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Formulation, Development & Evaluation of Oral Fast Dissolving Anti-Allergic Film of Levocetrizine Dihydrochloride

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Abstract
Fast dissolving film of levocetrizine dihydrochloride were prepared by solvent casting method by using Maltodextrin & HPMC E15 as the main film forming polymers.To decrease the disintegration time,concentration of maltodextrin & HPMC E15 were optimized be using 2^2 factorial design. 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. Batch F1 was found to be the optimized batch as its disintegration was completed within the minimum time as compared to all other batches. The formulation (F1) was also showing sufficient drug release after 5 min. All the 6 formulation was showing approximately 90% drug release after 5min.

Keywords: Levocetrizine hydrochloride, fast dissolving film, Maltodextrin,HPMC E15 & solvent casting technique.

INTRODUCTION

Recent developments in the technology have presented viable dosage alternatives from oral route for pediatrics, geriatric, bedridden, nauseous or noncompliant patients[1]. Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid-dosage forms[2].

Mouth dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It

then rapidly disintegrates and dissolves to release the medication for oromucosal absorption 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].

Levocetirizine dihydrochloride, is an orally active H1-receptor antagonist. The chemical name is (R)-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride. Levocetirizine dihydrochloride is the R enantiomer of cetirizine hydrochloride, a racemic compound with antihistaminic properties. The empirical formula of levocetirizine dihydrochloride is $C_{21}H_{25}ClN_2O_3$•2HCl. The molecular weight is 461.82 [3]. 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[4].

HPMC E15 is primarily used as binder,in film coating and as an extended release tablet matrix.It is also known as Hypromellose.HPMC E15 stands for HPMC of 15cps viscosity[5,10].

Maltodextrin is used as film former in aqueous film-coating process.It is used in 2-10 % concentration[6].

Glycerine possess a unique combiAation of physical properties. Although chemical reactivity and versatility make glycerine one of the basic building blocks of the chemical industry, each year large volumes go into non-chemical uses. In these processes and products, glycerine's function-as a plasticizer, humectant, solvent, bodying agent. Lubricant[7].

Neotame is a dipeptide methyl ester derivate. Its chemical structure is N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester. It is intended for use in food as a sweetener and flavour enhancer. Neotame has a sweetness factor approximately 7000 to 13000 times greater than that of sucrose and approximately 30 to 60 times greater than that of aspartame, depending upon the food application[8].

MATERIALS AND METHODS

Levocetrizine Dihydrochloride ,maltodextrin,HPMC E15,neotame,glycerine & all other chemicals was obtained from Morepen labs ltd ,Parwanoo(HP). All other chemicals and reagent were of analytical grade.

Table 1: Formulation of fast dissolving film

Ingredient/per film(mg)	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*
Levocetrizine dihydrochloride	2	2	2	2	2	2
Maltodextrin	15	20	25	30	35	40
HPMC E15	15	15	15	15	15	15
Col.tartrazine	0.05	0.05	0.05	0.05	0.05	0.05
Glycerine(ml)	2	2	2	2	2	2
Neotame	0.05	0.05	0.05	0.05	0.05	0.05
Flav.pineapple(ml)	0.05	0.05	0.05	0.05	0.05	0.05
Sodium Benzoate	0.5	0.5	0.5	0.5	0.5	0.5
Dist.water(ml)	q.s	q.s	q.s	q.s	q.s	q.s

Formulation of films

For formulating the film maltodextrin and HPMC E15 was dissolved in distilled water. Levocetrizine hydrochloride ,neotame,flavor pineapple,tartrazine and sodium benzoate were added to the polymer solution. When the entire solid material was dissolved in the water, required amount of plasticizer (glycerine) was added to the solution. The solution was then casted on the plastic films and dried in oven at 60 0C. Dried films were removed and stored in dessicator till further use[9].

Evaluation of films

Thickness: All the batches were evaluated for thickness by using calibrated digital micrometer. Three readings from all the batches were taken and mean thickness was Evaluated[10].

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[11].

Drug content: Drug content of all nine batches was determined by UV-spectrophotometric
method. For this 1.4x1.2 cm^2 strip from the each batch was cut and dissolved in 50ml methanol. Than 5 ml of this solution was diluted upto 50 ml.So 4ppm solution was made, filtered and absorbance was recorded at 231 nm in comparison of 4ppm standard solution. Drug content was calculated by comparison method[10].

Uniformity of drug content: For determining the uniformity of drug content in the film at least
10 strips (1.4x1.2 cm^2) ware taken and assayed . Same procedure was repeated for all the 6 batches [10].

***In vitro* disintegration time:** Disintegration test was performed in the USP disintegration time testing apparatus. Simulated salivary fluid (PH 6.8) was used as medium. The films were placed in the tubes of the container and the disks were placed over it. All the batches were disintegrated within 40 second[10]**.**

Bursting strength: It is also known as tensile strength.It is the maximum tolerance power of a oral fast dissolving film. How much grams of the weight when applied through a pointed subject on the film will be the bursting strength of that film.

Moisture permeation: This test is to chech weather a film is moisture permeable or not.For this in a vial dessicated silica was kept,and on the mouth of vial oral film was bounded and placed in 90%RH for 2 days.

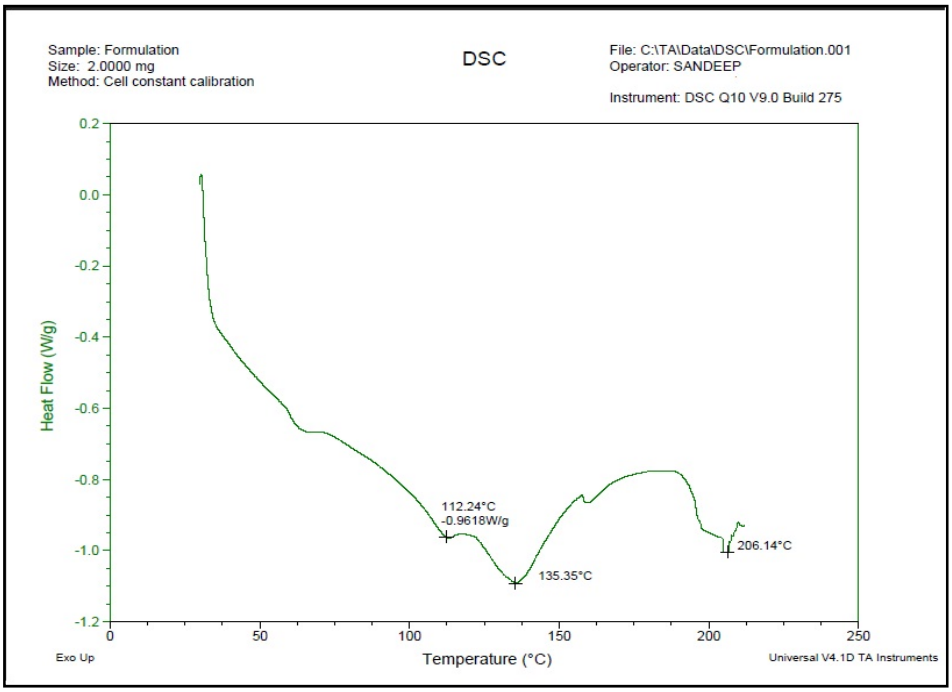
***In-vitro* dissolution studies:** Dissolution study was carried out in USP basket type apparatus using the stimulated salivary fluid (pH 6.8) as a dissolution medium at 50 rotations per minute. 10 ml aliquots were withdrawn at one minute time intervals and same amount of fresh dissolution medium was added. The aliquots were assayed for drug content at 231nm wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated[10].

RESULTS 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 of drug polymers mixture are given in Figure 1, DSC thermo gram showed endothermic peak of levocetirizine at 206.14°C, which corresponded to its melting point. Thermo grams of HPMC E15 showed peak at 112.24°C itself,Thermogram of maltodextrin showed peak at 135.35 °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



Fast dissolving films were prepared using Maltodextrin and HPMC E15 as polymers.. 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 2.0 to 2.03 mg. 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 6.8). The results indicated that disintegration of films was with in 25 sec .

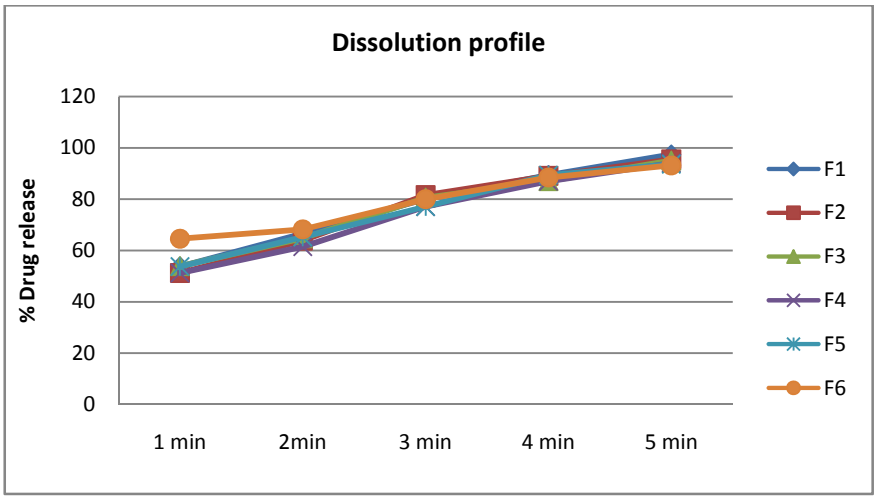
Table 2: Evaluation of levocetrizine dihydrochloride films

Batch	*Thickness (mm)*	*Weight (mg)*	*Drug content(mg)*	*Disintegration Time(sec)*	*Folding Endurance*	*Bursting Strength(gm)*	*Moisture Permeation*
F1	0.540	35.0	2.03	24	4	138.21	NIL
F2	0.541	35.1	2.03	19	3	125.35	NIL
F3	0.538	35.1	2.01	18	3	121.33	NIL
F4	0.542	35.0	2.00	18	2	120.23	NIL
F5	0.544	35.1	2.03	19	2	118.0	NIL
F6	0.540	35.0	2.01	19	2	117.8	NIL

Table-3 In-vitro Dissolution (% release) Profile of fast dissolving films

Batch	1 min	2 min	3 min	4 min	5 min
F1	53.75	66.60	80.11	89.43	97.43
F2	51.22	63.84	81.58	89.10	96.48
F3	53.91	64.79	80.59	87.02	95.01
F4	51.22	61.48	77.09	87.02	94.11
F5	53.72	65.26	77.09	89.41	93.64
F6	54.60	68.25	80.02	89.49	93.20

Figure-2 Dissolution profile



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