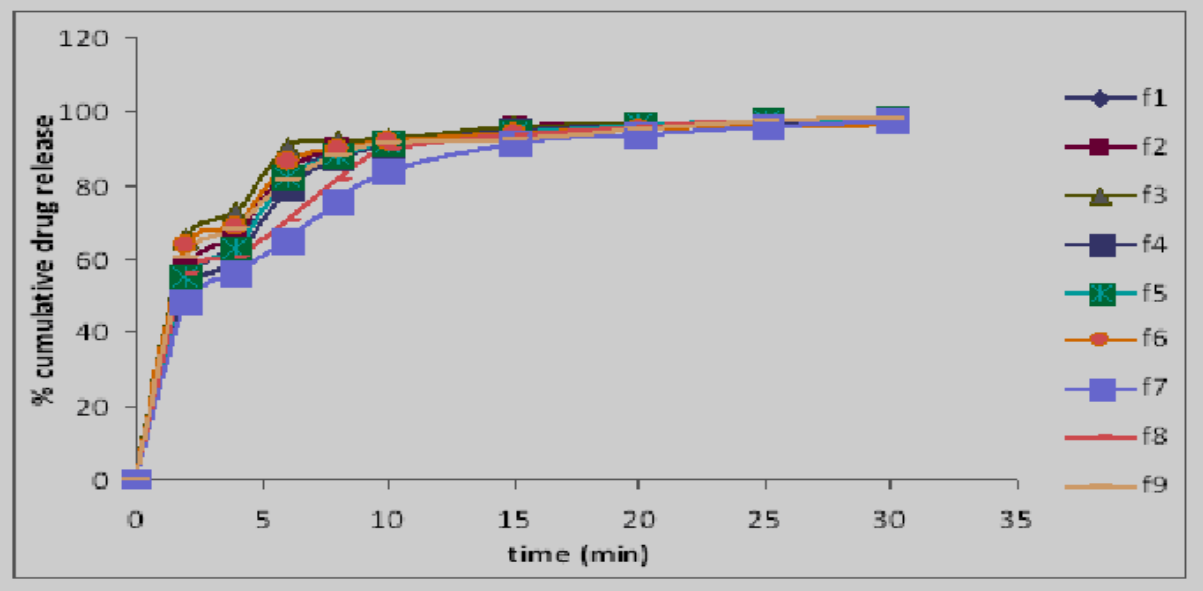

Fig 1: *In-vitro* dissolution studies of fast dissolving films

Table 3: Regression equation for each response variable determined by multiple regression analysis

S. No.	Independent variables	Regression coefficient	Y_1 (% cumulative drug released after 6 minutes	Y_2 (disintegration time)
1	b_0	-	80.1356	32.6667
2	b_1	X_1	-6.5667	3.5000
3	b_2	X_2	5.4683	-3.1667
4	b_{12}	X_1X_2	-	-
5	b_1b_2	X_1X_1	-	-
6	b_2b_2	X_2X_2	-	-

A full 3^2 factorial design was applied to study the effect of independent variables (conc. of sodium alginate and conc. of sodium starch glycolate) on the dependent variable (disintegration time and % cumulative drug release after 6 min). Various coefficients have been shown in table

3. Response surface plots were plotted which are shown in figure 2 & figure 3. Response surface plots showed that the % cumulative drug release after 6 minutes inversely proportional to the concentration of sodium alginate and directly proportional to concentration of sodium starch glycolate. The disintegration time is inversely proportional to concentration of SSG and directly proportional to concentration of sodium alginate.

Fig 2: Response surface curve for levocetrizine hydrochloride films after 6 minutes dissolution

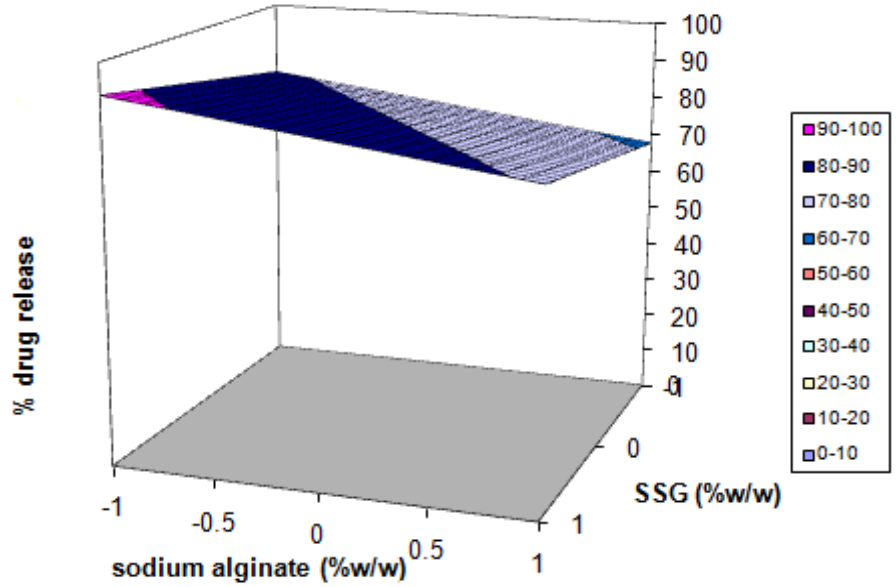

Fig 3: Response surface curve for films showing the time at which disintegration initialized

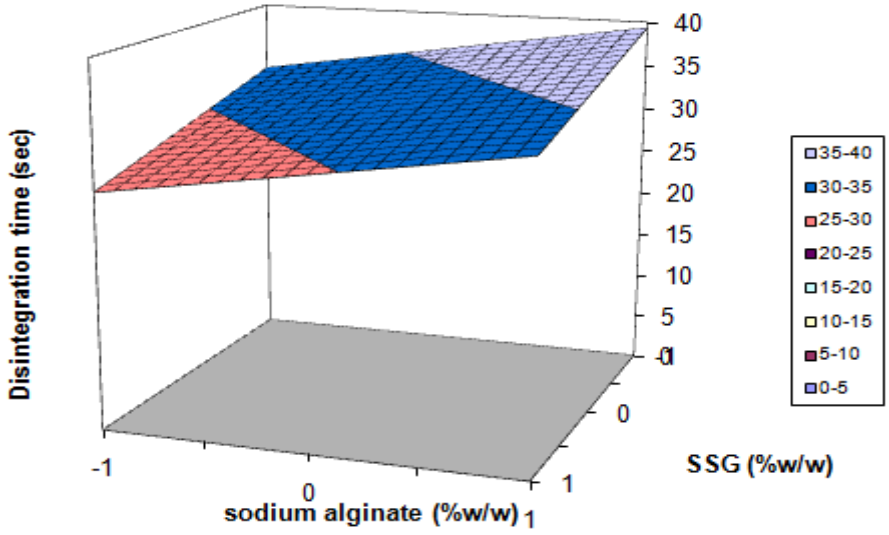

Table 4: Actual vs. Predicted response of various dependent variables

S.No.	Code	% cumulative drug release after 6 minutes		Disintegration time (Sec)	
		Actual	Predicted	Actual	Predicted
1	F1	81.45	80.12968	32	32.29165
2	F2	84.43	82.86383	28	30.7083
3	F3	90.4	85.59798	25	29.12495
4	F4	79.2	78.488	35	33.16665

5	F5	82.19	81.22215	38	31.5833
6	F6	86.67	83.9563	30	29.99995
7	F7	65.09	76.84633	39	34.04165
8	F8	70.31	79.58048	35	32.4583
9	F9	81.48	82.31463	32	30.87495

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