



Development and characterization of mouth dissolving films of montelukast sodium

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Abstract

The aim of this investigation was to develop rapid dissolving oral films containing Montelukast Sodium, with the goal of achieving a high onset of action to enhance the management of allergic rhinitis. The solvent-casting method is used for preparation of mouth dissolving film of Montelukast Sodium, there were six batches were prepared of mouth dissolving films, by using polymer HPMC K4M, HPMC K100, and HPMC K15M as film-forming ingredient. Various parameters were evaluated for thickness, weight variations, folding endurance, surface pH, disintegration, drug content, and *in-vitro* drug release, etc. Among all the formulated batches, Batch F4 exhibited exceptional characteristics, boasting a minimal disintegration time of only 17 seconds. Moreover, it demonstrated the highest drug release, with an impressive 96.32% of the drug being released within just 30 minutes, surpassing the performance of the other formulated batches. Thus, F4 was selected as the optimized formulation. Analysis through FTIR indicated that there were no significant interactions between the drug and the polymers used in the optimized formulation. In conclusion, the development of fast dissolving film formulations of Montelukast represents a promising approach for the treatment of allergic rhinitis. These films offer the advantage of rapid dissolution, leading to enhanced therapeutic efficacy.

Keywords: Mouth dissolving films, montelukast sodium, allergic rhinitis

Introduction

Oral film technology was initially created in the late 1970s to overcome the difficulties in elderly and young patients who have problem in swallowing tablets and capsules. However, it has gained popularity in the pharmaceutical industry due to its numerous advantages, including increased durability, rapid release, precise dosing, and easy administration [1-5]. The oral route of drug delivery is preferred for its cost-effectiveness and convenience, leading to high patient adherence, especially among the elderly and pediatric populations. Nevertheless, the challenge of swallowing difficulties necessitates the development of innovative and safer drug delivery systems such as oral strips and buccal films [6-10].

Fast-dissolving films have become increasingly popular as an alternative to fast-dissolving tablets because they quickly dissolve upon contact with wet surfaces like the tongue, without any need of additional liquids. This convenience not only provides a marketing advantage but also enhances patient compliance. Furthermore, the drug is directly absorbed into the systemic circulation, bypassing degradation in the gastrointestinal tract and the first-pass effect. These advantages have contributed to the wide spread acceptance and popularity of this formulation, particularly among pediatric and geriatric patients and individuals with a fear of choking. Oral thin films are now approved and utilized as a technique for achieving systemic distribution of active pharmaceutical ingredients (APIs) in over-the-counter (OTC) medications and some prescription treatments [11-14].

Fast-dissolving oral films are formulated by using water loving polymers that dissolve rapidly on the tongue or buccal cavity when comes in a contact with saliva. The user applies the film on or under the tongue (sublingual) or along the inside of the cheek (buccal) for oral administration.

These films are typically postage stamp-sized, with a similar shape and thickness. By bypassing first-pass metabolism through this drug delivery method, the medication's bioavailability is enhanced. A major challenge in developing fast-dissolving oral films lies in taste masking, as medications administered in the oral cavity should have an acceptable taste. Taste plays a crucial role in the development of oral pharmaceuticals, particularly in pediatric medicine, as it influences patient acceptance, compliance, and the market success of oral formulations regardless of the administration mode [14-19].

Materials

Montelukast are obtained from Concept Pharma Aurangabad. HPMC (K4M, K15 and K100) was obtained by Research-lab fine chemicals industries in Mumbai, along with Mannitol and Aspartame. Vanillin is sourced from Ranbaxy Fine Chemicals Limited, located in New Delhi. Citric Acid is supplied by Thomas Baker Pvt. Ltd, based in Mumbai. And at last, Polyethylene glycol is obtained from Gateefoseas, a company located in Mumbai.

Pre-formulation Study

Characterization of Montelukast

Description: Color and physical form of Montelukast were checked visually.

Solubility: Solubility of Montelukast was checked in water and different pH buffers (pH 1.2, 4.5, 6.8, and 7.4).

Melting Point: The melting point of Montelukast was determined by introducing a small amount of the substance in a capillary attached to a graduated thermometer, and constant heat was applied with the assembly suspended in a melting point apparatus. The temperature at which the substance melted was noted.

Spectroscopy

Determination of λ max of Montelukast

Weigh accurately 10 mg of Montelukast, transfer it into a 100 mL volumetric flask, and make up the volume to 100 mL with phosphate buffer (pH 6.8). From this solution, 1 mL was withdrawn and added to a 10 mL volumetric flask and diluted up to 10 mL with phosphate buffer (pH 6.8). Finally, the sample was scanned in the range of 200-400 nm. The wavelength of the maximum absorption was noted, and the UV spectrum was recorded.

Standard Calibration Curve of Montelukast in Phosphate Buffer (pH 6.8)

Accurately weigh 100 mg of Montelukast and add it to a 100 mL volumetric flask. Make up the volume to 100 mL with phosphate buffer (pH 6.8) (1000 μ g/mL). From this solution, 1 mL was withdrawn and added into a 10 mL volumetric flask, and the volume was made up to 10 mL with phosphate buffer (pH 6.8) (100 μ g/mL). This solution was used as the stock solution. From the stock solution, 2,4,6,8,10,12 and 14 mL of solution was withdrawn and added into a 10 mL volumetric flask and finally diluted up to 10 mL with phosphate buffer (pH 6.8). The absorbance was measured for each solution at 345 nm using a UV-Visible spectrophotometer. The graph was plotted for absorbance vs. concentration.

Formulation of Fast Dissolving Films

Dose Calculation

The drug to be loaded in the film was determined by the dose of the drug and the drug loading in the glass plate was determined by the area of the glass plate.

Preparation of films by solvent casting method:

All the ingredients were weighed accordingly. The polymer was dissolved in ethanol. Kept aside for swelling. The drug mannitol, citric acid and vanillin were dissolved separately

in ethanol. Then polymer solution added to drug solution and plasticizer (PEG-400) added then stirred for 15 minutes to produce a clear solution, which kept aside for 15 minutes to get bubble free solution. Then solutions were casted slowly with continuous flow on glass plate to prevent formation of bubbles then it kept for drying. The dried films were gently separated from glass plate and evaluated.

Formulation design

Fast dissolving oral films were prepared using various grades of HPMC as polymer.

Sr. No	Ingredients	F1	F2	F3	F4	F5	F6
1	Montelukast	10	10	10	10	10	10
2	HPMC K4M	25	30	35	-	-	-
3	HPMC K15	-	-	-	25	30	35
4	PEG 400 (ml)	0.03	0.03	0.03	0.03	0.03	0.03
5	Aspartame	5	5	5	5	5	5
6	Mannitol	10	10	10	10	10	10
7	Citric Acid	5	5	5	5	5	5
8	Vanillin	1.5	1.5	1.5	1.5	1.5	1.5
9	Ethanol(ml)	q.s	q.s	q.s	q.s	q.s	q.s

Results and Discussion

Standard calibration curve of Montelukast

Table 1: Calibration Curve of Montelukast

Concentration	Absorbance
0	0
2	0.1343
4	0.2346
6	0.3401
8	0.4599
10	0.5587
12	0.6822
14	0.7654

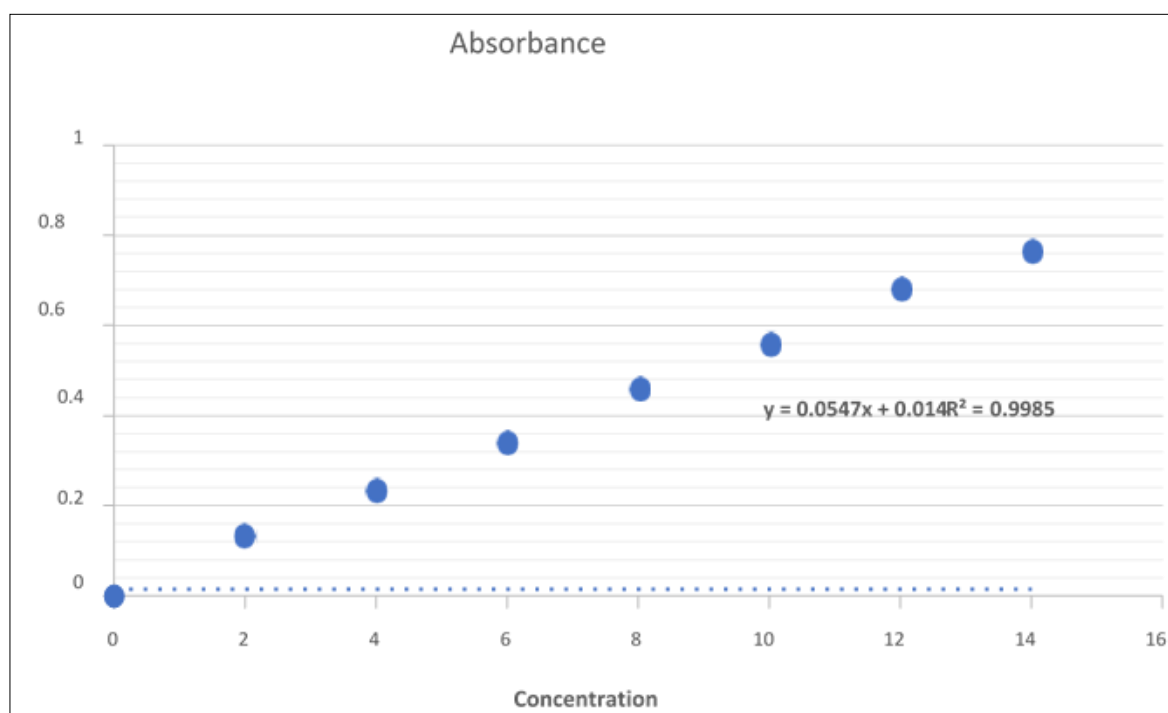


Fig 1: Calibration Curve of Montelukast Sodium

Evaluation

Table 2: Evaluation of Films for, Appearance Tack test, Thickness and Tensile Strength

Formulation Batch	Appearance	Tack Test	Film Thickness (mm)	Tensile Strength (Kg/mm)
F1	Transparent	NonTacky	0.7±0.04	0.216±0.004
F2	Transparent	Tacky	0.9±0.10	0.220±0.002
F3	Transparent	Non Tacky	1.3±0.21	0.221±0.006
F4	Transparent	Non Tacky	0.7±0.10	0.410±0.002
F5	Transparent	Tacky	1.0±0.06	0.416±0.002
F6	Transparent	Non Tacky	1.1±0.24	0.421±0.004

Physical Appearance and Surface Texture of Fast Dissolving films

These parameters were checked simply with visual inspection of Fast dissolving film and by feel or touch. The observation suggests that Fast dissolving films are having smooth surface and they are elegant enough to see.

Tack Test

All Strips were evaluated for tack test out of that only F2 and F5 batches were found to be tacky and other batches were found to be non-tacky. The tack test of all fast dissolving oral films is given in above table.

Tensile Strength

Tensile strength was found to increase with increase in concentration of the polymers. Tensile strength range of the films varied from to 0.216 ± 0.004 to 0.516 ± 0.002 for formulated films.

Thickness of Fast Dissolving films

The thickness of fast dissolving films were measured using screw gauge and the average thickness of Fast dissolving film given in above Table The thickness of Fast dissolving film prepared with HPMC K4, K15 respectively.

Thickness of fast dissolving films was found between 0.7 ± 0.04 to 1.3 ± 0.25 .

Table 3: Evaluation parameter of formulation batches.

Batch	Disintegration Time (sec)	Folding Endurance	%Drug Content	Weight Variation (mg)	pH
F1	19.6±0.24	74±0.24	95.43±0.38	4.5±0.09	6.26
F2	20.3±0.26	76±0.38	98.47±0.27	6.7±0.08	6.81
F3	28.3±0.64	79±0.51	89.12±0.28	7.9±0.21	6.73
F4	17.23±0.12	78±0.24	96.54±0.98	5.5±0.11	6.81
F5	23.01±0.37	80±0.45	92.12±0.44	7.1±0.24	6.38
F6	34.77±0.39	82±0.54	90.25±0.16	6.5±0.42	6.70

Disintegration Time of Fast Dissolving film

Strip of 2 x 2 cm² size taken and disintegration time checked visually. In each case three fast dissolving films were used and the average drug content was calculated, the results were shown in above table.

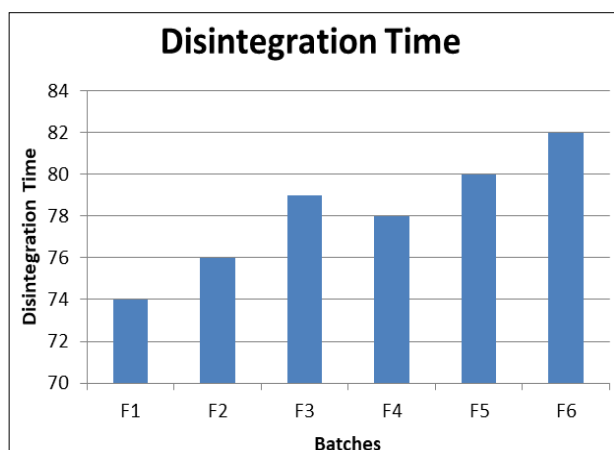


Fig 3: Disintegration Time Prepared Films

Disintegration time of fast dissolving films was found between 15.60 ± 30 to 34.7 ± 0.39 .

Folding Endurance of Fast dissolving films

The folding endurance of Fast dissolving film was determined by repeatedly folding a small film of Fast dissolving film at same place till it broke and the average

folding endurance of all Films given in Table which ranges between in table sin between range 74 ± 0.24 to 82 ± 54 .

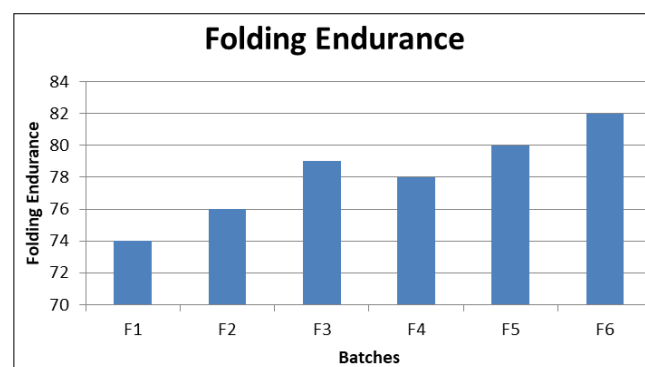


Fig 4: Folding Endurance of Prepared Batches

Drug Content Uniformity of Fast Dissolving Films

In each case three fast dissolving films were used and the average drug content was calculated, the results were shown in above table. The drug was dispersed in the range of 89.12 ± 0.14 to 98.47 ± 0.12 . Suggesting that drug was uniformly dispersed in fast dissolving films. The S.D. value calculated for such formulation is very less which suggests that the results are reproducible and accuracy in the method used to prepare fast dissolving films.

Weight Variation of Fast Dissolving films

Weight of Fast dissolving Films was determined using digital balance and the average weights of Fast dissolving

films were given in above table. The weight variation of formulated films in between 4.5 ± 0.09 to 7.9 ± 0.57 .

Surface pH of Fast Dissolving Films

The surface pH was noted by pH meter near the surface of fast dissolving film and allowing to equilibrate for 1 min

and the surface pH of fast dissolving films was given in above table the surface pH of fast dissolving film was found to be in- between 6.26 to 6.81 pH (n=3).

In-Vitro dissolution Studies of Montelukast

Table 4: In-Vitro dissolution studies of Montelukast

Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	22.58	21.35	20.01	24.35	22.65	21.27
10	37.25	35.95	34.32	41.67	39.97	38.75
15	51.85	50.47	49.55	66.94	64.68	61.24
20	65.25	63.25	61.34	78.16	76.14	74.32
25	81.34	79.78	78.25	89.64	86.75	84.54
30	92.74	91.35	90.04	96.32	92.35	90.35

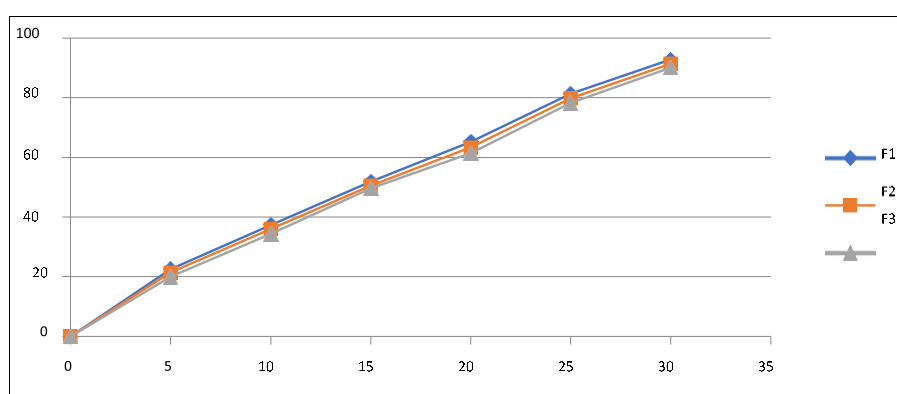


Fig 5: Cumulative % Drug Release from F1-F3

The better release of drug in batches containing HPMC K4M can be observed and the % drug release of

corresponding batches can be ranked in following descending order. $F1 > F2 > F3$

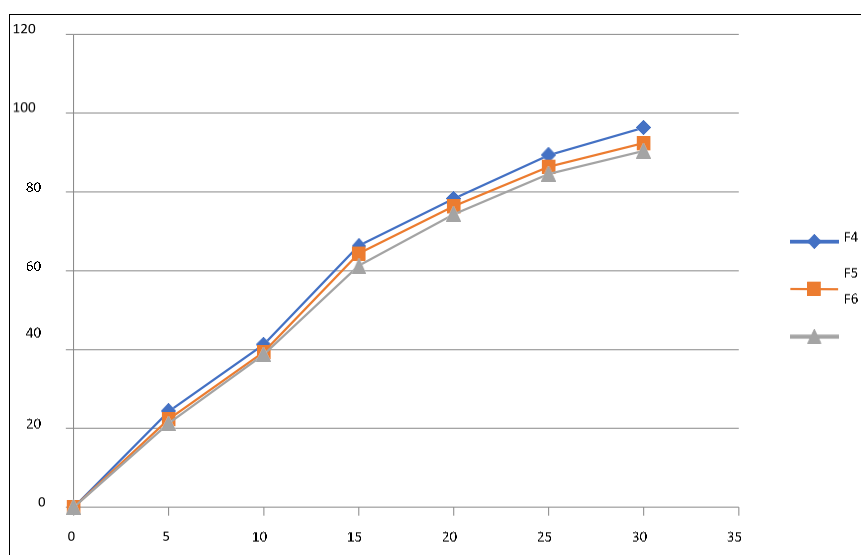


Fig 6: Cumulative % Drug Release from F4-F6

The better release of drug in batches containing HPMC K15M can be observed and the % drug release of corresponding batches can be ranked in following descending order.

$F4 > F5 > F6$.

In these all aspects the formulation F4 satisfied all the pharmaceutical parameters of mouth dissolving films, and

appears to give better therapeutic effects, with disintegration time 17.23 ± 0.12 seconds 96.32 % drug release.

Stability Studies

Stability studies for the optimized formulation (F4) were carried out in order to determine the physical stability of the formulation. The results were shown in there was no significant change in the parameters which are evaluated during the study period in the accelerated conditions.

Table 6: Parameters studies on F4 formulation before and after stability study

Evaluation Parameters	0 Days	30 Days	60 Days
Thickness	0.9	0.9	0.9
Weight Variation	0.79	0.79	0.76
Folding Endurance	14.24	14.24	13.51
Surface pH	6.8	6.7	6.7
Disintegration Time (Sec)	17.23	16.57	16.21
% Drug Content	96.54	96.45	96.31
Visual Inspection	Transparent	Transparent	Transparent
% Drug Release	96.32±0.21	96.11±0.47	95.84±0.24

There were no considerable changes in physical parameter of film such as Thickness, Weight variation, Folding endurance, Disintegration time, % Drug content of formulation F4 before and after accelerated stability study.

Summary

Bilastine and Montelukast are the drugs used in allergic rhinitis which is very common. The absolute bioavailability of Montelukast it is 64%. To overcome the above-mentioned problems an attempt was made to develop and to improve the solubility of drug and reduce side effects, it was attempted to develop fast dissolving films using different film forming polymers. FTIR spectroscopic studies were carried out in order to establish compatibility between drug and excipients. The results were concluded that there were no chemical interactions between drug and the excipients used, so they could be used for the formulation of fast dissolving films.

Total 6 formulations of mouth dissolving films were developed using various excipients which were found to be compatible using FTIR of films. Formulations were prepared using three different polymers such as HPMC K4M, HPMC K15.

Films were evaluated for quality control tests such as Appearance, Tack test, Thickness, Tensile strength, disintegration time, folding endurance, % Drug content, Weight variation, *in-vitro* dissolution, Comparison with marketed product and stability study.

The appearance of the formulations was found to be transparent. Results of tack test shown F2 and F5 were tacky and all the other formulations were non tacky.

The thickness of formulations was between 0.7 ± 0.04 to 1.3 ± 0.21 . Tensile Strength of all 6 formulations was found to be in between 0.0216 ± 0.004 to 0.516 ± 0.002 . The Disintegration time of the formulations was found to be between 17.23 ± 0.12 to 34.77 ± 0.97 .

The surface pH of all formulations was found to be in between 6.26 to 6.81. The Folding endurance of the formulations was found to be in between 74 ± 0.24 to 82 ± 0.54 . The % drug content of all the formulations was found to be in between 89.12 ± 0.28 to 98.47 ± 27 . The Weight variation of the formulations was found to be in between 4.5 ± 0.09 to 7.9 ± 0.57 .

The % drug release of Montelukast was found to be 92.74 %, 91.35 % and 90.04 % respectively. In this study we observed that as we increase the concentration of polymer the % drug release decreases.

The drug release percentages for Montelukast in batches F4, F5, and F6, the drug release percentages were found to be 96.32%, 92.35%, and 90.35% respectively. It was observed in this study that an increase in the concentration of the polymer resulted in a decrease in the percentage of drug release.

In these all aspects the formulation Batch F4 satisfied all the pharmaceutical parameters of mouth dissolving films. So, the F4 batch was selected as optimized batch.

Conclusion

Overall, this study successfully developed fast dissolving films for Montelukast, which showed desirable physical characteristics and drug content. The findings suggest that the formulation approach using these film-forming polymers can be a promising strategy to enhance the solubility and minimize side effects of the drugs in the treatment of allergic rhinitis. Further investigations, including *in vivo* studies and clinical trials, may be warranted to assess the efficacy and safety of these formulations for potential therapeutic applications.

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