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Original Research Article

Design, Development and Evaluation of Oral Dissolving film of Montelukast Sodium

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Abstract:
Montelukast Sodium (MS) is widely used for managing asthma and allergic rhinitis due to its leukotriene receptor antagonist properties. However, traditional oral dosage forms often lead to challenges in patient compliance and delayed onset of action. This study focuses on the design, development, and optimization of oral dissolving films (ODFs) of Montelukast Sodium, aimed at improving patient compliance and ensuring rapid drug release. Using the solvent casting method, various formulations were prepared with different concentrations of hydroxypropyl methylcellulose (HPMC), Eudragit, and Xanthum Gum and plasticizers like polyethylene glycol (PEG). The films were evaluated for their thickness, drug content uniformity, disintegration time, in vitro dissolution, and mechanical properties. The optimized ODFs F5 demonstrated rapid disintegration (10 seconds) and high drug release (99.99% within 5 minutes), indicating their potential to enhance therapeutic efficacy and patient adherence.
Keywords: HPMC, Eudragit, Xanthum Gum, PEG, Film.

Introduction

Montelukast Sodium, an oral leukotriene receptor antagonist, is often prescribed for asthma prophylaxis and chronic treatment, as well as for relieving symptoms of allergic rhinitis. Traditional oral dosage forms like tablets and capsules face challenges such as delayed onset of action and patient non-compliance, particularly among pediatric and geriatric patients. Oral dissolving films (ODFs) offer a promising alternative by dissolving rapidly in the oral cavity, thereby providing a quick therapeutic effect and improved patient adherence.

Pre-formulation Studies

Pre-formulation testing examines the chemical and physical characteristics of the therapeutic ingredient both by itself and in combination with excipients. It is the initial phase in the methodical creation of dosage forms. Pre-formulation testing's overarching goal is to produce data that will assist the formulator in creating stable and bioavailable dosage forms.

Pre-formulation parameter scope maximises the changes in forming a stable, effective, safe, and acceptable product.

1) Melting Point Determination

It is one of the parameter to justifying the purity of the drugs. In case of pure API the melting points recorded very sharp and constant. Since the drug contains the mixed chemicals, excipients, they are described with certain range of melting point. Melting point of Montelukast Sodium was determined with the open capillary melting point apparatus.

2) Preparation of calibration curve of Montelukast Sodium

a) **Preparation of simulated gastric fluid without enzymes:**

70 ml ofconcentrated HCL and 20 mg of NaCl was added to 10 liters of distilled water. Its pH was adjusted to 2.

b) **Preparation of calibration curve:**

A standard stock solution of Montelukast Sodium was created by dissolving 100 mg of the medication in the bare minimum of distilled water, and then adding SGF to make up remaining volume. From the standard stock solution, secondary stock solution was prepared by diluting the primary stock solution ten times so that secondary stock solution with a concentration of 100µg/ml. From this secondary stocksolution, aliquots of 0.5 ml to 2.5 ml were transferred in a series of 10 ml volumetric flasks and final volume was made up with buffer to give the concentration ranging from 5µg/ml to 30µg/ml. the absorbance of these given solutions was measured against the SGF as blank in UV/Visiblespectrophotometer recorded at 287nm. Three determinations were averaged.

3) Compatibility Studies

a) **Physical compatibility:**

A physical mixture of ratio (1:1) of drug and excipients and excipients alone were prepared in 20 ml glass vials and keptfor open (40°C/75% RH), closed (40◦C/75% RH) and control conditions (room temp.) for four weeks. Physical changes was observed in the end of every week.

Chemical Compatibility: To find any potential chemical reaction between the medication and the polymer, an infrared spectrum matching technique was employed. The medication and polymer were combined in a physical mixture (1:1) together with the appropriate amounts of potassium bromide. This combination was compacted into a pellet of around 100 mg. It was examined using an FTIR spectrophotometer between 4000 and 400 cm^{-1}.

Method of Preparation

Calculation of Montelukast Sodium fast dissolving oral film
Diameter of Petri dish:
The petri dish's diameter is 6 cm. Diameter/ 2 = 6 / 2 = 3 cm is the radius.
πr^2 is equal to 3.14 x 3 x 3 = 28.26 cm.
Dose is now% mg, and the pieces are chopped into 2 cm by 2 cm, or 4 cm^2.
The medication contains 10 milligrams in 4 cm^2.
Consequently, 28.26 cm^2 contains 28.26/4 = 7.06 and 7.06 x 10 = 70.65 mg of medication.
Thus, 2 millilitres contain 70.65 milligrams of medication. Consequently, 10 ml of medicine contain 353.25 mg of drug.

Method of preparation of (Drug Incorporated)

- Accurately weighed the polymer and soaked it in 10 milliliters of water.
- The required amount of sodium montelukast was dissolved in ten milliliters of water.
- After adding the specified amount of aspartame and citric acid to the mixture, stir it for 45 minutes.
- The solution was properly mixed and the polymer solution was added while stirring continuously.
- Lastly, add PEG 400 plasticizer while continuously stirring.
- After 45 minutes of vigorous stirring the final dispersion, the solution was sonicated for 15 minutes to eliminate any remaining air bubbles.

- Subsequently, the dispersion was placed aside for an hour in order to reduce the foam.
- In the meanwhile, use glycerol to lubricate the petri dish to reduce the possibility of damaging the films during removal.
- Moved 2 milliliters of the last dispersion into the measuring cylinder and poured the mixture into the dry, cleaned petri dish ($28.26cm^2$).
- After that, the films were dried for one to two hours at 40°C in a vacuum tray dryer.
- After removal, the films were chopped into a 2x2 cm^2 size and contained 5 mg of montelukast sodium.
- After that, these films were kept in appropriate packaging at room temperature.

Table 1: Formulation of Oral Dissolving Films (Drug Incorporated)

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Montelukast Sodium (Mg)	353	353	353	353	353	353	353	353	353
Banana Powder (gm)	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Xanthum Gum (gm)	1.0	1.5	2.0	-	-	-	-	-	-
Eudragit (gm)	-	-	-	1.0	1.5	2.0	-	-	-
HPMC (gm)	-	-	-	-	-	-	1.0	1.5	2.0
PEG-400 (ml)	1	1	1	1	1	1	1	1	1
Citric Acid (mg)	200	200	200	200	200	200	200	200	200
Aspartame (mg)	15	15	15	15	15	15	15	15	15
Coloring Agent (Amaranth)	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*
Flavoring Agent (Mint)	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*
Water (ml)	10	10	10	10	10	10	10	10	10

Pre- formulation studies of pure drug (Identification of drug)

The IR spectrum obtained of pure drug shows characteristics peaks as given below anddepicted in figure.

Table 2: IR Spectrum of Montelukast Sodium

Functional Group Presents	Standard Wave Range Cm^{-1}	Peaks
C – Cl (Aliphatic)	800 – 600	795
C = N (Aromatic)	1690 -1640	1696
C = O (Aliphatic)	1800 -1640	1680
C = C (Aromatic)	1650 – 1475	1610
C – H (Aliphatic)	3000 – 2850	2940

Melting Point determination

Melting point is determined by capillary fusion method. The values are shown in thetable below:

Table 3: Melting Point of Montelukast Sodium

S. No.	Method	Literature Melting Point	Practical melting point
1.	Capillary Method	134-138° C	136° C

Drug excipients compatibility study:

a) Physical Parameter:

The sample was maintained in controlled, closed, and open environments. To identify physical incompatibility, both open and closed vials are maintained at accelerated temperatures (40°C/75%RH) and monitored at the end of each week for a period of four weeks. The physical characteristics that indicate the drug's and polymers' physical compatibility remained unchanged.

b) Chemical Compatibility:

Before the films were made, a compatibility study was done between the pure drug

Montelukast Sodium and several excipients. The IR spectra of the pure medication and the DSC of the physical combination of medication and excipients are displayed below. The spectra of the Montelukast Sodium showed each of its characteristic peaks at the right wavelength. This illustrates the compatibility of the medicine and excipients. The drug's chemical composition did not change much.

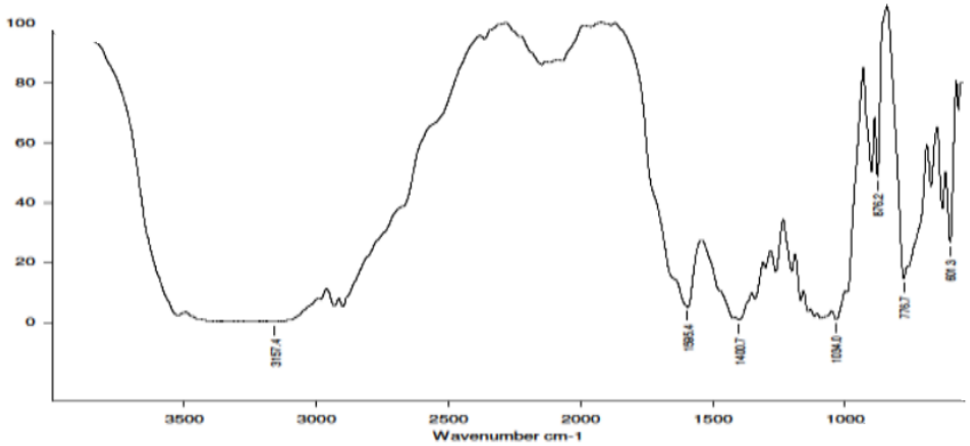

Figure 1: FTIR Spectrum of Montelukast Sodium

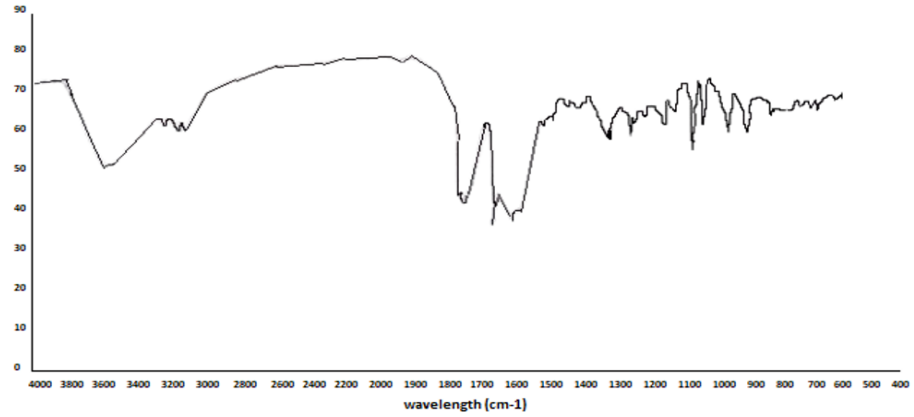

Figure 2: FTIR Spectrum of Montelukast Sodium+Xanthum Gum

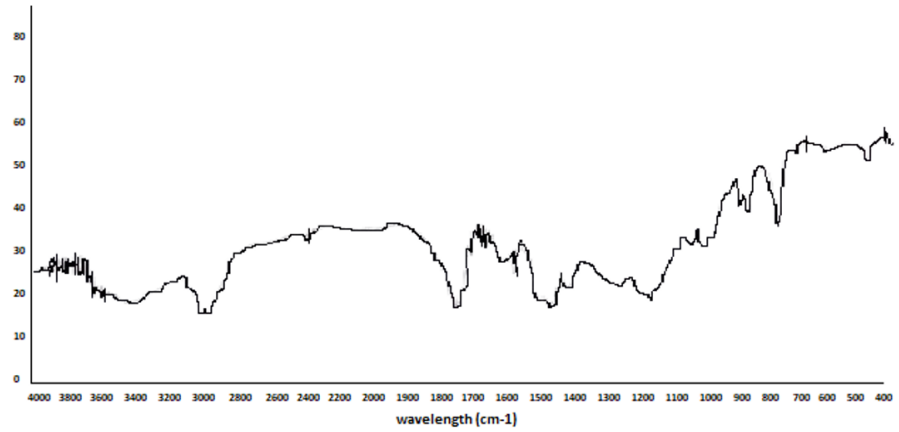

Figure 3: FTIR Spectrum of Montelukast Sodium+Banana Powder

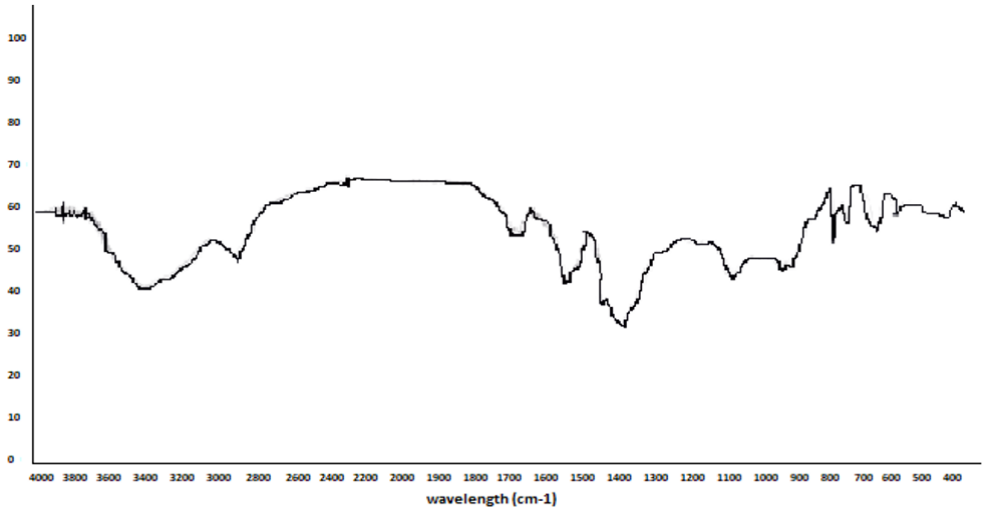

Figure 4: FTIR Spectrum of Montelukast Sodium+Eudragit

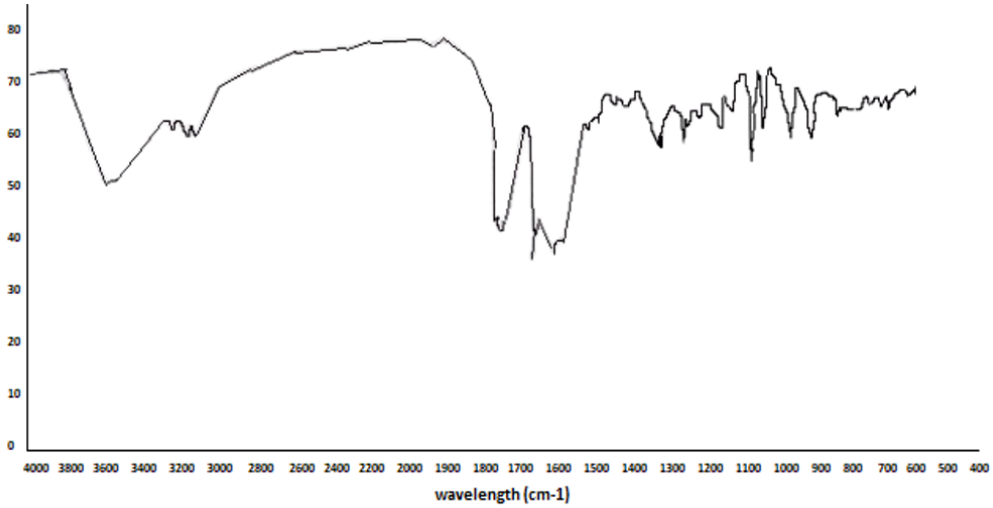

Figure 5: FTIR Spectrum of Montelukast Sodium+HPMC

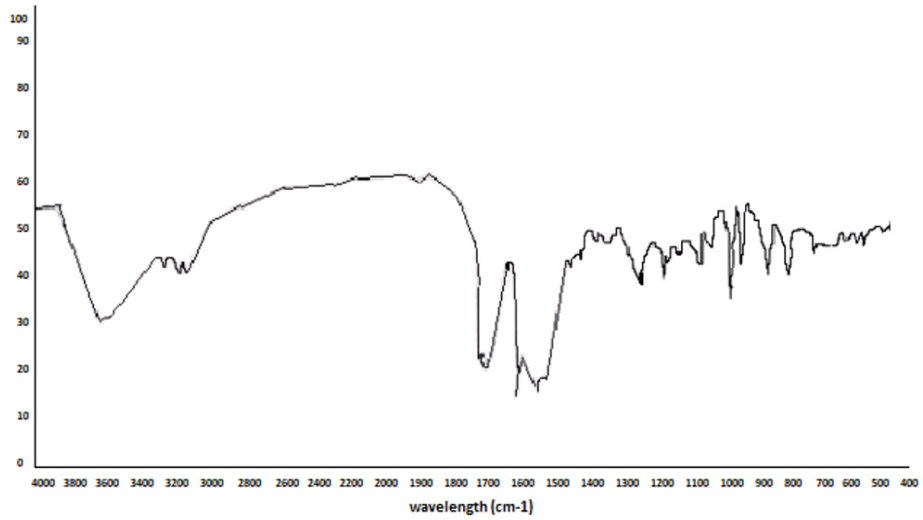

Figure 6: FTIR Spectrum of Montelukast Sodium+ All polymers

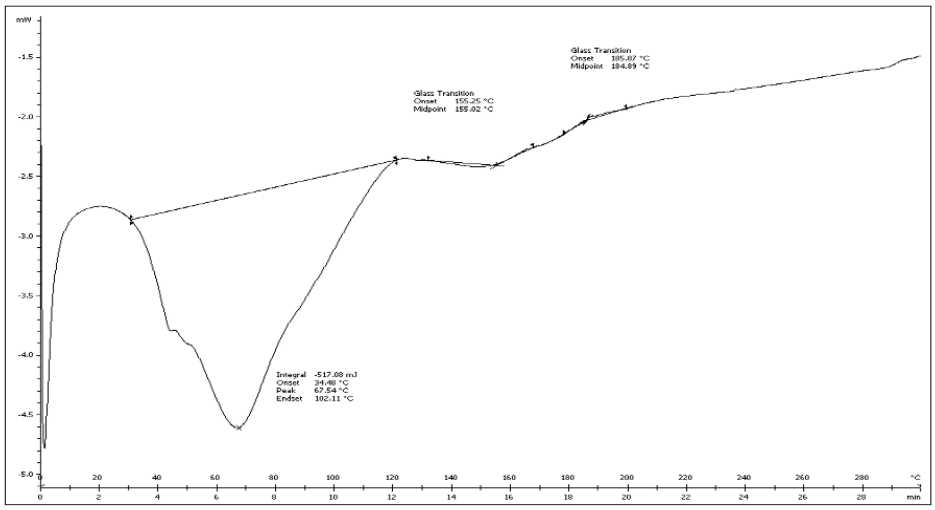

Figure 7: DSC of Montelukast Sodium

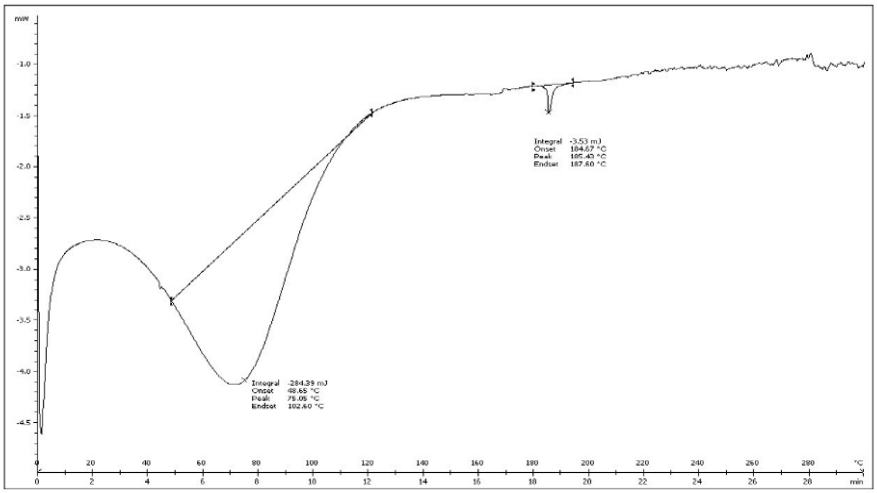

Figure 8: DSC Of Physical Mixture: Optimized Formulation

Pure Montelukast Sodium: **Melting Point**: An endothermic peak at approximately 136°C.
Excipients:
Shows an endothermic peak at around 190°C-200°C.

Mixture of Montelukast Sodium and Excipients If the DSC thermogram shows the melting point of Montelukast Sodium at 136-138°C with no significant shift and no new peaks, the materials are likely compatible.

Table 4: IR Compatibility Study of Drug with Different Polymers

Combination (Drug+polymer)	IR Peaks	Compatibility
Montelukast Sodium	790,670,1490,1690, 1605,2930	Compatible
Montelukast Sodium + Banana Powder	790,665,1490,1685, 1610,2935	Compatible
Montelukast Sodium + Xanthum Gum	795,660,1490,1685, 1605,2940	Compatible
Montelukast Sodium + Eudragit	800,670,1505,1695, 1605, 2925	Compatible
Montelukast Sodium + HPMC	790,660.1495,1690, 1605,2920	Compatible
Montelukast Sodium + All Polymers	790,680,1505,1680, 1610,2930	Compatible

Development of calibration curve of Montelukast Sodium:
Mean absorbance values are shown in table:

Table 5: Mean Absorbance Values and Statistical Data of the CalibrationCurve for the Estimation of Montelukast Sodium

S. No.	Concentration (µg/ml)	Mean Absorbance
1	0	0.00
2	2	0.076 ± 0.001
3	4	0.173± 0.002
4	6	0.321± 0.001
5	8	0.472± 0.004
6	10	0.621± 0.003

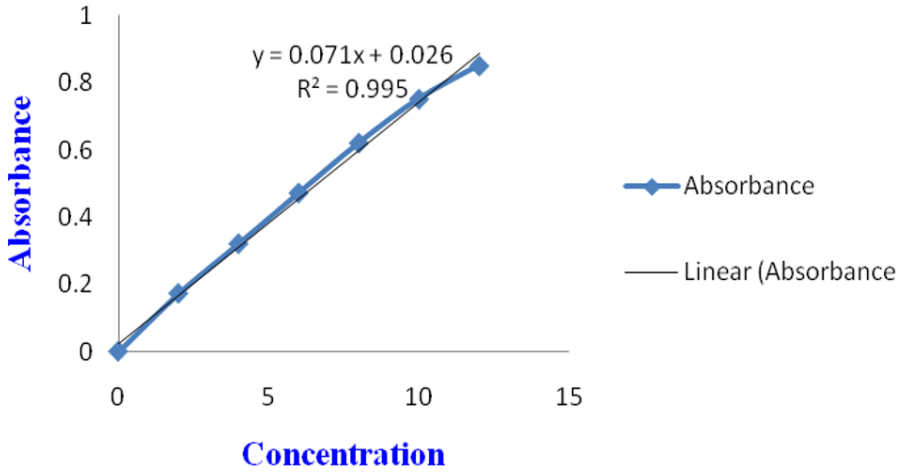

Figure 9: Calibration Curve of Montelukast Sodium

Evaluation of Montelukast Sodium Oral Dissolving Films

a) **Appearance**

Eudragit HPMC films had an opaque appearance, while formulations with a lower Xanthum Gum concentration were translucent and those with a greater concentration were transparent. Although the HPMC films were clear as well, the Xanthum gum-containing films felt and had a nice texture.

b) **Weight of film**

Using an electronic balance, 4 cm^2 of films were weighed, and the average weight was determined. Films weigh between 15 and 20 milligrams.

c) Film thickness

Three films were chosen at random, and their thicknesses were measured with a standard Vernier calliper. The films' thicknesses ranged from 0.035 to 0.055.

d) The film's pH surface

To look into the potential for any in vivo adverse effects, the film's surface pH was measured. It was decided to maintain the surface pH as near to neutral as feasible because an acidic or alkaline pH could irritate the buccal mucosa. Films have a pH of 6.5 to 7.0.

e) Folding endurance:

This was assessed by folding the film repeatedly in the same direction until it broke. Films have a folding endurance range of 210–260.

f) Disintegration Time:

After adding a film to the water's surface and adding two millilitres of distilled water to a petridish, the time it took for the film to dissolve entirely was recorded. The disintegration period varies between 10 and 40 seconds.

g) Percent elongation:

At the point when stress is applied to the film test extends and alluded to as a strain. Generally, elongation of the film increase as the plasticizer concentration increases. The percentage elongation of the film was determined by the following formula Percentage elongation = Increase in length of strip/ Initial length of strip × 100

b) Assay of content uniformity

Absorbance of standard preparation and test preparation was taken using UV double beam spectrophotometer. The drug content of films was found to be between 95.99-99.99%. The result of assay and content uniformity of all batches is shown in table.

Content uniformity and assay complies in all batches as all batches are within the specified limit of 95.99% to 99.99% as per USP. The formulation F5 shows maximum drug content which is 99.99%

Table 6: Result of Assay of Content Uniformity

Batch No.	Assay (%)
F1	96.47±0.12
F2	98.53±0.21
F3	97.32±0.21
F4	96.58±0.35
F5	99.99±0.15
F6	98.87±0.16
F7	98.47±0.22
F8	95.99±0.25
F9	97.30±0.21

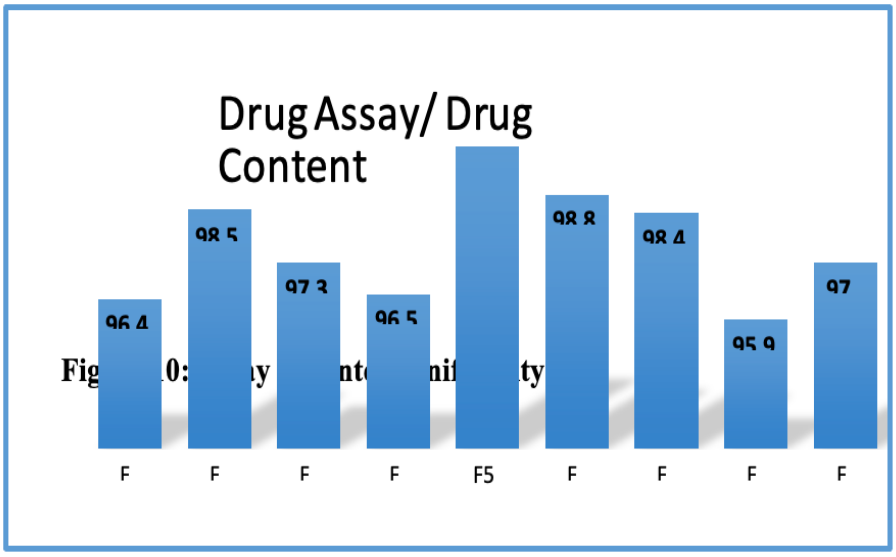

Figure 10: Assay of content uniformity

Table 7: Physical Characterization of Oral Dissolving Films

PARAMETER	FORMULATION CODE								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Weight variation	19.37 ±0.152	19.07 ±0.223	20.00 ±0.231	19.50 ±0.125	19.69 ±0.360	15.00 ±0.126	19.75 ±0.235	18.75 ±0.256	20.00 ±0.125
Thickness	0.035 ±0.012	0.036 ±0.010	0.037 ±0.071	0.055 ±0.060	0.048 ±0.011	0.050 ±0.052	0.047 ±0.055	0.051 ±0.022	0.053 ±0.019
Surface pH	6.50	6.50	6.40	6.87	7.00	6.89	6.58	6.98	6.87
Folding endurance	211	219	230	238	260	218	232	246	257
Percent Elongation (%)	2.31	2.10	2.31	2.30	2.45	2.36	2.35	2.34	2.34
Disintegration time	29 ±0.22	25 ±0.13	19 ±0.26	26 ±0.16	10 ±0.01	36 ±0.10	40 ±0.12	31 ±0.15	29 ±0.19
Drug content	96.47 ±0.12	98.53 ±0.21	97.32 ±0.21	96.58 ±0.35	99.99 ±0.15	98.87 ±0.16	98.47 ±0.22	95.99 ±0.25	97.30 ±0.21

i) In – Vitro Drug Release

The samples were collected using a UV-visible spectrophotometer that was calibrated to detect absorbance at 283 nm. Two widely used data treatment models were fitted with the outcomes of the in vitro release data collected for each formulations, are as follows:

i) Cumulative percent of medication released vs time using a Zero-order kinetic model.

ii) Log cumulative percent of medication remaining vs time in a first order kinetic model.

Data treatment

The in vitro release data were plotted for various kinetic models. To find out mechanism of drug release from all the formulations of Montelukast Sodium mouth dissolving films, the data were fitted according to zero order and first order pattern as illustrated in table. The correlation coefficient (R^2) values of all formulations showed that the formulations follow first order release pattern, as indicated by their high regression coefficient. The R^2 value of zero order was found to be very low i.e. 0.63 while that for first order was found to be 0.98 which indicates that the release from formulation F5 was found to be nearly first order release, governed by dissolution through polymer. The release of drug from polymer also depends upon polymer viscosity. High molecular weight polymer retards release of drug from formulation.

Table 8: Kinetic Value Obtained From In Vitro Release

Formulation Code	Zero order		First order	
	Ko (mg/h)	**R^2**	**K1 (hr^{-1})**	**R^2**
F1	8.536	0.556	0.490	0.960
F2	8.457	0.495	0.485	0.910
F3	8.601	0.510	0.475	0.975
F4	8.450	0.475	0.399	0.989
F5	9.510	0.599	0.485	0.946
F6	9.125	0.555	0.460	0.823
F7	8.810	0.530	0.310	0.989
F8	7.490	0.460	0.302	0.954
F9	9.856	0.599	0.401	0.897

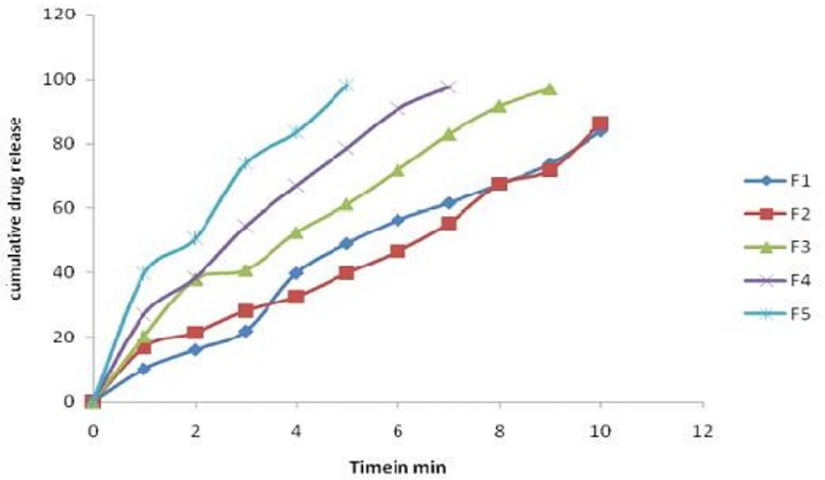

Figure 11: Cumulative % Drug Release V/S Time of formulation F1, F2, F3, F4 and F5 (pH 6.8 Phosphate Buffer

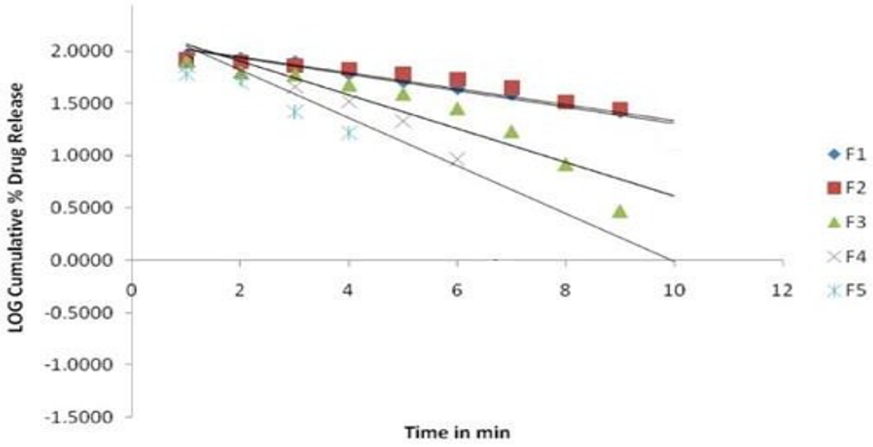

Figure 12: Log Cumulative Drug Remaining V/S Time of formulation F1, F2, F3, F4 and F5

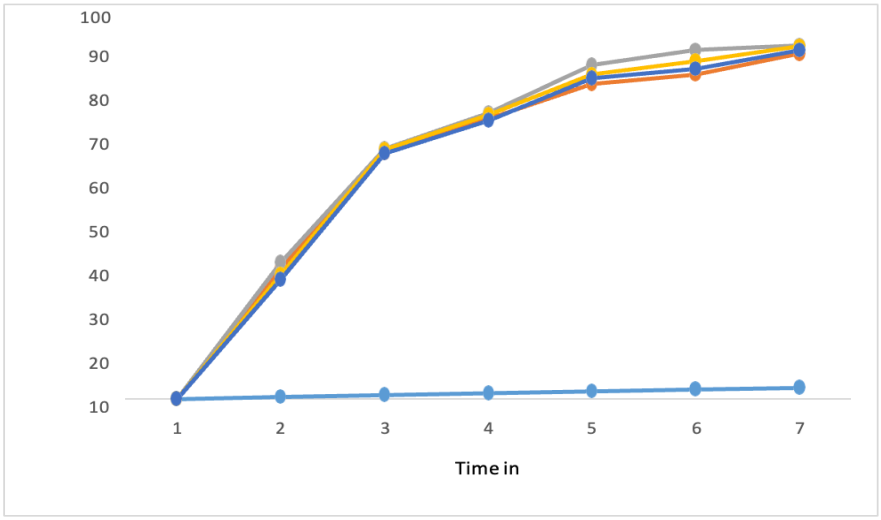

Figure 13: Cumulative Percent Drug Released Vs Time Plots (Zero Order) Of Formulations F6, F7, F8 and F9

Stability studies for the formulation F5

Stability study for the best formulation was done as per the procedure. The ODF was both physically and chemically stable at 4-5^0 c, Room temperature and 37±5^0 c. The results were tabulated in Table 9.

Table 9: Results of stability studies

Parameters	**Room Temperature**	**37±5^{0}C**	**4-5^{0}C**
Visual appearance InitialFinal	Transparent Transparent	Transparent Transparent	Transparent Transparent
pH InitialFinal	7.0 7.0	6.9 6.9	6.9 6.9
Leakage	Not found	Not found	Not found
Nature InitialFinal	Smooth Smooth	Smooth Smooth	Smooth Smooth

Chemical evaluation

The drug content of the formulation was estimated over a period of 3 months.
The results were tabulated as follows.

Table 10: Drug content of formulation F5

Storage condition	**Withdrawal period (monthly)**			
	0	**1**	**2**	**3**
4-5^{0}C	99.99	98.99	98.65	97.85
Room Temperature	99.99	98.95	98.64	97.75
37±5^{0}C	99.99	98.95	98.60	97.75

Conclusion:

Films with the F5 formulation underwent additional stability testing, and they were kept for a month in an airtight plastic bag. The assay, content homogeneity, pH, weight, and in vitro release profile of the films were then assessed. Throughout the study period, no discernible changes were seen in any of the measures under investigation. The measured thickness, folding endurance, disintegration duration, and drug content all showed that the produced fast-dissolving films had good film characteristics. The produced formulation was deemed stable as the films exhibited uniformity and flexibility, and the formulation F5 released 99.99% of the medication within ten minutes, which was desirable for rapid absorption.

References

1. Cheng E, et al., (2024) Development of Vitamin C-Loaded Electrospun Nanofibers of Mixture of Polysaccharides of Pullulan/Xanthan Gum for Fast Dissolving Oral Film Applications. Materials (Basel). 2024 Feb 12;17(4):861.
2. Navdeep Singh, et al. (2024) A Concise Overview on Orodispersible Film along with their Formulation and Characterization Technique's. Research Journal of Pharmaceutical Dosage Forms and Technology.2024; 16(1):98-6.
3. Hasanen Pinjari, et al., (2024) Fast Dissolving Oral Films: A Review. IJRPAS, 2024; 3(1): 29-28.
4. Vemula SK, Daravath B, Gummadi SB, Repka M. Formulation and Development of Flurbiprofen Colon-Specific Eudragit Coated Matrix Tablets: Use of a Novel Crude Banana Peel Powder as a Time-Dependent Polymer. AAPS PharmSciTech. 2023 Sep 19;24(7):189.
5. Sowjanya JN, Rao PR. (2023) Development, optimization, and invitro evaluation of novel fast dissolving oral films (FDOF's) of Uncaria tomentosa extract to treat

osteoarthritis. Heliyon. 2023 Mar 10;9(3):e14292.
6. Ozakar E, Sevinç-Ozakar R, Yılmaz B. (2023) Preparation, Characterization, and Evaluation of Cytotoxicity of Fast Dissolving Hydrogel Based Oral Thin Films Containing Pregabalin and Methylcobalamin. Gels. 2023 Feb 9;9(2):147.
7. Zaki RM, et al., (2023) Fabrication and characterization of orodispersible films loaded with solid dispersion to enhance Rosuvastatin calcium bioavailability. Saudi Pharm J. 2023 Jan;31(1):135-146.
8. Wermuth HR, et al., (2023) Montelukast. 2023 Mar 22. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 29083616.
9. Wang H, et al., (2023) A systematic review and meta-analysis of loratadine combined with montelukast for the treatment of allergic rhinitis. Front Pharmacol. 2023 Oct 17;14:1287320.
10. Westholter D, et al (2023) Asthma – was ist neu? [Advances in the management of asthma]. Dtsch Med Wochenschr. 2023 Sep;148(17):1123-1128. German.
11. Rashid, et al., (2023) In Vitro and In Vivo Evaluation of Composite Oral Fast Disintegrating Film: An Innovative Strategy for the Codelivery of Ranitidine HCl and Flurbiprofen. Pharmaceutics 2023, 15, 1987.
12. Aashli, et al., (2023) Fabricating transdermal film formulations of montelukast sodium with improved chemical stability and extended drug release. Heliyon. 2023 Mar 11;9(3):e14469.
13. Sams L, et al., (2023) The Effect Of Percussive Therapy On Musculoskeletal Performance And Experiences Of Pain: A Systematic Literature Review. Int J Sports Phys Ther. 2023 Apr 1;18(2):309-327.
14. Polonini et al., (2023) Compatibility Assessment of Novel Orodispersible Film Vehicle for Personalized Medicine with Selected Active Pharmaceutical Ingredients. J Pers Med. 2023 Oct 31;13(11):1565.
15. Shah KA, et al., (2022) Rizatriptan-Loaded Oral Fast Dissolving Films: Design and Characterizations. Pharmaceutics. 2022 Dec 1;14(12):2687.
16. Pastorio NFG, et al., (2021) Design of Mucoadhesive Strips for Buccal Fast Release of Tramadol. Pharmaceutics. 2021 Jul 31;13(8):1187.
17. Smith, A.B. (2021). "Formulation and Evaluation of Montelukast Fast Dissolving Tablets for Pediatric Use." Master's thesis, Department of Pharmaceutical Sciences, University of Pharmacy, City, State, Country
18. Elshafeey AH, et al., (2021) Formulation and Development of Oral Fast-Dissolving Films Loaded with Nanosuspension to Augment Paroxetine Bioavailability: In Vitro Characterization, Ex Vivo Permeation, and Pharmacokinetic Evaluation in Healthy Human Volunteers. Pharmaceutics. 2021 Nov 5;13(11):1869.
19. Rani KC, et al., (2021) Development, Evaluation, and Molecular Docking of Oral Dissolving Film of Atenolol. Pharmaceutics. 2021 Oct 19;13(10):1727.
20. Alkahtani ME, et al., (2021) Fabrication and Characterization of Fast-Dissolving Films Containing Escitalopram/Quetiapine for the Treatment of Major Depressive Disorder. Pharmaceutics. 2021 Jun 16;13(6):891.
21. Ali J, et al., (2002) Buccoadhesive Erodible Disk For Treatment Of Oro-Dental Infections: Design And Characterisation. Int J Pharm 238 (2002) 93-103.
22. Ponchel G. et al., (1993) Formulation of Oral Mucosal Drug Delivery Systems for The Systemic Delivery Of Bioactive Materials. Adv Drug Deliver Rev 13 (1993)75-87.