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RESEARCH ARTICLE

DESIGNING, OPTIMIZATION, FABRICATION AND EVALUATION MOUTH DISSOLVING FILM OF MONTELUKAST SODIUM

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ABSTRACT

Montelukast sodium is a selective, high affinity, competitive leukotriene receptor antagonist specifically the cysteinyl leukotriene (cyst-LT1) receptor. It suppresses both early and late bronchoconstrictor responses to inhaled antigens or irritants and is used in prevention and long-term symptomatic management of asthma. The objective of present research work is to formulate and evaluate mouth dissolving film of currently used therapeutic molecule (Montelukast sodium) for faster disintegration, faster drug availability and improved convenience to patients. The selected formulations (MF2 and MF4) were compared with a mouth dissolving film formulation available in market (MMDF) containing different drug, as the drug under present study (Montelukast sodium) is available as tablet dosage form only. The comparison was done for various evaluation parameters. When the appearance of optimized film MF2 and MF4 was compared with marketed MDF, it was observed that all three films were homogenous. Film MF2 was white in color; MF2 was colorless while marketed film was light orange in color. Films MF2 and MF4 were slightly opaque while marketed film was opaque. Films MF2 and MF4 were smooth from one side, but rough on the other side, while marketed film was smooth on both sides. It was observed from the results of comparison of selected formulations (MF2 and MF4) and marketed film, that the films prepared and optimized under the present study exhibited results that were comparable to that of a similar dosage form (marketed mouth dissolving film) with respect to various evaluation parameters.

Key words: mouth dissolving film, Montelukast sodium, Oral administration

INTRODUCTION:

Oral route of drug administration has been one of the most convenient and accepted route of drug delivery and amongst it the intraoral route is the most preferred due to its convenience and rapid onset of action. Intraoral dosage forms have evolved as an alternative to conventional tablets, capsules and liquid preparations [1-3]. Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Many pharmaceutical dosages are administered orally in the form of pills that include tablets and capsules. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance [2-6].

Asthma is a chronic lung disease that inflames and narrows the airways. Asthma causes recurring periods of wheezing (a whistling sound when one breaths), chest tightness, shortness of breath, and coughing. Montelukast sodium is a selective, high affinity, competitive leukotriene receptor antagonist specifically the cysteinyl leukotriene (cyst-LT1) receptor. It suppresses both early and late bronchoconstrictor responses to inhaled antigens or irritants and is used in prevention and long-term symptomatic management of asthma. Montelukast sodium is a selective, high affinity, competitive leukotriene receptor antagonist specifically the cysteinyl leukotriene (cyst-LT1) receptor. It suppresses both early and late bronchoconstrictor responses to inhaled antigens or irritants. Peak plasma concentrations of montelukast sodium are achieved in 2-4 hrs after oral administration. The mean oral bioavailability is 64%. Montelukast sodium is >99% bound to plasma proteins. It is extensively metabolized in the liver by cytochrome P-450 isoenzymes CYP3A4, CYP2A6 and CYP2C9, and is excreted principally in the feces via the bile. The t½ of montelukast sodium is between 3-6 hrs. Metabolism was reduced and the elimination t½ prolonged in patients with mild to moderate hepatic impairment. Adverse effects of montelukast sodium include edema, agitation and restlessness, allergy including anaphylaxis, angioedema and urticaria, chest

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pain, tremor, dry mouth, vertigo and arthralgia. Further suspected adverse events included nightmares, sedation, palpitations and increased sweating. Churg-Strauss syndrome has been reported in association with montelukast sodium [4, 5-10].

Recently, rapidly dissolving dosage forms (RDDF) have started gaining popularity and acceptance as new drug delivery systems due to their unique properties. They quickly disintegrate and dissolve in the mouth and can be administered without water, making them particularly suitable for pediatric and geriatric patients as well as in emergency requirement of drug. Asthma is a chronic lung disease that inflames and narrows the airways. Asthma causes recurring periods of wheezing (a whistling sound when one breaths), chest tightness, shortness of breath, and coughing.

The objective of present research work is to formulate and evaluate mouth dissolving film of currently used therapeutic molecule (Montelukast sodium) for faster disintegration, faster drug availability and improved convenience to patients.

MATERIAL AND METHODS

CHEMICALS AND REAGENTS USED

Montelukast Sodium was obtained from Ind-Swift, Baddi, India. Pullulan was purchased from Gangwal Chemicals Pvt. Ltd., Mumbai, India, Gelatin was purchased from CDH, India, METHO E5P was collected from Colorcon Asia Pvt. Ltd., Goa, India, Maltodextrin was purchased from Ind-Swift, Baddi, India and POLYOX WSR N80 was purchased from Colorcon Asia Pvt. Ltd., Goa, India. Water was glass-double distilled and further purified from Milli Q water purification system. All the other chemicals were used in analytical grades.

Method of preparation of MDF

MDF containing MLS were prepared using solvent casting method. An aqueous solution of polymer was prepared in distilled water. For preparing the solution, polymer was soaked in water for some time (wherever required). This was followed by addition of MLS in the aqueous solution of the polymer. Now, plasticizer (Sorbitol and/or Propylene glycol), sweetening agent (Aspartame and/or Sucralose), citric acid and flavor were also added to this solution. This solution was cast on a 9.8 cm diameter petri dish, containing a lining of liquid mercury (for leveling purpose). It was then dried at room temperature for 24 hour. The film was carefully removed from the petri dish, checked for imperfections, and cut to the desired size (3x2 cm^2) to deliver the equivalent dose per film. Film samples with air bubbles, cuts or imperfections were excluded from the study. The films were packed individually into aluminium foil and stored in a desiccator until further analysis.

Appearance

The appearance of prepared films was observed visually. Properties such as homogeneity, color, transparency and surface of the prepared films were evaluated.

Weight variation of mouth dissolving film

The weight of films was determined by an analytical balance with three decimal places/ sensitivity of 1 mg (Shimadzu BL-220H, Japan). Weight was determined to check weight variation of films within each petri dish and among different petri dish for same formulation.

Uniformity of thickness

The thickness of film was determined by digital Vernier Calipers and average thickness was calculated. Thickness was determined to check thickness variation of films within each petri dish and among different petri dish for same formulation.

Folding Endurance

The folding endurance is expressed as number of folds (number of times a film is folded at the same place) required to break the film or to develop visible cracks. This gives an indication of brittleness of the film. The film was subjected to this test by folding the film at the same place repeatedly several times until a visible crack was observed.

Drug content (Content uniformity)

The films were tested for content uniformity. The films was placed in 100 ml volumetric flask and dissolved in distilled water. Volume was made upto 100 ml with distilled water. Solutions were suitably diluted. The absorbance of solution was measured at 349 nm and amount of drug in each film was calculated.

Tensile Strength

Tensile strength was measured using modified analytical two pan balance method. The film was clamped between two clamps on one side; weights were added to the pan on other side until the film breaks. The weight required for breaking the film was taken as a measure of tensile strength of the films.

Percentage Elongation

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

$$\% \text{ Elongation} = [(L - L_0) \times 100] / L_0$$

Where, L = Final length at breaking of film

L_0 = Initial length

Moisture Content

Moisture content of the prepared films was determined using Karl-Fischer-Titration.

Disintegration Time (In-vitro)

In case of mouth dissolving films, the disintegration and dissolution is hardly distinguishable. If the mouth dissolving film disintegrates, it concurrently dissolves in a small amount of saliva, which makes it difficult to mimic these natural conditions and measure with an adequate method.

In the present work, consideration was given to developing a simple test and so, In-vitro disintegration time was determined using two independent methods – beaker method and slide frame method.

(A) Beaker method

In-vitro DT of the prepared mouth dissolving films was determined visually in a glass beaker containing 50ml water and swirling every 05 seconds. Average of 3 films was taken for this purpose.

(B) Frame Method

In the frame method, the films were clamped into frames. One drop of distilled water was dropped by a pipette on to the mouth dissolving film. The time taken for the drop to dissolve the film and form a hole in the film was recorded.

Disintegration Time (In-vivo)

In-vivo DT of the prepared mouth dissolving films was determined by mouth in three human volunteers. A mouth dissolving film was placed on the tongue of the volunteers and the time required to for disintegration of mouth dissolving film in the mouth was noted.

Taste Assessment (In-vivo)

Evaluation of taste was done by a taste panel with 10mg drug and subsequently one film held in the mouth for 10-15 seconds. The volunteers were asked to spit out, and the bitterness level was recorded. Volunteers were asked to gargle with distilled water before and after each taste evaluation. The taste of the mouth dissolving film was rated on a scale from 1 to 5. Scale 1 was equivalent to best taste and 5 was equivalent to the taste of the pure drug.

1 = no bitter taste
2 = very slightly bitter
3 = slightly bitter
4 = moderately bitter
5 = bitter (equivalent to pure drug)

Dissolution Studies

Dissolution medium = Acid buffer, pH 1.2 and Phosphate buffer pH 6.8

USP Dissolution apparatus – 2 (Paddle Apparatus)
RPM = 50
Time = 0 - 300 Seconds
Volume of media = 500 ml
Sampling volume = 5ml
Sampling interval = 0, 30, 60, 90, 120, 150, 180, 240, 300 seconds
Temperature = 37 ± 0.5^0 C

The film was added to the dissolution media. Samples were withdrawn at specified time interval. To maintain the volume, an equal volume of fresh dissolution medium maintained at same temperature was added after withdrawing samples. The amount of Montelukast sodium released from mouth dissolving film was determined by measuring UV absorbance at the wave-length of maximum absorbance at 349 nm using filtered portions of the solution under test (after suitable dilutions), using dissolution medium as the blank. The test solution was filtered through Whatmann filter paper (No.1).

Specification of sinker

Size: 4cm×3cm, sieve no. 100,

Scanning Electron Microscopy (SEM)

Surface morphology of the prepared films was observed under a scanning electron microscope.

Accelerated Stability Testing (AST)

Short term accelerated stability studies of the selected formulations were carried out at 40^0 C/75%RH (ICH guidelines) over a period of 6 months. The films were wrapped with aluminium foil, and stored in humidity controlled oven for 6 months. Samples were analysed for residual drug contents at time interval of 30 days.

RESULT AND DISCUSSIONS

APPEARANCE

The appearance of prepared Mouth dissolving film was observed visually. Results are shown in table. All prepared mouth dissolving films were homogenous. Mouth dissolving films prepared with Pullulan, Maltodextrin and POLYOX WSR N80 were white in color, while MDF prepared with Gelatin and METHOCEL E5 PREMIUM were colorless. Mouth dissolving films prepared with Pullulan, Gelatin and Maltodextrin were slightly opaque, MDF prepared with METHOCEL E5 PREMIUM were transparent, while MDF prepared with POLYOX WSR N80 were opaque. Mouth dissolving films prepared with Pullulan, Gelatin and POLYOX WSR N80 were smooth from one side, but rough on the other surface, while MDF prepared with METHOCEL E5 PREMIUM and Maltodextrin were smooth on both sides. It can be concluded that mouth dissolving films having good appearance can be prepared using above polymers, excipients and procedure.

WEIGHT VARIATION

The weight of films was determined by an analytical balance with three decimal places/ sensitivity of 1 mg (Shimadzu BL-220H, Japan). Weight was determined to

check weight variation within each petri dish and among different petri dish for same formulation.

All the prepared films showed good uniformity of weight within each petri dish and among different petri dishes of same formulations. The average weight of prepared films was ranging from 63.45 mg to 76.66 mg depending on the type and amount of polymer, drug and other excipients used in the formulations.

Among films prepared with Pullulan (MF1 and MF2), for MF1, average film weight was 70.23 mg (ranging from 67 mg to 74 mg); and for MF2, average film weight was 71.21 mg (ranging from 67 mg to 75 mg). Among films prepared with Gelatin (MF3 and MF4), for MF3, average film weight was 76.66 mg (ranging from 73 mg to 80 mg); and for MF4, average film weight was 76.39 mg (ranging from 73 mg to 80 mg). Among films prepared with Methocel E5 Premium HPMC (MF5 and MF6), for MF5, average film weight was 66.50 mg (ranging from 63 mg to 70 mg); and for MF6, average film weight was 65.66 mg (ranging from 62 mg to 69 mg). Among films prepared with Maltodextrin (MF7 and MF8), for MF7, average film weight was 75.25 mg (ranging from 71 mg to 80 mg); and for MF8, average film weight was 75.02 mg (ranging from 72 mg to 79 mg). Among films prepared with Polyox WSR N80 (MF9 and MF10), for MF9, average film weight was 63.45 mg (ranging from 59 mg to 68 mg); and for MF10, average film weight was 63.96 mg (ranging from 60 mg to 69 mg).

The prepared films showed good uniformity of weight both within each petri dish and among different petri dish for same formulation. It can be concluded that mouth dissolving films having good weight uniformity can be prepared using above polymers, excipients and procedure.

UNIFORMITY OF THICKNESS

The thickness of film was determined by digital Vernier Calipers and average thickness was calculated. Thickness was determined to check thickness variation within each petri dish and among different petri dish for same formulation. All the prepared films showed good uniformity in thickness within each petri dish and among different petri dish of same formulations. The average thickness of prepared films was ranging from 310.7 µm to 417.1 µm depending on the type and amount of polymer, drug and other excipients used in the formulations. Among films prepared with Pullulan (MF1 and MF2), for MF1, average film thickness was 378.6 µm (ranging from 370 µm to 390 µm); and for MF2, average film thickness was 370.4 µm (ranging from 360 µm to 380 µm). Among films prepared with Gelatin (MF3 and MF4), for MF3, average film thickness was 410.5 µm (ranging from 400 µm to 420 µm); and for MF4, average film thickness was 417.1 µm (ranging from 400 µm to 430 µm). Among films prepared with Methocel E5 Premium HPMC (MF5 and MF6), for MF5, average film thickness was 330.1 µm (ranging from 310 µm to 340 µm); and for MF6, average film thickness was 337.5 µm (ranging from 320 µm to 350 µm). Among films prepared with Maltodextrin (MF7 and MF8), for MF7, average film thickness was 390.0 µm (ranging from 380 µm to 400 µm); and for MF8, average film thickness was 397.1 µm (ranging from 380 µm to 410 µm). Among films prepared with Polyox WSR N80 (MF9 and MF10), for MF9, average film thickness was 315.2 µm (ranging from 300 µm to 330 µm); and for MF10, average film thickness was 310.7 µm (ranging from 300 µm to 320 µm).

The prepared films showed good uniformity in thickness both within each petri dish and among different petri dish for same formulation. It can be concluded that mouth dissolving films having good uniformity in thickness can be prepared using above polymers, excipients and procedure.

FOLDING ENDURANCE

The folding endurance is expressed as number of folds (number of times a film is folded at the same place) required to break the film or to develop visible cracks. This gives an indication of brittleness of the film. The film was subjected to this test by folding the film at the same place repeatedly several times until a visible crack was observed. Three films were selected randomly from each formulation to evaluate folding endurance of prepared mouth dissolving film.

All the prepared films showed good folding endurance. The average folding endurance of the prepared films was ranging from 106 to 258 folds depending on the type of polymer and the plasticizer used in the formulations. The films prepared with Gelatin (MF3 and MF4) showed maximum average value of folding endurance, i.e. 229 and 258 folds for MF3 and MF4 respectively. Films prepared with Polyox WSR N80 (MF9 and MF10) showed minimum average values of folding endurance, i.e. 106 and 109 folds for MF9 and MF10 respectively. Remaining polymers showed intermediate folding endurance, i.e. 227 and 233 folds for films prepared with Pullulan (MF1 and MF2 respectively), 169 and 174 folds for films prepared with Methocel E5 Premium HPMC (MF5 and MF6 respectively) and 142 and 151 folds for films prepared with Maltodextrin (MF7 and MF8 respectively). Films showed better folding endurance when combinations of plasticizers (Sorbitol and propylene glycol) were used in combination than when they were used alone. It can be concluded that mouth dissolving

films having good folding endurance can be prepared using above polymers, excipients and procedure.

DRUG CONTENT (CONTENT UNIFORMITY)

The films were tested for content uniformity. The films was placed in 100 ml volumetric flask and dissolved in distilled water. Volume was made upto 100 ml with distilled water. Solutions were suitably diluted. The absorbance of solution was measured at 349 nm and amount of drug in each film was calculated. Three films were selected randomly from each formulation to evaluate drug content of prepared mouth dissolving film.

All the prepared films had almost 100% drug content. The average % drug content ranges from 102.4% to 96.5%. Average % drug content values for films prepared with Pullulan (MF1 and MF2) were found to be 99.0% and 99.6% respectively; for films prepared with Gelatin (MF3 and MF4) average % drug content were found to be 100.6% and 102.4% respectively; for films prepared with Methocel E5 Premium HPMC (MF5 and MF6) average % drug content were found to be 98.2% and 102.4% respectively; for films prepared with Maltodextrin (MF7 and MF8) average % drug content were found to be 96.5% and 98.7% respectively; and for films prepared with Polyox WSR N80 (MF9 and MF10), average % drug content were found to be 98.2% and 101.4% respectively. It can be concluded that mouth dissolving films having good drug content can be prepared using above polymers, excipients and procedure.

TENSILE STRENGTH

Tensile strength was measured using modified analytical two pan balance method. The film was clamped between two clamps on one side; weights were added to the pan on other side until the film breaks. The weight required for breaking the film was taken as a measure of tensile strength of the films. Three films were selected randomly from each formulation to evaluate tensile strength of the prepared mouth dissolving films.

All the prepared films showed good tensile strength. The average tensile strength of the prepared films was ranging from 1.19 kg to 5.01 kg depending on the type of polymer and the plasticizer used in the formulations.

The films prepared with Gelatin (MF3 and MF4) showed maximum average value of tensile strength, i.e. 4.67 kg and 5.01 kg for F3 and F4 respectively. Films prepared with Polyox WSR N80 (MF9 and MF10) showed minimum average values of tensile strength, i.e. 1.34 kg and 1.19 kg for MF9 and MF10 respectively. Remaining polymers showed intermediate tensile strength, i.e. 4.06 kg and 4.18 kg for films prepared with Pullulan (MF1 and MF2 respectively), 3.70 kg and 3.46 kg for films prepared with Methocel E5 Premium HPMC (MF5 and MF6 respectively) and 1.95 kg and 2.08 kg for films prepared with Maltodextrin (MF7 and MF8 respectively). It can be concluded that mouth dissolving films having good tensile strength can be prepared using above polymers, excipients and procedure.

PERCENTAGE ELONGATION

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

$\% \text{ Elongation} = [(L - L_0) \times 100] / L_0$

Where L = Final length at breaking of film

L_0 = Initial length

Three films were selected randomly from each formulation to evaluate percentage elongation of the prepared mouth dissolving films. All the prepared films showed good percent elongation. The average percent elongation of the prepared films was ranging from 5.17% to 11.15% depending on the type of polymer and the plasticizer used in the formulations.

The films prepared with Gelatin (MF3 and MF4) showed maximum average value of percent elongation, i.e. 10.22% and 11.15% for MF3 and MF4 respectively. Films prepared with Polyox WSR N80 (MF9 and MF10) showed minimum average values of percent elongation, i.e. 5.26% and 5.17% for MF9 and MF10 respectively. Remaining polymers showed intermediate percent elongation, i.e. 8.05% and 9.96% for films prepared with Pullulan (MF1 and MF2 respectively), 6.57% and 6.11% for films prepared with Methocel E5 Premium HPMC (MF5 and MF6 respectively) and 5.98% and 5.79% for films prepared with Maltodextrin (MF7 and MF8 respectively). It can be concluded that mouth dissolving films showing good percent elongation can be prepared using above polymers, excipients and procedure.

MOISTURE CONTENT

Moisture content of the films was determined using Karl-Fischer-Titration. Three films were selected randomly from each formulation to determine moisture content of the prepared mouth dissolving films.

The average moisture content of the prepared films was ranging from 4.48% to 8.67% (%w/w) depending on the type of polymer and other excipients used in the formulations. The films prepared with Gelatin (MF3 and MF4) showed maximum average value of moisture content, i.e. 8.13% and 8.67% for MF3 and MF4 respectively. Films prepared with Maltodextrin (MF7 and MF8) showed minimum average values of moisture content, i.e. 4.82% and 4.48% for MF7 and MF8 respectively. Remaining polymers showed intermediate moisture content, i.e. 6.32% and 7.52% for films prepared with Pullulan (MF1 and MF2 respectively); 7.13% and

5.42% for films prepared with Methocel E5 Premium HPMC (MF5 and MF6 respectively) and 5.88% and 4.55% for films prepared with Polyox WSR N80 (MF9 and MF10 respectively).

As per the literatures available regarding mouth dissolving films, the moisture contents must be from 4% to 12%. And in all the prepared films, the moisture content is within this range. So, it can be concluded that mouth dissolving films having optimum moisture content can be prepared using above polymers, excipients and procedure.

DISINTEGRATION TIME (IN-VITRO)

In case of mouth dissolving films, the disintegration and dissolution is hardly distinguishable. If the mouth dissolving film disintegrates, it concurrently dissolves in a small amount of saliva, which makes it difficult to mimic these natural conditions and measure with an adequate method.

In the present work, consideration was given to developing a simple test and so, In-vitro disintegration time was determined using two independent methods – beaker method and slide frame method.

Beaker method

In-vitro DT of the prepared MDF was determined visually in a glass beaker containing 50ml water and swirling every 05 seconds. Average of 3 films was taken for this purpose.

Three films were selected randomly from each formulation to determine In-vitro disintegration time of the MDF using beaker method.

Table 1: In-vitro disintegration time of prepared films using beaker method

S. No.	Formulation Code	Disintegration time (Sec.) (Mean± S.D.*)
	MF 1	37.7±3.1
	MF 2	36.7±2.1
	MF 3	36.7±2.1
	MF 4	32.0±2.6
	MF 5	41.0±2.0
	MF 6	42.3±1.5
	MF 7	37.7±2.1
	MF 8	39.7±3.1
	MF 9	42.3±2.1
	MF 10	40.3±3.1

* Standard deviation, n=3

Frame Method

In the frame method, the films were clamped into frames. One drop of distilled water was dropped by a pipette on to the oral films. The time taken for the drop to dissolve the film and form a hole in the film was recorded. Three films were selected randomly from each formulation to determine In-vitro disintegration time of the MDF using frame method.

Table 2: In-vitro disintegration time of prepared films using frame method

S. No.	Formulation Code	Disintegration time (Sec.) (Mean± S.D.*)
	MF 1	34.7±2.5
	MF 2	35.3±2.5
	MF 3	34.3±2.5
	MF 4	30.0±1.0
	MF 5	38.0±2.6
	MF 6	39.3±2.5
	MF 7	38.7±2.5
	MF 8	38.0±3.0
	MF 9	39.7±1.5
	MF 10	39.3±1.5

* Standard deviation, n=3

Disintegration Time (In-vitro)

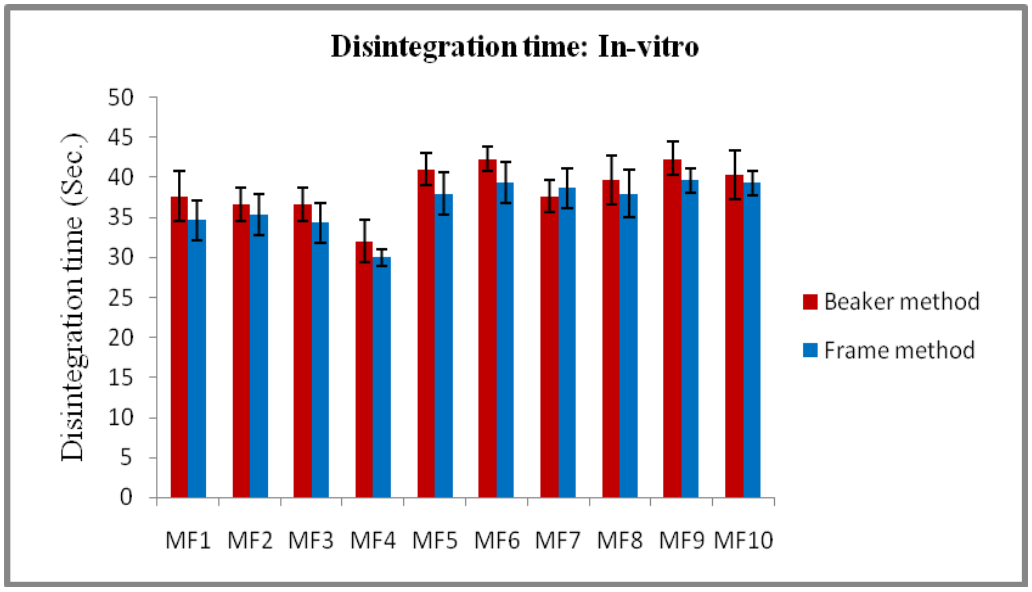


Fig. 1: Comparison of In-vitro disintegration time of prepared films using beaker & frame method, n=3

All the prepared films disintegrate rapidly in-vitro. Also, there was very less variation in In-vitro disintegration time by two methods (beaker method and frame method). It was observed that the average In-vitro disintegration time of the prepared films was ranging from 30.0 seconds to 42.3 seconds depending on the type of polymer and other excipients used in the formulations.

The films prepared with Gelatin (MF3 and MF4) showed minimum average value of In-vitro disintegration time, i.e. for MF3 and MF4, it was found to be 36.7 seconds and 32.0 seconds respectively (using beaker method) and 34.3 seconds and 30.0 seconds respectively (using frame method). Films prepared with Methocel E5 Premium HPMC (MF5 and MF6) showed maximum average value of In-vitro disintegration time, i.e. for MF5 and MF6, it was found to be 41.0 seconds and 42.3 seconds respectively (using beaker method) and 38.0 seconds and 39.3 seconds respectively (using frame method). Films prepared with other polymers showed intermediate values of In-vitro disintegration time. Average values of In-vitro disintegration time for films prepared with Pullulan (MF1 and MF2) were found to be 37.7 seconds and 36.7 seconds respectively (using beaker method) and 34.7 seconds and 35.3 seconds respectively (using frame method). Average values of In-vitro disintegration time for films prepared with Maltodextrin (MF7 and MF8) were found to be 37.7 seconds and 39.7 seconds respectively (using beaker method) and 38.7 seconds and 38.0 seconds respectively (using frame method). Average values of In-vitro disintegration time for films prepared with Polyox WSR N80 (MF9 and MF10) were found to be 42.3 seconds and 40.3 seconds respectively (using beaker method) and 39.7 seconds and 39.3 seconds respectively (using frame method). Films prepared using sorbitol or propylene glycol showed almost same In-vitro disintegration time and there is very less difference in In-vitro disintegration time using both plasticizers. It can be concluded that mouth dissolving films can be prepared using above polymers, excipients and procedure, which disintegrate rapidly.

DISINTEGRATION TIME (IN-VIVO)

In-vivo DT of the prepared mouth dissolving films was determined by mouth in three human volunteers. An MDF was placed on the tongue of the volunteers and the time required for disintegration of MDF in the mouth was noted. Three films were selected randomly from each formulation to determine In-vivo disintegration time of the prepared mouth dissolving films.

All the prepared films disintegrate rapidly in-vivo. It was observed that the average In-vivo disintegration time of the prepared films was ranging from 33.0 seconds to 40.3 seconds depending on the type of polymer and other excipients used in the formulations.

The films prepared with Gelatin (MF3 and MF4) showed minimum average value of In-vivo disintegration time, i.e. for MF3 and MF4, it was found to be 34.3 seconds and 33.0 seconds respectively. Films prepared with Methocel E5 Premium HPMC (MF5 and MF6) showed maximum average value of In-vivo disintegration time, i.e. for MF5 and MF6, it was found to be 39.3 seconds and 40.3 seconds respectively. Films prepared with other polymers showed

intermediate values of In-vivo disintegration time. Average values of In-vivo disintegration time for films prepared with Pullulan (MF1 and MF2) were found to be 35.0 seconds and 34.3 seconds respectively. Average values of In-vivo disintegration time for films prepared with Maltodextrin (MF7 and MF8) were found to be 40.0 seconds and 37.3 seconds respectively. Average values of In-vivo disintegration time for films prepared with Polyox WSR N80 (MF9 and MF10) were found to be 39.7 seconds and 37.7 seconds respectively.

It can be concluded that mouth dissolving films can be prepared using above polymers, excipients and procedure, which disintegrate rapidly in the mouth.

TASTE ASSESSMENT

Evaluation of taste was done by a taste panel with 10 mg drug and subsequently one film held in the mouth for 10-15 seconds. The volunteers were asked to spit out, and the bitterness level was recorded. Volunteers were asked to gargle with distilled water before and after each taste evaluation. The taste of the MDF was rated on a scale from 1 to 5. Scale 1 was equivalent to best taste and 5 was equivalent to the taste of the pure drug. All the prepared films showed good taste masking property. The level of bitterness of the prepared films was ranging from 1 to 3 on the bitterness scale of 1 (no bitter taste) - 5 (bitter, equivalent to pure drug) depending on the type of polymer, plasticizer and taste masking agent(s) used in the formulations.

The average level of bitterness for films prepared with Pullulan (MF1 and MF2) was 1.7 for both. The average level of bitterness for films prepared with Gelatin (MF3 and MF4) was found to be 2.0 and 1.7 respectively. For films prepared with Methocel E5 Premium HPMC (MF5 and MF6), the average level of bitterness was found to be 1.7 and 2.0 respectively. For films prepared with Maltodextrin (MF7 and MF8), the average level of bitterness was 2.0 and 1.7 respectively. And, for films prepared with Polyox WSR N80 (MF9 and MF10), the average level of bitterness was 2.3 for both. A significant difference was found in the level of bitterness even for the same formulation. This may be due to the sensitivity of individual towards bitterness.

It can be concluded that mouth dissolving films having good taste masking property can be prepared using above polymers, taste masking agent(s), other excipients and procedure.

DISSOLUTION STUDIES

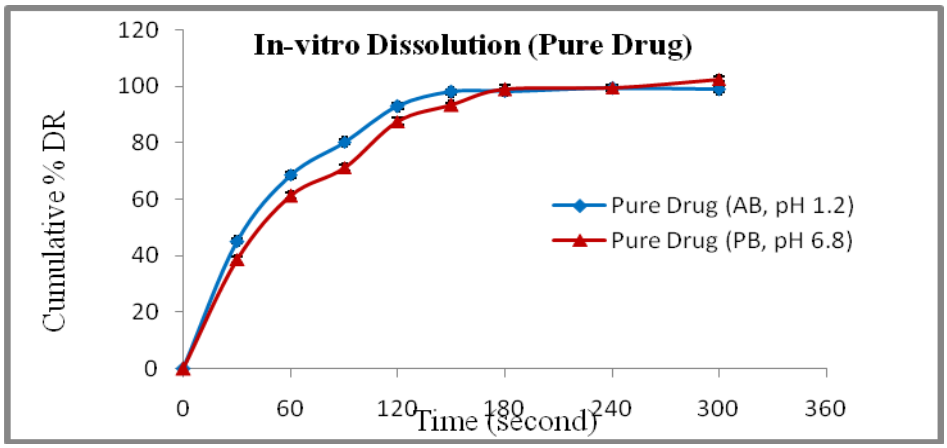


Fig. 2: Dissolution profile of pure drug-MLS, n=3

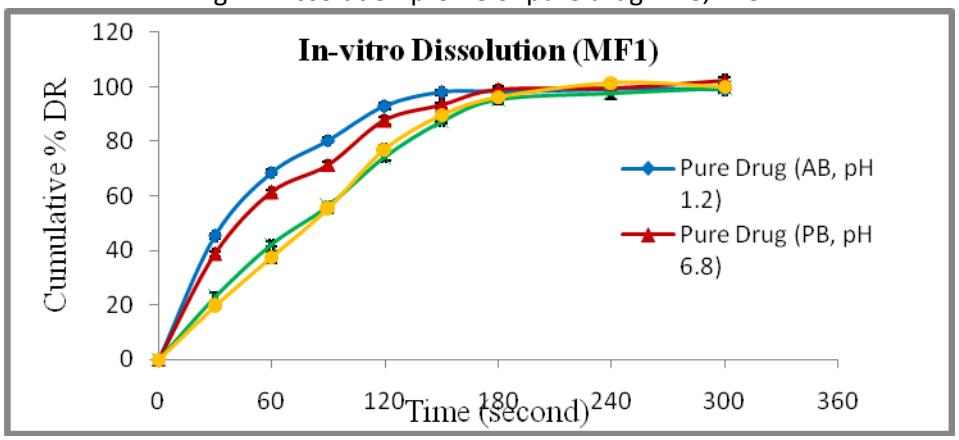


Fig. 3: Dissolution profile of formulation MF1, n=3

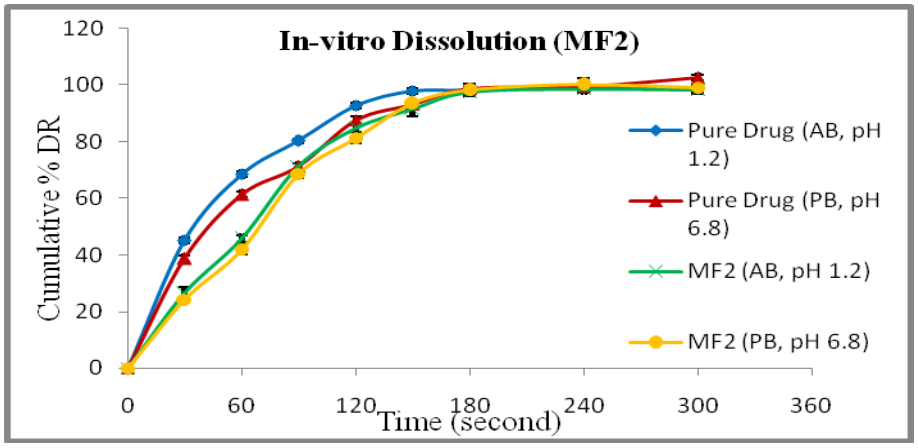


Fig.4: Dissolution profile of formulation MF2, n=3

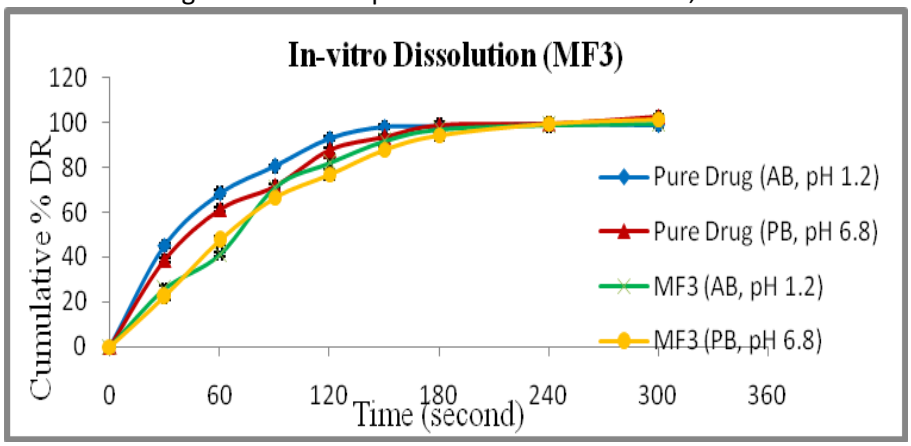


Fig. 5: Dissolution profile of formulation MF3, n=3

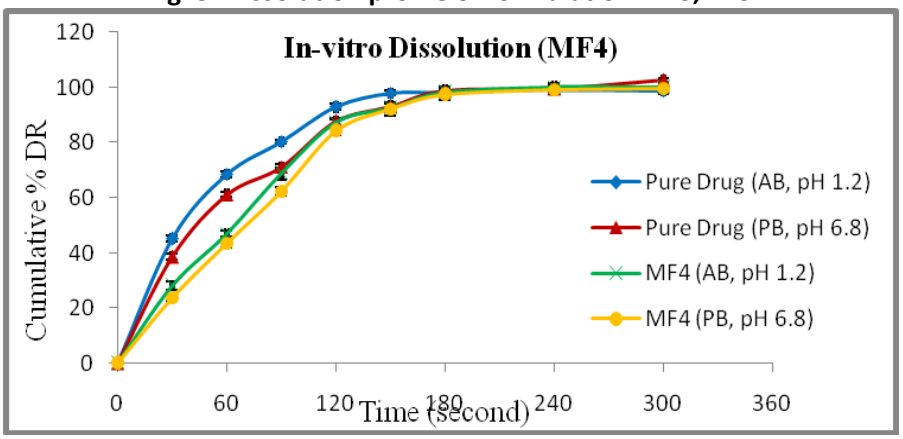


Fig. 6: Dissolution profile of formulation MF4, n=3

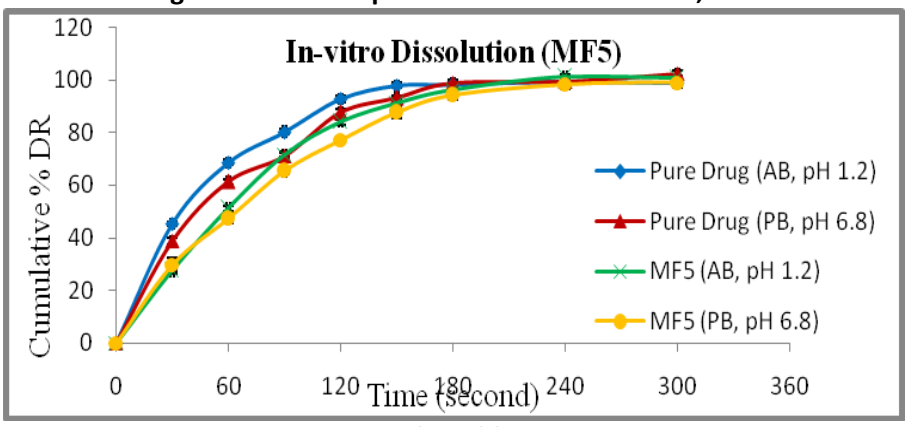


Fig. 7: Dissolution profile of formulation MF5, n=3

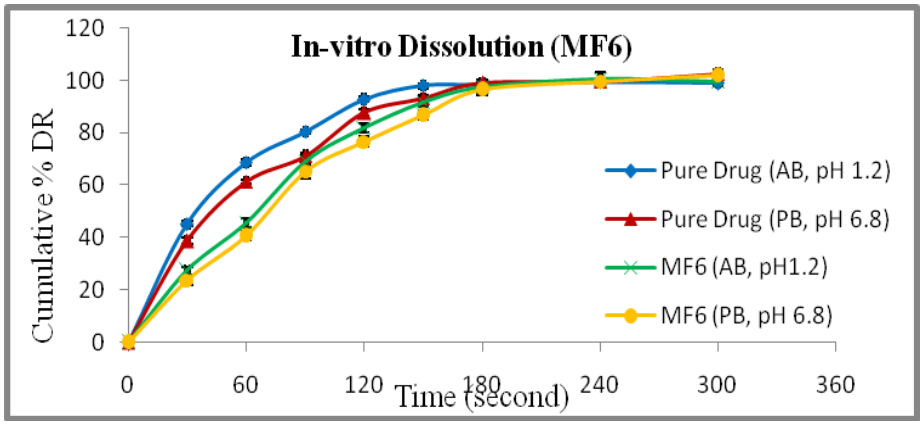


Fig. 8: Dissolution profile of formulation MF6, n=3

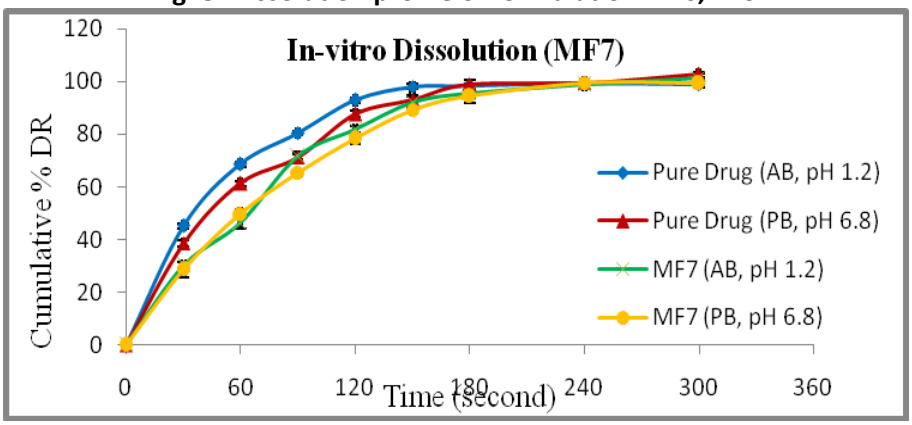


Fig.9: Dissolution profile of formulation MF7, n=3

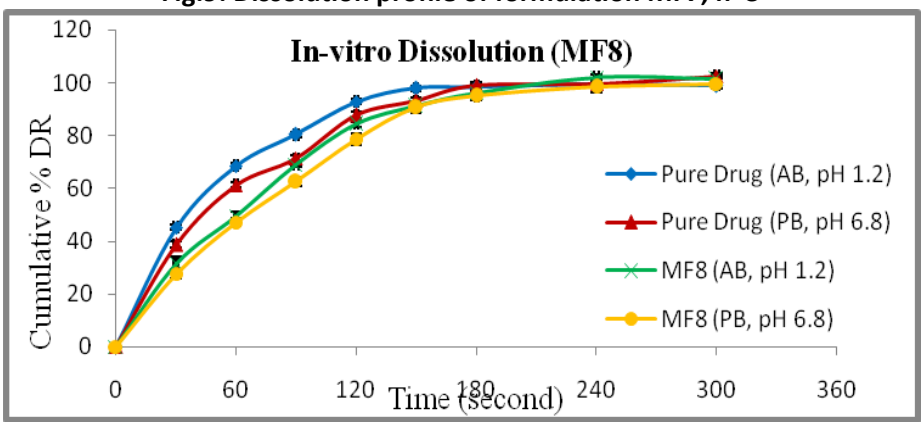


Fig. 10: Dissolution profile of formulation MF8, n=3

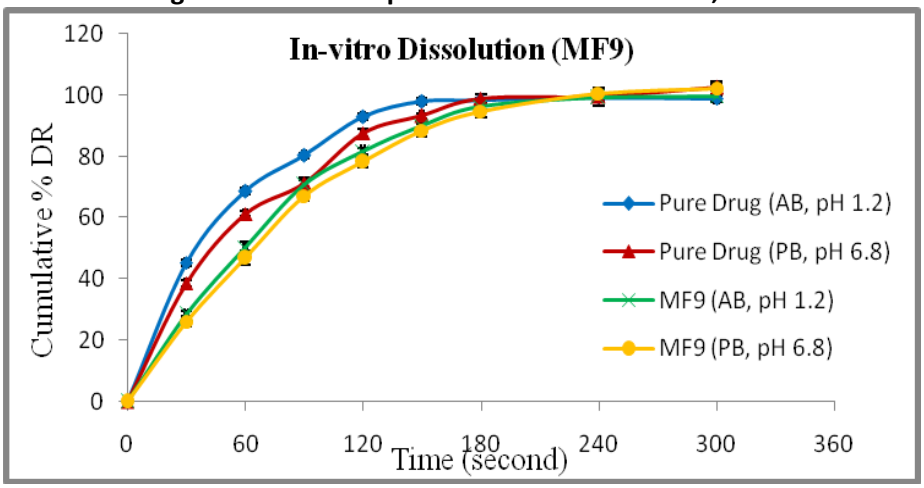


Fig. 11: Dissolution profile of formulation MF9, n=3

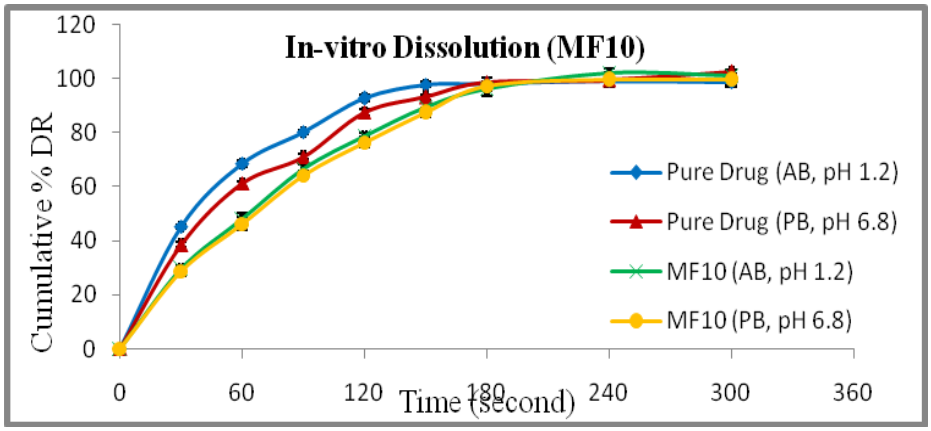


Fig. 12: Dissolution profile of formulation MF10, n=3

All the prepared films showed fast dissolution profile. Dissolution of Montelukast sodium starts immediately when the film is added to the dissolution media. It was observed that for all the films, 90% drug was dissolved within 150-180 seconds.

There was not much difference in the release profile of drug from the prepared films in both the medium, i.e. acid buffer pH 1.2 and phosphate buffer pH 6.8. This can be due to the fact that the solubility of drug (Montelukast sodium) is almost same in both the medium. It can be concluded that mouth dissolving films can be prepared using above polymers, other excipients and procedure that release the drug rapidly.

SCANNING ELECTRON MICROSCOPY (SEM)

Surface morphology of the prepared films was observed under a scanning electron microscope. SEM was done for one preparation of each polymer.

SEM was done for MF1, MF3, MF5, MF7 and MF9 formulations.

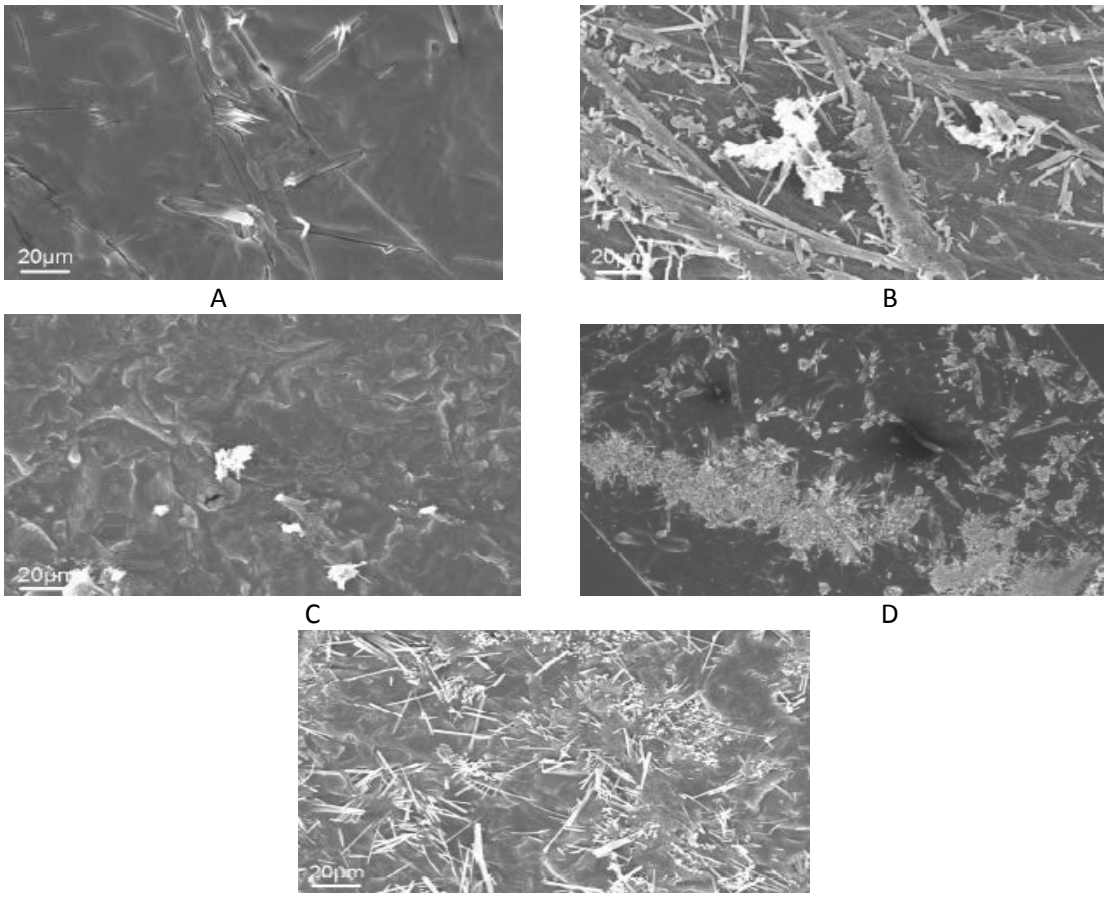


Fig. 13: SEM of formulations-A: MF1, B: MF3, C: MF5, D: MF7, E: MF9

SEM photographs indicate homogenous film formation and uniform distribution of MLS in the polymer.

ACCELERATED STABILITY TESTING (AST)

Short term accelerated stability studies of the selected formulations were carried out at 40^0 C/75%RH (ICH guidelines) over a period of 6 months. The films were wrapped with aluminium foil, and stored in humidity controlled oven for 6 months. Samples were analysed for residual drug contents at time interval of 30 days (1 month). Average of 3 films was taken for this purpose.

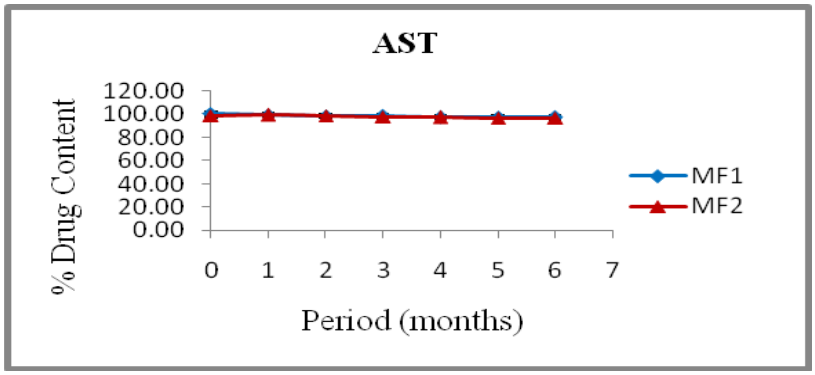


Fig. 14: AST of formulation MF1, MF2; n=3

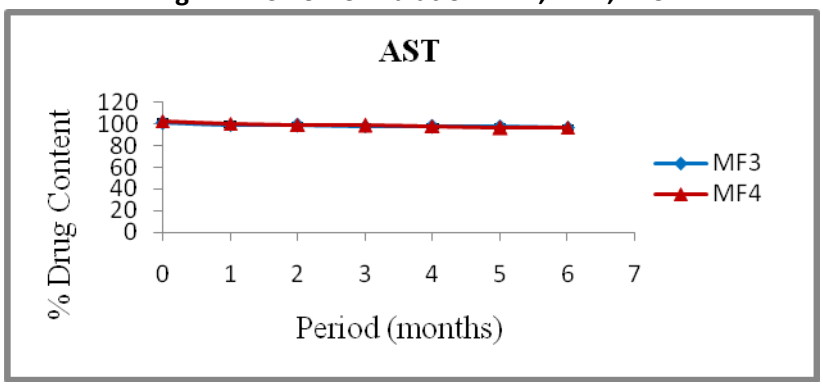


Fig.15: AST of formulation MF3, MF4; n=3

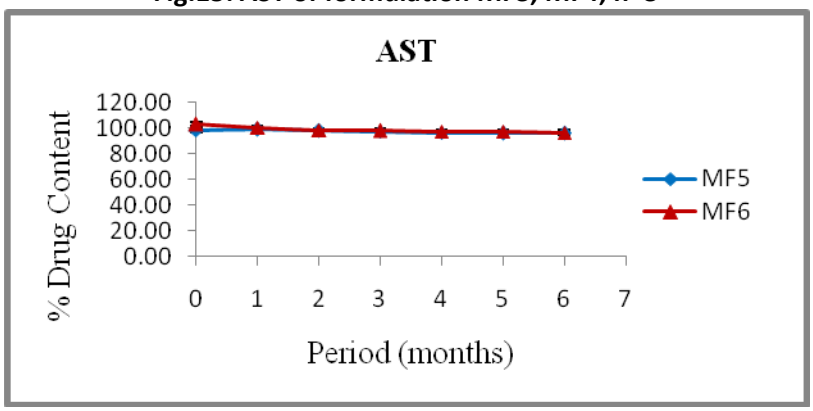


Fig.16: AST of formulation MF5, MF6; n=3

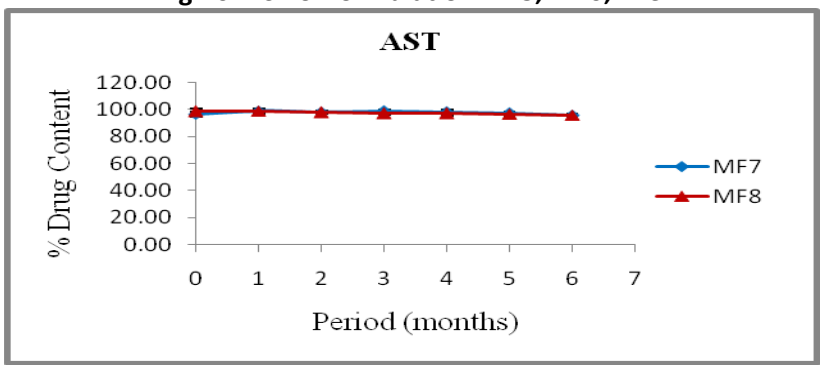


Fig.17: AST of formulation MF7, MF8; n=3

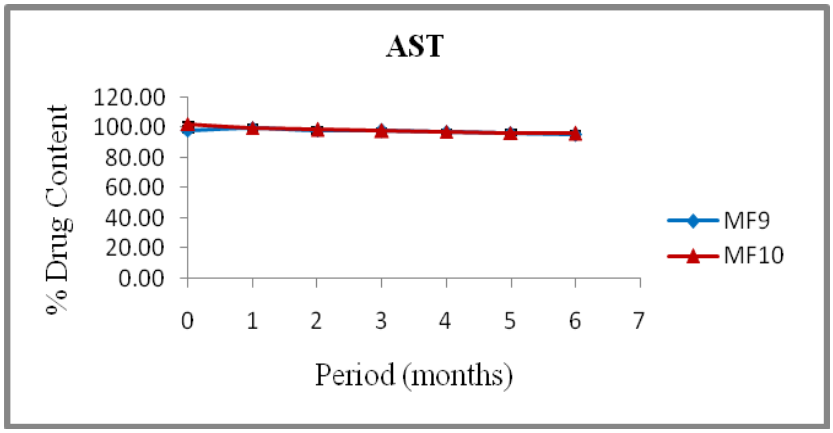


Fig.18: AST of formulation MF9, MF10; n=3

All the prepared films showed good stability at accelerated conditions. When content of Montelukast sodium were analysed at various time interval, it was found to be 95.27% to 97.21% for all the formulations. For the films prepared with Pullulan, % drug content remained after 6 months for MF1 was 97.21% while for MF2, it was 96.84%. For films prepared with Gelatin, % drug content remained after 6 months for MF3 was 96.74% while for MF4, it was 96.53%. For films prepared with Methocel E5 Premium HPMC, % drug content remained after 6 months for MF5 was 95.82 % while for MF6, it was 96.45%. For films prepared with Maltodextrin, % drug content remained after 6 months for MF7 was 96.04 % while for MF8, it was 95.86%. For films prepared with Polyox WSR N80, % drug content remained after 6 months for MF9 was 95.27% while for MF10, it was 95.95%. It can be concluded that mouth dissolving films can be prepared using above polymers, excipients and procedure, which show good stability.

Table 3: Optimization of prepared mouth dissolving films

S. No.	Formulation code	Folding endurance (No. of folds*)	Tensile strength (Kg*)	Percentage Elongation*	DT (In-vitro) (Sec.*)		DT (In-vivo) (Sec.*)	Taste/ Level of Bitterness*
					Beaker method	Frame method		
1.	Pure Drug	-	-	-	-	-	-	5.0±0.0
2.	MF 1	227.3±9.3	4.06±0.27	8.05±0.55	37.7±3.1	34.7±2.5	35.0±2.6	1.7±0.6
3.	**MF 2**	**233.0±10.0**	**4.18±0.24**	**9.96±0.36**	**36.7±2.1**	**35.3±2.5**	**34.3±2.1**	**1.7±0.6**
4.	**MF 3**	229.3±9.1	4.67±0.28	10.22±0.25	36.7±2.1	34.3±2.5	34.3±3.1	2.0±1.0
5.	**MF 4**	**258.0±14.0**	**5.01±0.15**	**11.15±0.56**	**32.0±2.6**	**30.0±1.0**	**33.0±2.6**	**1.7±0.6**
6.	**MF 5**	169.0±15.4	3.70±0.07	6.57±0.42	41.0±2.0	38.0±2.6	39.3±2.1	1.7±0.6
7.	**MF 6**	174.3±10.7	3.46±0.24	6.11±0.17	42.3±1.5	39.3±2.5	40.3±2.5	2.0±0.0
8.	**MF 7**	142.3±9.1	1.95±0.16	5.98±0.27	37.7±2.1	38.7±2.5	40.0±4.4	2.0±1.0
9.	**MF 8**	151.0±10.5	2.08±0.20	5.79±0.40	39.7±3.1	38.0±3.0	37.3±3.1	1.7±0.6
10.	**MF 9**	106.0±10.5	1.34±0.21	5.26±0.14	42.3±2.1	39.7±1.5	39.7±3.2	2.3±0.6
11.	**MF 10**	109.0±13.2	1.19±0.16	5.17±0.09	40.3±3.1	39.3±1.5	37.7±2.1	2.3±0.6

*Mean± S.D., (n=3)

The prepared mouth dissolving films were evaluated with respect to various parameters, and the results were found to be satisfactory. For the purpose of selecting best two formulations, folding endurance, tensile strength, percentage elongation, In-vitro disintegration time, In-vivo disintegration time and taste/level of bitterness were considered as critical parameters.

Based upon these critical parameters, it was concluded that formulation MF2 and MF4 showed optimum values. Folding endurance, tensile strength and percentage elongation of MDF must be as high as feasible. It was observed that the average value of folding endurance was 233.0 and 258.0, average value of tensile strength was 4.18 kg and 5.01 kg and that of percentage elongation was 9.96% and 11.15% for MF2 and MF4 respectively. In-vitro disintegration time, In-vivo disintegration time and level of bitterness must be as low as feasible. Average value of In-vitro disintegration time was 37 second and 32 second (using beaker method) and 35 second and 30 second (using frame method), average value of In-vivo disintegration time was 34 second and 33 second and average level of bitterness was found to be 1.7 (on a scale of 1-5) for both the formulations MF2 and MF4 respectively. Based on the same, formulations MF2 and MF4 were selected as best two formulations.

OPTIMIZATION BY COMPARISON WITH A SIMILAR DOSAGE FORM AVAILABLE IN MARKET

The selected formulations (MF2 and MF4) were compared with a mouth dissolving film formulation available in market (MMDF) containing different drug, as the drug under present study (Montelukast sodium) is available as tablet dosage form only. The comparison was done for various evaluation parameters. When the appearance of optimized film MF2 and MF4 was compared with marketed MDF, it was observed that all three films were homogenous. Film MF2 was white in color; MF2 was colorless while marketed film was light orange in color. Films MF2 and MF4 were slightly opaque while marketed film was opaque. Films MF2 and MF4 were smooth from one side, but rough on the other side, while marketed film was smooth on both sides.

All three films (MF2, MF4 and marketed MDF) showed good uniformity of weight. For MF2, average film weight was 71.21 mg (ranging from 67 mg to 75 mg); for MF4, average film weight was 76.39 mg (ranging from 73 mg to 80 mg); and for marketed MDF, average film weight was 44.67 mg (ranging from 44 mg to 45 mg). All three films (MF2, MF4 and marketed MDF) showed good uniformity in thickness. For MF2, average film thickness was 370.4 µm (ranging from 360 µm to 380 µm); for MF4, average film thickness was 417.1 µm (ranging from 400 µm to 430 µm); and for marketed MDF, average film thickness was 316.7 µm (ranging from 310 µm to 320 µm). All three films (MF2, MF4 and marketed MDF) showed good folding endurance. For MF2, average folding endurance was 233 folds; for MF4, average folding endurance was 258 folds; and for marketed MDF, average folding endurance was 227 folds. All three films had almost 100% drug content. Average drug content for MF2 was found to be 99.6%; for MF4, average drug content was found to be 102.4% and for marketed MDF, average drug content was found to be 99.8%. All three films showed good tensile strength. Average tensile strength for MF2 was 4.18 kg, for MF4 average tensile strength was 5.01 kg and for marketed MDF, average tensile strength was found to be 4.82 kg. All three films showed good percent elongation. Average percent elongation for MF2 was 9.96%, for MF4 average percent elongation was 11.15% and for marketed MDF, average percentage elongation was found to be 8.54%. All three films showed optimum moisture content. Average moisture content for MF2 was 7.52%, for MF4 average moisture content was 8.67% and for marketed MDF, average moisture content was found to be 9.13%. All three films disintegrated rapidly in-vitro. Average value of in-vitro disintegration time for MF2 was found to be 36.7 seconds (using beaker method) and 35.3 seconds (using frame method); average value of in-vitro disintegration time for MF4 was found to be 32.0 seconds (using beaker method) and 30.0 seconds (using frame method); and average value of in-vitro disintegration time for marketed MDF was found to be 33.7 seconds (using beaker method) and 29.0 seconds (using frame method). All three films disintegrated rapidly in-vivo. Average value of in-vivo disintegration time for MF2 was 34.3 seconds, average value of in-vivo disintegration time for MF4 was 33.0 seconds and average in-vivo disintegration time for marketed MDF was found to be 31.7 seconds. All three films showed good taste masking property. Average level of bitterness for MF2 and MF4 was found to be 1.7 (on a scale of 1-5), and average level of bitterness for marketed MDF was found to be 1.3 (on a scale of 1-5) on comparing with the respective pure drug.

Comparison of Dissolution profiles:

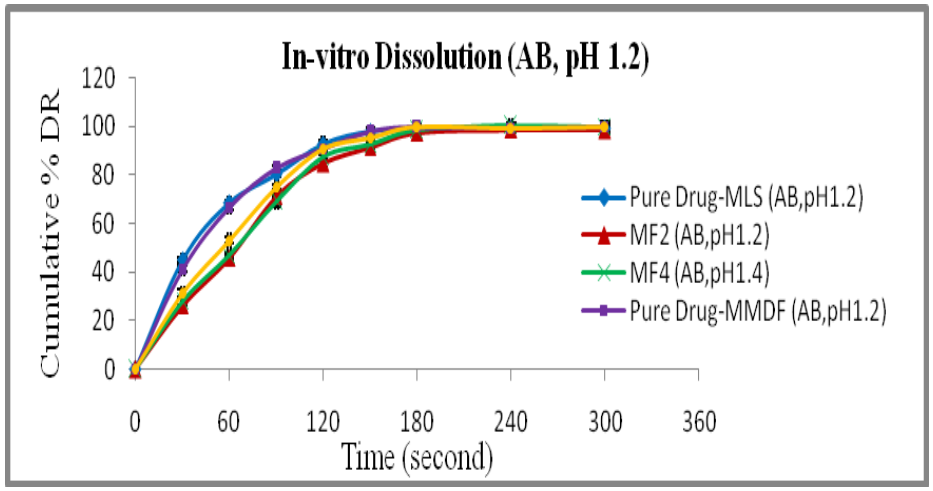


Fig.19: Comparison of dissolution profiles for optimized formulations and marketed MDF in acid buffer, pH 1.2, n=3

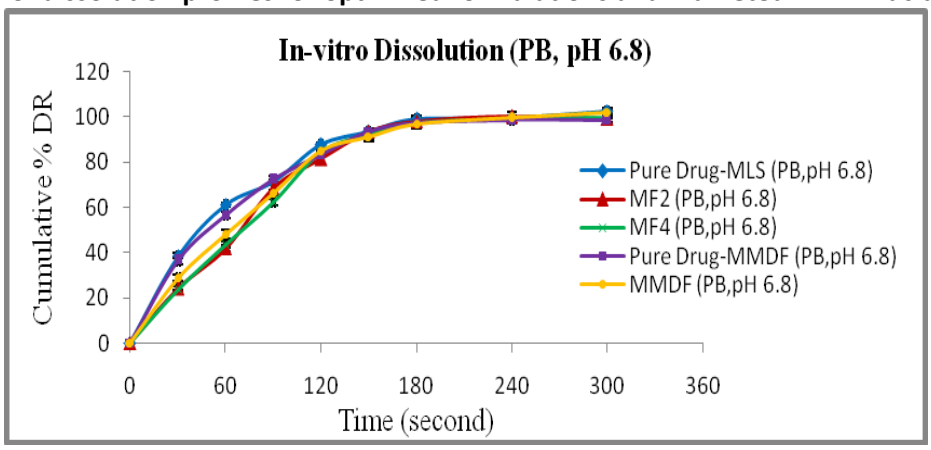
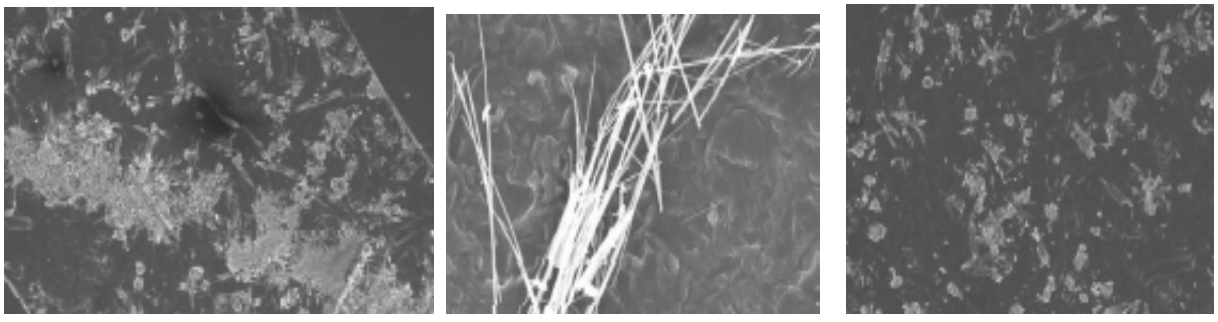


Fig. 20: Comparison of dissolution profiles for optimized formulations and marketed MDF in phosphate buffer, pH 6.8, n=3

All three films showed fast dissolution profile. Dissolution of the drug started immediately when the film was added to the dissolution media. It was observed that for all the three films, 90% drug was dissolved within 120-150 seconds in both (acid buffer pH 1.2 and phosphate buffer pH 6.8) the medium.

Scanning Electron Microscope (SEM):



A B C

Fig. 21: SEM of formulation A: MF2, B: MF4, Marketed MDF

SEM photographs of all three films indicated homogenous film formation and uniform distribution of respective drug in the polymer in the films.

It was observed from the results of comparison of selected formulations (MF2 and MF4) and marketed film, that the films prepared and optimized under the present study exhibited results that were comparable to that of a similar dosage form (marketed mouth dissolving film) with respect to various evaluation parameters.

CONCLUSION

Recently, mouth dissolving drug delivery systems have started gaining popularity and acceptance as they are easy to administer and hence are gaining improved patient compliance. Usually elderly people experience difficulty in swallowing the conventional dosage forms. Mouth dissolving film is a unique type of fast dissolving drug delivery system. Normally these films are soluble at room temperature in water and break up and disappear in seconds.

In the present work, mouth dissolving films containing Montelukast sodium were developed for faster disintegration, faster drug availability and improved convenience to patients. The work included the development, characterization and evaluation of mouth dissolving films for dissolution in mouth and release of the drug for absorption. Montelukast sodium was selected as model drug for the study. Montelukast sodium is used in prevention and long-term symptomatic management of asthma. In asthma, quick drug action is required and intake of water is also less preferred. So, mouth dissolving films of the drug were developed and evaluated.

Mouth dissolving films of the drug (Montelukast sodium) were prepared using various polymers and other excipients that dissolve rapidly and release the drug for rapid absorption. Solvent evaporation method was used for preparation of the films. Various polymers used in the study were: Pullulan, Gelatin, Methocel E5P, Maltodextrin and Polyox WSR N80. Sorbitol and Propylene glycol were used as plasticizer. Aspartame and sucralose were used as sweetening agent while citric acid was used as saliva stimulating agent. Vanilla fruit and orange flavour were used as flavouring agent.

The formulated mouth dissolving films were evaluated for various parameters and the results compiled. The parameters included appearance, weight variation, uniformity of thickness, folding endurance, drug content, tensile strength, percent elongation, moisture content, disintegration time (in-vitro), disintegration time (in-vivo), taste assessment (in-vivo), dissolution studies (in-vitro) and SEM. Accelerated stability studies of the prepared films were also performed.

From the results of various evaluation parameters, it was concluded that the films were homogenous in appearance; showed good uniformity in weight, thickness and drug content; showed good folding endurance, tensile strength and % elongation. The moisture content of the prepared films was within reported limits. The films showed good taste masking property and the prepared films also disintegrated rapidly in-vitro as well as in mouth (in-vivo). The dissolution profile also showed that the drug dissolves rapidly for absorption. Accelerated stability studies showed that the prepared films were stable under stress conditions of temperature and humidity.

Formulations MF2 and MF4 showed best results with respect to various evaluation parameters. The selected formulations (MF2 and MF4) were compared with a mouth dissolving film formulation available in market (MMDF) containing different drug, as the drug under present study (Montelukast sodium) is available as tablet dosage form only. The comparison was done for various evaluation parameters: appearance, uniformity of weight, uniformity of thickness, folding endurance, content uniformity, tensile strength, percentage elongation, moisture content, disintegration time (in-vitro), disintegration time (in-vivo), level of bitterness, dissolution profile and SEM.

From the results of comparison of selected formulations (MF2 and MF4) and marketed film, it was concluded that with respect to various evaluation parameters, the films prepared and optimized under the present study exhibited results that were comparable to that of a similar dosage form (marketed mouth dissolving film).

So, it can be concluded that mouth dissolving films containing Montelukast sodium can be prepared using the polymers (film formers) and other excipients selected under the present study that fulfill the objective of faster disintegration, faster drug availability and improved convenience to patients simultaneously meeting with the requirements of various pharmaceutical parameters.

Further studies may be carried out with other drugs and by altering the polymer(s) and other excipient(s) combinations to meet the needs of the pharma industry in bringing newer dosage forms in the market.

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