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FORMULATION AND EVALUATION OF QUICK DISSOLVING FILM OF LEVOCETIRIZINE DIHYDROCHLORIDE.

D R Choudhary*[1], V A Patel[2], H V Patel[1], A J Kundawala[1]
1. Indukaka Ipcowala College of Pharmacy, New V V Nagar-388121
2. A. R. College of Pharmacy, V V Nagar-388120
Email: dhaglaram@gmail.com

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Abstract

Quick dissolving films of levocetirizine dihydrochloride were prepared by solvent casting technique using carboxy methyl cellulose, hydroxy propyl cellulose, and hydroxy propyl methyl cellulose as film forming polymers. Neotame and citric acid were employed to mask the bitter taste of levocetirizine dihydrochloride. The prepared films were subjected to characterization for mechanical properties. Disintegration time, drug release pattern, mouth dissolving time and content uniformity were also evaluated. Compatibility between drug and recipients were studied by means of DSC analysis. Films with 3% hydroxyl propyl methyl cellulose and 10% w/v propylene glycol showed better results as compare to hydroxyl propyl cellulose and carboxy methyl cellulose. Films were transparent in appearance. Films showed good mechanical properties like, tensile strength (694 Kgf/cm^2), folding endurance (140) and % elongation (10.06) in comparison to other films prepared by using hydroxyl propyl cellulose and carboxy methyl cellulose. Films were disintegrated in time of 23 sec and dissolved in time of 55 sec. These results suggest that hydroxyl propyl methyl cellulose is an excellent film former which gives rapid drug release (80% in 120 sec) amongst different cellulose derivatives used to prepared films.

Key words: levocetirizine dihydrochloride, quick dissolving film, HPMC, solvent evaporation technique.

Introduction

Levocetirizine is a third-generation non-sedative antihistamine, developed from the second-generation antihistamine cetirizine. Chemically, levocetirizine is the active enantiomer of cetirizine. It is the L-enantiomer of the cetirizine racemate. Levocetirizine works by blocking histamine receptors. It does not prevent the actual release of histamine from mast cells, but prevents it binding to its receptors. This in turn prevents the release of other allergy chemicals and increased blood supply to the area, and provides relief from the typical symptoms of hayfever[1]. The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Solid dosage forms that can be disintegrated, dissolved, or suspended by saliva in the mouth resulting in easy swallowing can provide significant benefits to the pediatric and geriatric population, as well as other patients who prefer the convenience of easily swallowable dosage forms. These films disintegrate instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva[2-6]. In case of allergic or histaminic reaction a rapid action of the drug is required. The fast dissolving films fulfill all the requirements of potential solid dosage form for levocetrizine in treating allergic conditions[7]. Their characteristic benefits in terms of patient compliance, rapid on-set of action, increased bio-availability, (sometimes bi-pass first pass effect) and good stability make these films popular as a dosage form of choice[8-9].

Prepared films were subjected to different evaluations parameters like physical properties, disintegration time, content uniformity and dissolution studies.

Materials and Methods

Materials

Levocetirizine dihydrochloride and neotam were obtained from Alkem pharmaceutical Pvt Ltd. Mumbai. HPMC, CMC and HPC, and Propylene glycol (PG) and polyethylene Glycol 400 (PEG400) were purchased from Sigma chemicals. All other chemicals used were of analytical grade.

Selection of base material for preparation of quick dissolving films.

All three polymers (HPMC, HPC and CMC) were employed in a concentration range of 1-4% w/v to prepare QDF and plasticizer like: Propylene glycol (PG) and polyethylene glycol 400 (PEG400) were used in the range of 10-40% of polymer concentration.

Preparation of QDF

Polymers (HPMC, HPC and CMC) were soaked in half the quantity of water for 8 hours to get uniform dispersion. Plasticizers and levocetirizine were mixed in water. This solution was added to polymer containing solution and mixed well to obtain homogenous solution followed by addition of neotame and citric acid. Solution was then casted into petridishes having area of 64 cm^2 and 1.3 cm wall height. Petridishes were kept in hot air oven for 8 hours at 50˚ C. After drying films were removed with the help of sharp blade and kept in desicator for 24 hrs before cutting into small piece having area of 6 cm^2. Films with air bubbles, cuts or imperfections were excluded from study. Selected films were subjected for different evaluation parameters.

Differential Scanning Calorimetry (DSC)

The DSC thermograms of pure levocetirizine (2.720 mg), HPMC (2.891 mg) and HPMC: levocetirizine (1:1) (2.702 mg) was carried out using DSC-PYRIS-1 (Perkin-Elmer, USA). The samples were heated from 50 to 230 °C at a heating rate of 10 °C/min in an inert nitrogen atmosphere.

Evaluation Parameters

Appearance

All prepared films were checked for their appearances either they are transparent or opaque.

Weight Variation and Thickness

All batches were evaluated for its weight variation and thickness. Weight variation was evaluated by using electronic balance (Shimadzu corp. Japan. Type AX200) and thickness was measured using Digital Vernier Calipers.

Mechanical properties[10]

Mechanical properties like tensile strength, % elongation, elastic modulus and folding endurance were evaluated. Tensile strength was measured using Shimadzu AG-100kNG (Winsoft tensile and compression testing). The films of size 5×2 cm^2 and free of physical imperfections were placed between two clamps held 10 mm apart. The films were pulled by clamp at a rate of 5mm/min. whole experiment was carried out in triplicate.

Percentage elongation was calculated by measuring the increase in length of the film after tensile measurement by using the following formulae.

Percent Elongation = $[L-L_0]$ X 100 / L_0

Where L was the Final length and L_0 was initial length.

Elastic modulus is calculated by formula

$$Elastic\ \mathrm{modulus} = \frac{Foece\ at\ corresponding\ strain}{Cross\ \mathrm{sectional}\ area\ \left(mm^2\right)} \times \frac{1}{Corresponding\ strain}$$

Folding endurance was measured by folding the film at the same place repeatedly until a visible crack was observed. This gives an indication of brittleness of the film.

Morphology study

Morphology of the prepared films was observed under a scanning electron microscope (SEM) (ESEM TMP with EDAX, Philips, Holland) The sample was attached to the slab surface with double sided adhesive tapes and the scanning electron photomicrograph was taken at 500 x magnification.

Surface pH

The films were allowed to swell in closed petridish at room temperature for 30 minutes in 1 ml of distilled water. Solution was placed under digital pH meter (Elico, India) to determine the surface pH [11-12].

Drug content: Total drug content per film was estimated by random sampling of the F3, F7 and F11. Film of 6 cm^2 was cut and placed in 50 ml volumetric flask and dissolved in buffer (6.4). Than 1 ml solution was pipette out and diluted to 10 ml with water. The absorbance of the solution was measured at 210 nm.

Disintegration and Dissolution time

Disintegration time provides an indication about the disintegration characteristics and dissolution characteristics of the film. The require size of film (3×2 cm^2) was placed in a stainless steel wire mesh containing 25 ml of pH 6.4 buffer solution. Time taken by film to break and dissolve was measured as *in-vitro* disintegration time and *in-vitro* dissolution time.

Uniformity of drug content

The uniformity of drug content were carried out using 10 sized films of F3, F7 and F11 and the drug content of was determined by UV spectrophometer. The acceptance value (AV) of the preparation is less than 15%, according to the JP15. While in USP 27, the content of preparations are between 85% and 115% and the relative standard deviation is less than or equal to 6.0%. AV was calculated according to the following equation.

$AV= (M - X) + ks$

Where M is label claim (100%), X is the average (%) of individual contents, k is the acceptability constant (2.2), and s is the standard deviation.

***In-vitro* dissolution studies**

An in-vitro dissolution study for all the three batches F3, F7 and F11 was performed for five minutes in USP basket apparatus. Dissolution medium was kept at 37º C ± 0.5 º C and baskets were rotated at 500 rpm. The samples (5 ml) were withdrawn after every one minute and replaced with fresh buffer solution. One ml sample was then taken and diluted up to 10 ml in volumetric flask. The samples were analyzed for the drug content using UV-VIS spectrophotometer at 231 nm against reference using pH 6.4 buffers as blank.

Stability study

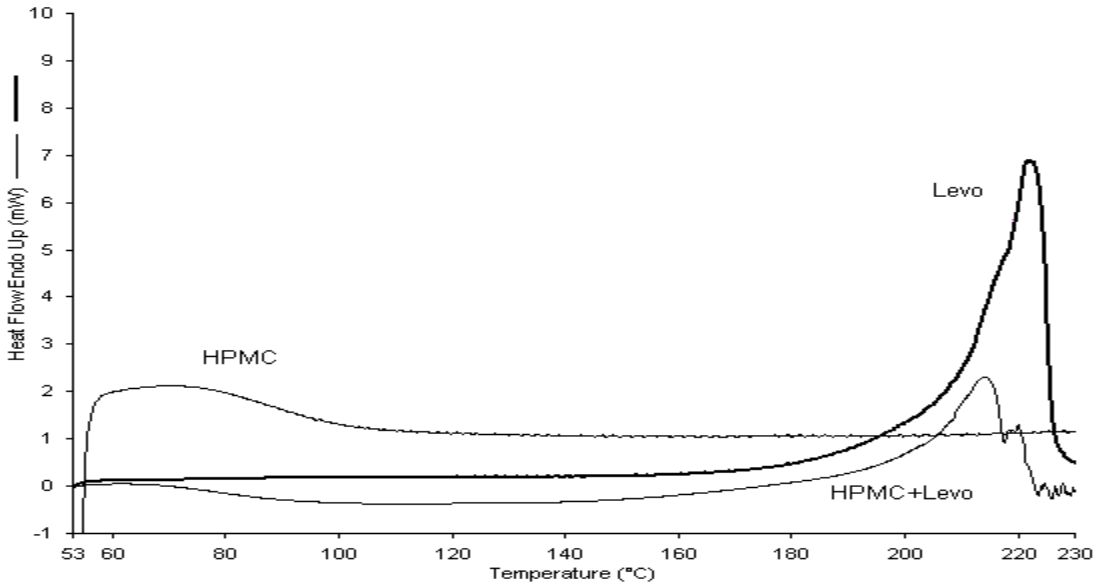
Short term accelerated stability studies of the selected formulation were carried out at 40˚C / 75 % RH (ICH guidelines) for a period of two months and drug content, folding endurance, taste and other parameters were evaluated at interval of one week

Result and discussion

Differential scanning calorimetry (DSC)

Differential Scanning Calorimeter (DSC) allows the fast evaluation of possible incompatibilities, because it shows changes in the appearance, Shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The results of DSC study are given in Figure 1, DSC thermo gram showed endothermic peak of levocetirizine at 221.7°C, which corresponded to its melting point. Thermo grams of drug loaded film of HPMC showed peak at 221°C itself. Placebo formulation (without drug) showed at 68°C. There was no change in the melting point of drug when prepared in the form of film. The evaluation of the thermo gram obtained from DSC revealed no interaction between the polymer and the drug in the film.

Figure-1: DSC curves.



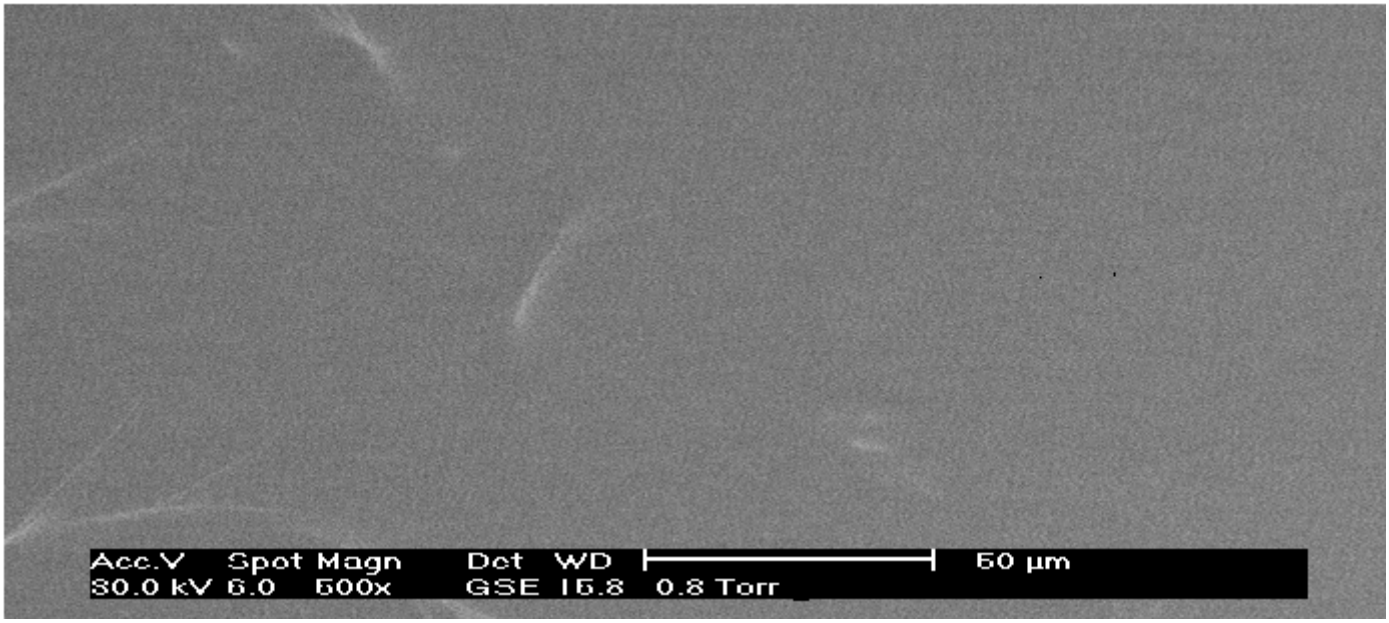
Cellulose derivatives are known for their good film forming properties and have excellent acceptability. Hence various cellulose derivatives namely HPMC, HPC and CMC were used as primary film former. Various trials were taken to formulate the quick dissolving films (QDF) where in all the polymers at different concentrations were assessed. Film containing HPMC were transparent where as HPC and CMC films were opaque in their appearance.

Films prepared with 1% polymer concentration with all three polymers (F1, F5, F9) as shown in table 2 were very thin (0.08-0.09 mm) with less disintegration time (8-9 sec) and tensile strength (124-356 Kgf/cm^2). Films

prepared with 4% w/v of all polymers (F4, F8, F12) were very thick (0.12-0.13 mm) with higher disintegrations time (43- 47 sec) so they were excluded from further studies. Films containing 3% of all polymers (F3, F7, and F11) showed better tensile strength (239-607 Kgf/cm^2) with satisfactory D.T. (23-27 sec) in comparesion to 2% polymer concentrations (F2, F6, and F10) tensile strength (209-463 Kgf/cm^2) and D.T. (13-15 sec). The film containing 10% of PG showed good results as compare to all other concentration of PG. Increase in PG concentration resulted in distorted and sticky films. However, PEG400 films became patchy with increased DT. Addition of plasticizer has shown significance difference in folding endurance and tensile strength.

The prepared film containing Levocetirizine was clear and colorless. The scanning electron photomicrograph of the film at 500 x magnification showed smooth surface with some pores and wrinkles without any scratches or transverse striations as shown in figure 2.

Figure-2: Sem Image of the formulation with HPMC and drug.



Neotame was varied from 4-8 mg per film, but 6 mg was found to be acceptable. Film with 4 and 5 mg Neotam tasted bitter and 7 and 8 mg were very sweet. Citric acid amount was also varied from 30-80 mg. Film with 50 mg Citric acid were selected. Since, increase in the amount of citric acid resulted in distortion of films.

As all batches do not have uniform amount of ingredients in it, hence their weight and thickness were varied. Films containing 1% polymer were found to have 52-55 mg weight and 0.08-0.09 mm thickness, film with 2%

were having 61-64 mg weight and 0.09-0.10 mm thickness, film with 3% polymer were exhibited 68-71 mg weight and 0.10-0.11mm thickness and films with 4% were having 74-77 mg weight and 0.11-0.13 mm thickness. Surface pH of all the films was found in the range of pH 3-5. Films containing 3% polymers (F3, F7, and F11) showed good mechanical properties like tensile strength (239-607 kgf/cm^2), % elongation (10.06-22.04), folding endurance (128-140) and disintegrating time (23-27 sec). Films with 3% polymer were evaluated for further studies, while all other were excluded.

Disintegration and dissolution time of selected formulations (F3, F7, and F11) were found to be 23, 25, 27 and 55, 61, 65 sec respectively. Dissolution studies revealed, as shown in figure 2, that film containing HPMC has release its 80% of drug in 120 seconds where as film having HPC and CMC release its 60% of drug in the same time period. Drug content of F3, F7, and F11 was found to be more than 95-%. The average amount of drug of sized films of F3 was 3.86 ± 0.16 mg and the values of drug content were ranging from 94.7% to 108.5%. The relative standard deviation was 5.1%. Thus, the preparation met the criteria of USP27 content uniformity. Moreover, AV was 11.8%, a value that was within the limit (15%) of uniformity of dosage units for JP15.

Stability studies were carry out as mention earlier, drug content of all the formulations were found to be within the range of 94-97% for 6 six weeks but from 7th week onwards crystals were appeared in film, there for drug content reduced to 91-94%.

Figure 3: Dissolution profile.

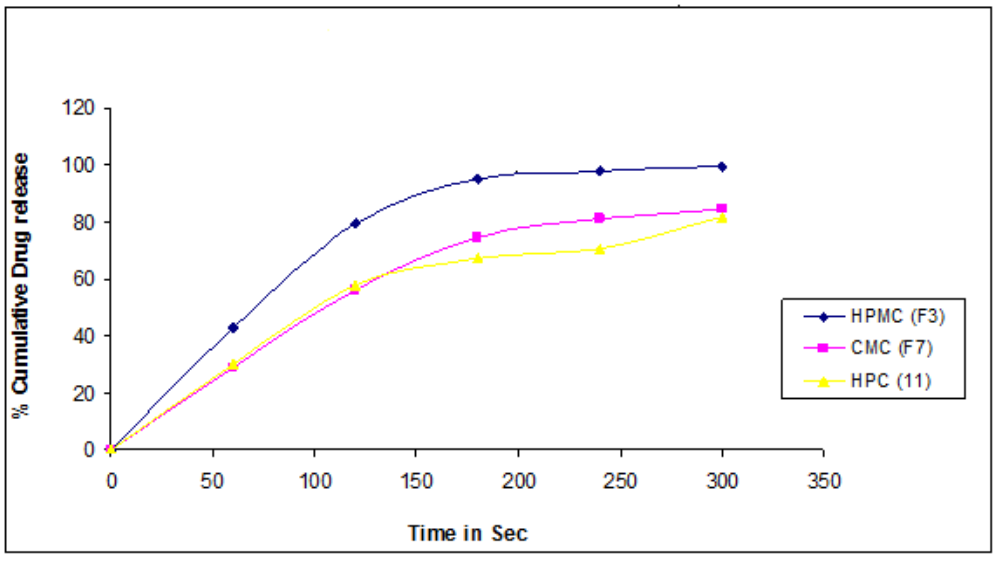


Table-1: Compositions of quick dissolving films.

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Levocetirizine (mg)	54	54	54	54	54	54	54	54	54	54	54	54
HPMC (mg)	250	500	750	1000	-	-	-	-	-	-	-	-
CMC (mg)	-	-	-	-	250	500	750	1000	-	-	-	-
HPC (mg)	-	-	-	-	-	-	-	-	250	500	750	1000
Propylene glycol (mg)	50	50	50	50	50	50	50	50	50	50	50	50
Neotam (mg)	55	55	55	55	55	55	55	55	55	55	55	55
Citric acid (mg)	50	50	50	50	50	50	50	50	50	50	50	50
Water	25	qs	qs	Qs	qs	qs	qs	qs	qs	qs	qs	Qs

Table-2: Evaluation parameters of QDF.

	Appearance	Weight (mg)	Thickness (mm)	Tensile strength Kgf/cm²	% Elongation	Modulus Kgf/cm²	Folding Endurance	D.T. (sec)
F1	Transparent	54.77	0.09	356	15.12	2230.45	78	9
F2	Transparent	63.29	0.11	463	22.76	2321.89	119	15
F3	Transparent	70.30	0.12	607	29.44	2340.46	128	23
F4	Transparent	76.89	0.13	758	30.30	2302.23	153	47
F5	Opaque	52.67	0.08	124	9.34	2845.67	68	8
F6	Opaque	62.67	0.09	159	11.13	2790.01	124	14
F7	Opaque	68.78	0.11	239	14.66	2826.38	136	25
F8	Opaque	74.26	0.12	357	16.45	2845.62	145	43
F9	Opaque	55.08	0.10	189	8.13	2890.08	76	8
F10	Opaque	61.26	0.11	209	9.89	2934.89	121	13
F11	Opaque	69.56	0.12	287	10.06	2929.32	140	27
F12	Opaque	75.12	0.13	356	11.67	2899.83	165	44

Conclusion

The fast dissolving films containing levocetirizine dihydrochloride were prepared with an aim to have rapid onset of action and increased bioavailability in allergic conditions. Various cellulose derivatives like HPMC, CMC and HPC were employed for their film forming properties of which HPMC showed promising physicochemical properties as compare to all other grades therefore, it was selected for further studies. Prepared films were transparent with smooth surface and acceptable mechanical properties. There was no interaction between drug and polymer. Film were disintegrated in 27 seconds and dissolved in 55 seconds. Drug release was found to be 80% in 120 seconds.

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Corresponding Author:

D R Choudhary*[1]

Email:*dhaglaram@gmail.com*