Original Article

Formulation and Evaluation of Fast Dissolving Oral Films of Cetirizine Hydrochloride

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ABSTRACT

Background: Fast-dissolving oral delivery system is a solid dosage form, which is used as a novel approach, as it dissolves rapidly in the mouth and directly reaches the systemic circulation. This facilitates rapid absorption and reduces first-pass effects. These films provide better utilization without the need to chew and do not require the need for water for administration. Fast-dissolving oral films might be useful in special patients like those with swallowing difficulties and in that in chemotherapy. This study was aimed to formulate and evaluate the fast dissolving oral films of cetirizine hydrochloride.

Methods: Oral films of cetirizine hydrochloride were prepared using hydroxypropylmethylcellulose (HPMC), Polyvinyl alcohol, glycerol, aspartame in different concentrations by the solvent casting method. Films were evaluated for different physical Films were subjected to USP dissolution studies.

Results: The drug content of the nine formulations was found to be in the range as per Indian Pharmacopeia. In vitro release studies indicated 60-91% release within 30 min in the formulated oral films. The best release was found to be 91.58% of formulation F7, having a minimum concentration of HPMC alone as a polymer along with other common ingredients and minimum release was found to be 60.01% of formulation F1. Surface pH was found to be near to neutral (pH 7) which was good for buccal mucosa.

Conclusion: Increasing the concentration of polymer (PVA and HPMC) while keeping the plasticizer ratio constant showed enhanced folding endurance. The dissolution rates were also increased with the increase in the concentration of the polymers. The high concentration of polymers decreased the release rate of cetirizine while a low concentration of polymers causes an increment in the release rate of cetirizine.

Keywords: oral films, cetirizine, hpmc, polyvinyl alcohol, solvent casting, release rate.

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INTRODUCTION

Oral route is the most preferred route for the drug delivery system. About 60% of all dosage forms available are oral solid dosage form[1]. Oral fast-dissolving films are a novel drug delivery system in which the drug kept in the oral cavity, disintegrates or dissolves within a few seconds without the need to ingest water.[2] These films can be utilized for delivering the drug through both systemic and local routes for any groups of population- either special or general.[3]

Cetirizine hydrochloride is a potent second-generation histamine H-1antagonist that is effective in the treatment of allergic rhinitis, chronic urticaria, and pollen-induced asthma. Unlike many traditional antihistamines, it does not cause drowsiness or anticholinergic side effects.[4] many cetirizine tablets are potent and useful but due to their bitter and elegant taste and smell, and difficulty in swallowing, a patient feels uncomfortable to take them.[5] To overcome such problems the present study is carried out to formulate fast dissolving films of cetirizine hydrochloride.

Because of high permeability and perfusion, sublingual mucosa exhibits rapid drug absorption and enhanced bioavailability with a quick-onset of drug action. Also, it bypasses the pre-systemic metabolism since the drug is directly absorbed into the systemic circulation. Moreover, better patient compliance is expected, because this system does not require being swallowed as in the case of conventional tablet and no water needed.[3,5]

The novel approach of fast dissolving oral films can be advantageous to patients with swallowing difficulties or cancer patients to bypass the emetic side effects of chemotherapeutic agents. As the films easily dissolve in the saliva, these prove to be beneficial for such patients. These films also exhibit better bioavailability with reduced gastrointestinal irritation, thereby better patient compliance.[6] Oral films also have great potential of delivering the medicinal agent systematically as well as locally and have several advantages over many conventional dosage forms.[1,7] So, the main aim of this study is to formulate and evaluate the oral film of cetirizine hydrochloride.

MATERIALS AND METHODS

Chemicals used during formulation

API: Cetirizine hydrochloride

Polymers: Polyvinyl alcohol, Hydroxypropyl methylcellulose (HPMC)

Plasticizer: Glycerol

Sweeteners: Aspartame

Casting solvent: Distilled water

Other: Phosphate buffer pH 6.8, Dilute HCl

Preparation of oral fast dissolving films:

Film was formulated by the solvent casting method. First of all the specified quantity of polymer polyvinyl alcohol was dissolved in 5ml of distilled water by using a magnetic stirrer and kept aside. Similarly, a specified quantity of HPMC was dissolved in 10 ml of distilled water and kept aside for dissolution. Then both the solution was mixed in the required quantity. Plasticizer was added in a drop-wise and stirred to obtain a homogenous solution. Then the specified amount of aspartame was added to the mixture. Finally, drug Cetirizine was loaded in the mixture. The solution was kept for some time for the removal of bubbles and then

Table 1: Formulation of drug-loaded films by solvent casting method

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC	500mg	400mg	300mg	400mg	500mg	400mg	300mg	300mg	200mg
PVA	50mg	50mg	50mg	100mg	_	_	_	100mg	100mg
Glycerine	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg	300mg
Aspartame	55mg	55mg	55mg	55mg	55mg	55mg	55mg	55mg	55mg
Cetirizine	80mg	80mg	80mg	80mg	80mg	80mg	80mg	80mg	80mg
Water	15ml	15ml	15ml	15ml	15ml	15ml	15ml	15ml	15ml

cast into the Petri-dish (9 cm ² area). Petri dishes were kept at maintained room temperature for a few hrs and then kept in a hot air oven for 24hrs at 40°C. After drying films were removed and cut into the desired size i.e.2×2 cm², packed in aluminum foils and kept for further use. Evaluation of films.

General appearance[7,8]:

General appearance of the film was observed visually whether it is transparent, semi-transparent or opaque.

Thickness[2,5,9]:

Five films were selected randomly and then, thicknesses of the prepared films were measured in 5 different points central and the four corners using a digital vernier caliper. Then, average thickness was determined.

Folding endurance[1,2,9]:

The prepared film was measured manually. A strip of film was repeatedly folded at the same place till it was broken. The number of times the film could be folded at the same place without breaking/ cracking give the value of folding endurance.

Uniformity of weight[9]:

Weight variation was studied by individually weighing 10 randomly selected films and calculating the average weight. The individual weight should not deviate significantly from the average weight.

Percentage moisture loss[9]

Individually, the prepared films were weighed and kept in desiccators containing silica at room temperature successive three days. The films were taken out after 3 days and reweighted. Percentage moisture loss was calculated from the formula mentioned below.

% Moisture Loss = [Initial weight- Final weight/ Final weight] ×100

Percentage elongation[1,9]:

The increase in the length of a film when it is pulled under standard conditions of stress just before the point of break is known as percent elongation. Randomly 3 films were selected from each formulation and initial length was measured. Films were pulled manually until it was broken. Then final length was observed and average percentage elongation was determined. Percentage elongation was calculated from the formula mentioned below.

Percentage of Elongation = [Increase length/ Initial length] ×100

Disintegration time[1,9]:

The disintegration time of the film prepared using different polymers was determined visually in a beaker of 25 ml distilled water with shaking every 10 sec. The disintegration time of each patch was noted.

Surface pH[1,9]:

The film kept in a Petri dish was moistened with 5 ml of distilled water and kept for a few minutes. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min.

Drug content[5]:

10 randomly selected films of 5 mg were allowed to dissolve in 900ml of 0.1N HCl and then, the solution was shaken continuously until the patch dissolved. Then the whole solution was filtered through a Whattman filter paper. After filtration, the filtrate was examined for the drug content against the reference solution with the UV spectrophotometer at λmax 231 nm.

In vitro dissolution studies[5]:

The dissolution studied of the film of Cetirizine hydrochloride was carried out using USP type II (paddle apparatus) with 500 ml of phosphate buffer pH6.8 as dissolution medium maintained at 37 ± 0.5 °C. The medium was stirred at 50 rpm. Samples were withdrawn at every 5min interval, replacing the same amount with the fresh medium. Absorbance was determined by uv- spectrophotometer at 231 nm.

RESULTS

Calibration curve: Standard solution of different concentrations of Cetirizine hydrochloride was prepared and their absorbance was measured in UV spectrophotometer at 231 nm in distilled water. When absorbance versus concentration was plotted, a straight line was obtained which suggests that the process used to measure the absorbance of the sample is validated. (fig.1)
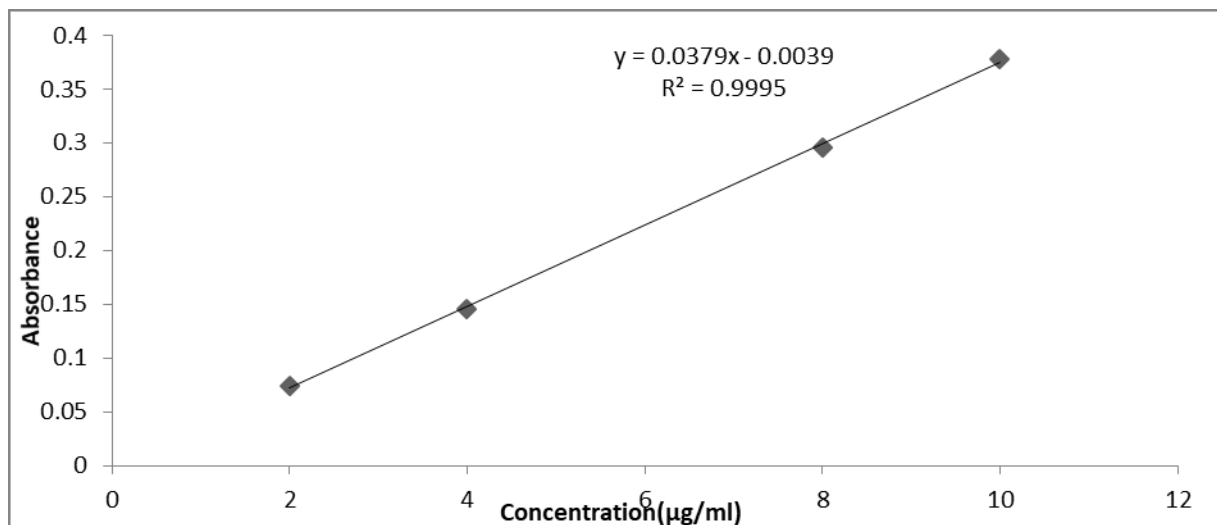
Fig 1: Calibration curve of cetirizine hydrochloride

The calibration curve shows the linear equation $y = 0.0379x - 0.0039$ with $R^2 = 0.9995$.

Table 2: Evaluation of films for physicochemical parameters

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness (mm)	0.22 ± 0.04	0.15 ± 0.007	0.29 ± 0.01	0.27 ± 0.02	0.21 ± 0.01	0.19 ± 0.03	0.23 ± 0.01	0.24 ± 0.01	0.25 ± 0.01
Weight variation(mg)	69 ± 5.46	68 ± 8.72	79 ± 3.77	64 ± 7.41	64 ± 3.22	66 ± 6.88	63 ± 4.24	69 ± 6.53	67 ± 4.69
Folding endurance(folds)	306	298	295	297	293	289	285	290	292
Surface pH	6.40	6.51	6.22	6.33	6.65	6.63	6.40	6.58	6.40
%Moisture loss	4.42	5.13	5.26	2.89	2.5	5.19	5.05	3.98	2.93
%Elongation	23	26	25	28	18	25	20	15	23
Disintegration time (seconds)	58	58	55	56	49	47	46	47	50

Table 3: Drug content of the different formulation

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
% Drug Content	98.82	102	98.31	97.89	98.91	103.28	97.85	104.22	108

Physiolochemical Evaluation:

Through visual evaluation, the films were found to be transparent. The thickness for all the films was found to be between 0.15mm to 0.29 mm. Average weight was found to be maximum in F3 (79mg) and minimum F7(63mg). Folding endurance ranged from 285 to 306 folds determining its strength. Surface pH was found to be near the neutral pH (7). Moisture loss was found to be varying from 2.5 to 5.6%. Elongation was maximum for formulation F4 (28%) and minimum for F8 (15%). Disintegration time was found to be less than 60 seconds. All the properties may be due to the different concentrations of the polymers and their nature (table 2). The assayed drug content was found to be between 97.85 to 108% maximum for formulation F9 and minimum for F7 (table 3).

DISCUSSION

Film appearance showed that the uniform films were formed. They were found to be transparent in the color, smooth, and soft because of the addition of glycerol as a plasticizer which helped in preparation of flexible films.

Thicknesses of the films were measured with the help of vernier calipers. The thickness of the films varies from 0.29mm to 0.15 mm. The difference in thickness may be due to the concentration of polymer used. The result was similar to the previous

Table 4: Cumulative % drug release of different formulations

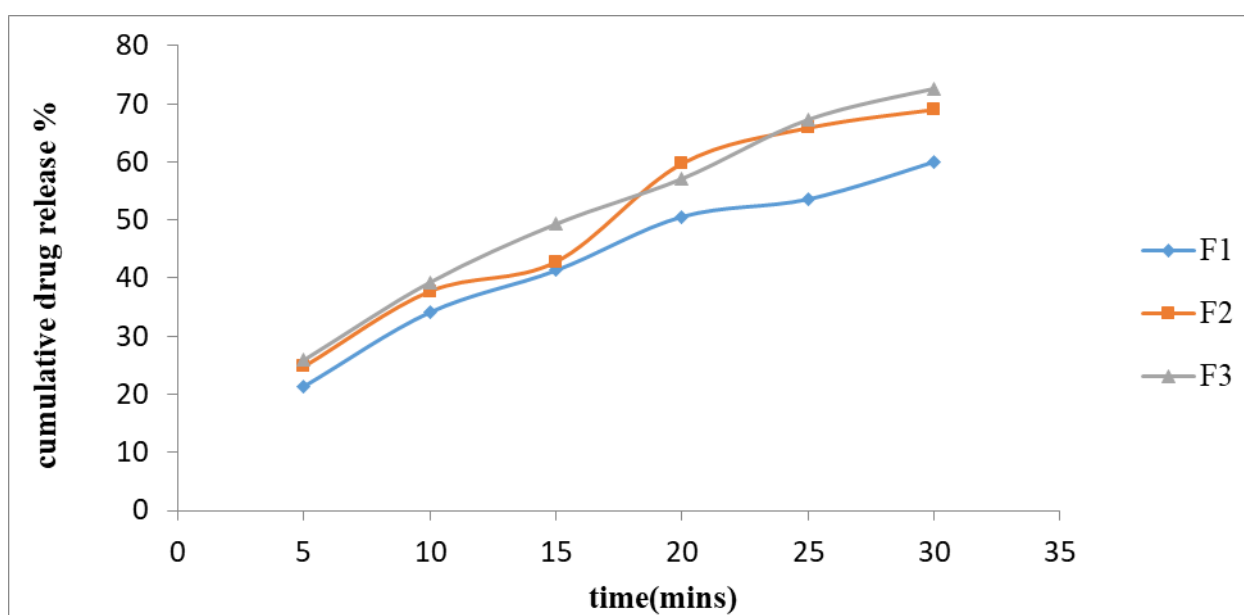| Time (min)	5	10	15	20	25	30
F1	21.35	34.12	41.32	50.58	53.58	60.01
F2	24.79	37.73	42.81	59.73	65.84	69.01
F3	25.89	39.27	49.32	57.12	67.28	72.64
F4	20.39	35.33	50.17	55.31	59.76	65.28
F5	27.80	39.46	56.12	61.77	76.14	81.25
F6	37.47	52.36	63.42	70.68	82.29	86.12
F7	41.04	52.42	67.28	82.34	87.11	91.58
F8	24.12	43.44	59.07	66.12	71.30	79.81
F9	26.33	39.16	48.79	52.86	63.78	73.16

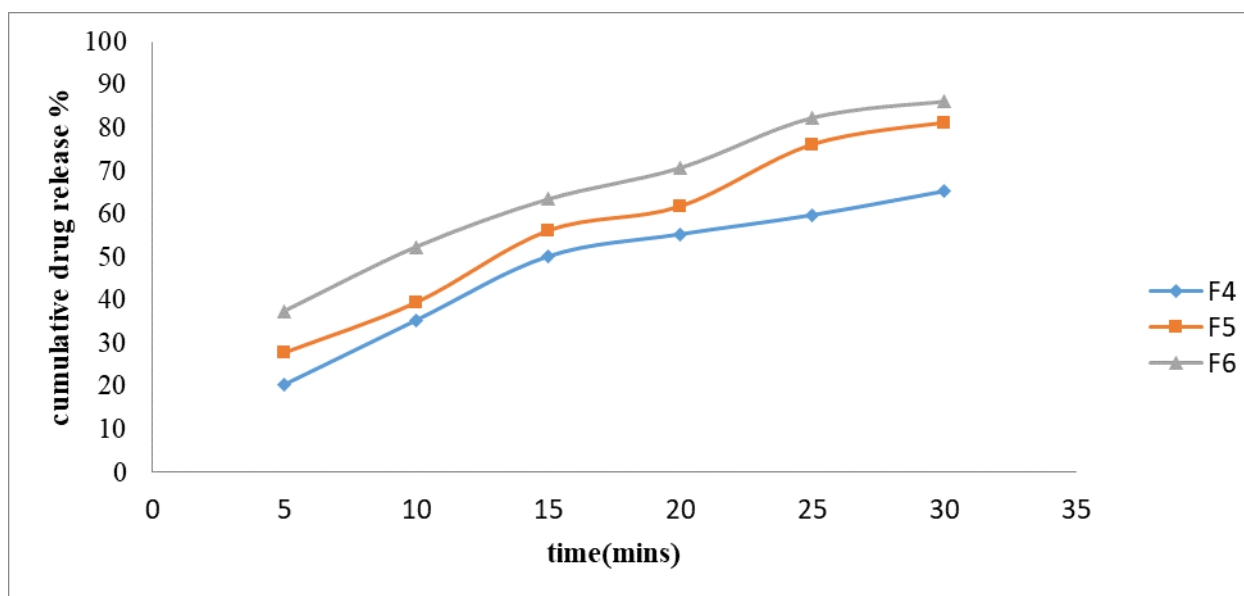Figure 2: Comparison of cumulative amount of drug release Vs time of formulation in F1, F2 and F3

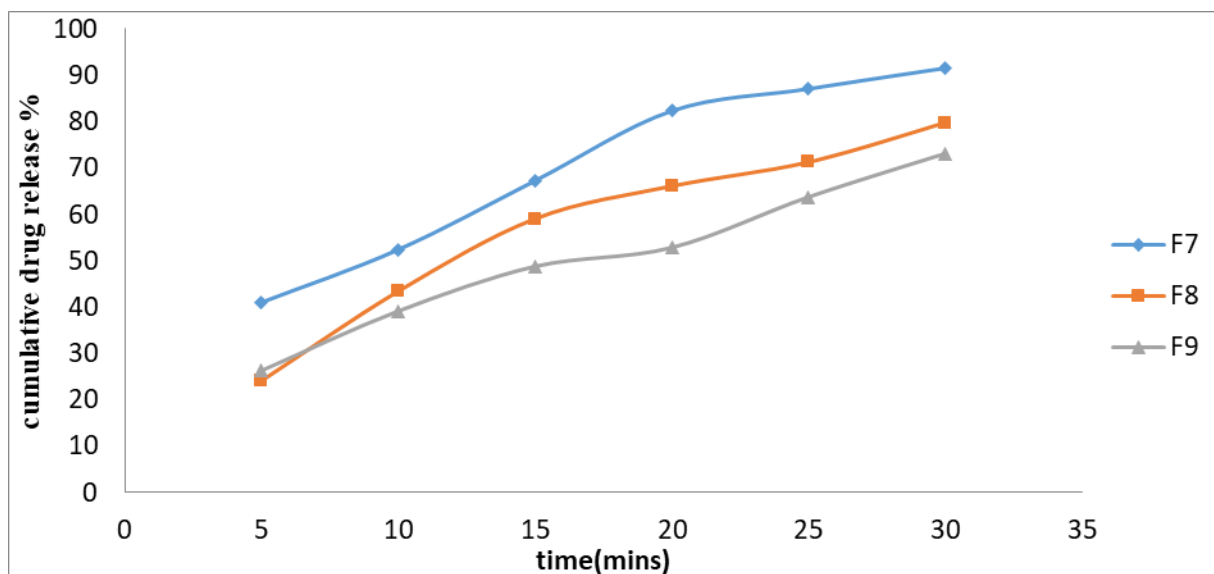Figure 3: Comparison of cumulative amount of drug release Vs time of formulation in F4, F5and F6

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Figure 4: Comparison of cumulative amount drug release vs time of formuation in F7, F8 and F9.

literature.[7]

The folding endurance varies from 285 to 306 folds. These show the films have good strength. In the previous literatures[2,7], folding endurance was ranging from 259 to 300 folds. Uniformity of weight

The result showed that the weight uniformity of the Cetirizine hydrochloride oral films ranges from 79 to 63 mg. Uniformity of weight was found to be maximum for formulation F3 (79mg) whereas uniformity of weight observed to be minimum for formulation F7 (63 mg). This indicates minimum batch variability, which demonstrates the homogenous distribution of the drug over the film. The variation in weight may be due to the concentration of polymer used. The results are similar to the reported literature.[2]

The disintegration time varies from 58 seconds to 46seconds in different formulation. Maximum time was taken in F1 and F2 formulation (58 secs) and minimum time in F7 (46 secs). It is due to the varying concentration of polymer. In a previous literature[2], it was found to be 17 seconds. In another literature[7] disintegration time was varying from 26 seconds to 60 seconds which is found to be similar with our study.

The surface pH was found to be close to neutral in all the formulations, insinuating that the films have less potential to irritate the buccal mucosa, and therefore more comfortable. The average range varies from 6.22 to 6.63.

Moisture loss was determined by placing the films in dessicator containing silica for 3 days. Moisture loss of the different films was found to be varying from 2.5% to 5.6%. In the research work7 moisture loss was found to be ranging from 1.53 to 2.9% which is quite similar to our research. The moisture loss variation may be due to different concentrations of polymer used. It may due to differences in room temperature. The optimum moisture content is a better requirement for fast dissolving oral delivery system.

The result showed that percentage elongation was found to be maximum for formulation F4 (28%) whereas, minimum for formulation F8 (15%). An increase in length varies according to the thickness of the film. The elongation was found to be quite similar to the previous research7 which ranges from 10.93% to 19.45%.

The result showed that the drug content of the Cetirizine hydrochloride ranges from 97.85 to 108%. Drug content was found to be maximum for formulation F9 (108%) whereas drug content observed to be minimum for formulation F7 (97.85%). This indicates the drug was distributed evenly. The range of cetirizine is from 90% to 110% according to IP.

In-vitro dissolution study of cetirizine was found to be from 60% with F1 and showing maximum up to 91.58% with F7. When there is a decrease in the concentration of polymer, there is an improvement in drug release. This may be due to the hydrophilic nature of the polymer as they swell rapidly. With

minimum amount of polymer in F7 more rapidly the drug was released from the films.

Phosphate buffer 6.8 was selected as a dissolution medium to mimic the oral environment to some extent and since the average oral pH of a healthy individual is nearly 6.8.

CONCLUSION

Increasing the concentration of polymer showed enhanced folding endurance which maybe because of the elastic nature of the polymer. The dissolution rates were also increased with the increase in the concentration of the polymer as the film-forming polymers are hydrophilic in nature. Films with only HPMC as a polymer showed the maximum drug release profile while the film with the highest HPMC concentration in the study showed better folding endurance. Overall analyses of the different formulations showed the F7 (with single polymer HPMC) as the best batch among all.

Hence the method of preparation was found to be simply requiring minimum excipients thus making the product cost-effective. Thus further studies can be conducted varying the concentration of polymers for better release of drugs from the films and hence improving the bioavailability of Cetirizine hydrochloride. Selection and combination of film-forming polymers and pharmaceutical excipients also play an important role in the dissolution rate and oral absorption.

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