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# Formulation and Evaluation of Fast Dissolving Oral Thin Film

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**Abstract:**
The objective of present work was to develop oral Fast dissolving film of montelukast sodium which was indicated for the prophylaxis and chronic treatment of asthma. This offers a solution for those patients having difficulty in swallowing tablets/capsules and allowing fast reproducible drug dissolution in oral cavity thus by passing first pass metabolism, to enhance the convenience and compliance by the elderly and pediatric patients. Montelukast oral fast dissolving oral thin films were prepared by solvent casting method with using different film-forming agents like pullulan gum, sodium CMC, PEG 400, glycerol as a plasticizer and mannitol as filler and sweetener. Oral films were evaluated for weight variation, thickness, surface pH, folding endurance, drug content, disintegration time and in-vitro dissolution studies. Montelukast oral films based on evaluation studies pullulan gum showed optimum performance against other formulations. The prepared films were clear, transparent and had a smooth surface. It was concluded that the fast dissolving oral thin films of montelukast can be made by solvent casting technique with enhanced dissolution rate, better patient compliance and effective therapy.

## INTRODUCTION

Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking or chewing. The first developed fast-dissolving dosage form consisted of tablet form and the rapid disintegrating properties were obtained through a special process or formulation modifications. [1]

More recently, fast-dissolving films are gaining interest as an alternative to fast-dissolving tablets to definitely eliminate patients' fear of chocking and overcome patent impediments. Fast-dissolving films are generally constituted of plasticized hydrocolloids or blends made of thereof that can be laminated by solvent casting or hotmelt extrusion. [2] According to the film forming material characteristics, the manufacture of the dosage forms can present different critical issues. Common problems are caused by foaming during the film formation due to the heating of the material or solvent evaporation, the flaking during the slitting and the cracking in the cutting phase. Furthermore, the films should be stable to moisture overtime. Finally, to facilitate the handling they have to be flexible and exhibit a suitable tensile strength and do not stick to the packaging materials and fingers. Formulation of these systems is usually straightforward; the polymer and drug are dissolved in a solvent and a film is cast by solvent evaporation. [3, 4]. Most commercially available oral thin formulations, such as Oral film TM, (benzocaine) or Theraflu ®, (dextromethorphan /Phenylephrine HCl or Diphenhydramine HCl) are designed to deliver locally acting drugs or for mouth-freshening (such as Listerine Pocket Paks TM,). Montelukast sodium is a leukotriene receptor antagonist (LTRA) used in maintenance treatment of asthma and to relieve symptoms of seasonal allergies. [5] It is usually administered

orally. Montelukast blocks the action of leukotriene D4 on the cysteinyl leukotriene receptor CysLT1 in lungs and bronchial tubes by binding to it. This reduces the bronchoconstriction otherwise caused by the leukotriene and results in less inflammation. Montelukast sodium bioavailability is 63%. It has extensive first-pass metabolism and show a very poor dissolution rates in order to overcome this problem.

**Special Features of Mouth Dissolving Film [4]**

1. Thin elegant films
2. Various sizes
3. Unobstructive
4. Mucoadhesion
5. Quick dissolving
6. Fast disintegrating
7. Rapid release

**Advantages of Mouth Dissolving Film [5]**

1. Larger surface area promotes rapid disintegration and dissolution in the oral cavity.
2. Oral films are flexible and thus less fragile as compared to ODTs. Hence, there is ease of transportation and during consumer handling and storage.
3. Precision in the administered dose.
4. No risk of choking.
5. Good mouth feel.
6. With the help of Mouth dissolving film drug delivery system those drugs can be given to the patients that are not crushed and not injected by patients.
7. Improved patient compliance.
8. Ease of swallowing and no need of water has led to better acceptability amongst the dysphagic patients.
9. Dosage form can be consumed at any place and anytime as per convenience of the individual.
10. Enhanced oral bioavailability of molecules that undergo first pass effect.
11. Bypassing the first pass effect leads to reduction of dose which can lead to reduction in side effects associated with the molecules.
12. Mouth Dissolving Films are typically the size of a postage stamp and disintegrate on a patient's tongue in a matter of seconds for the rapid release of one or more APIs.

**Ideal Characteristic of a Suitable Drug Candidate**

1. The drug should have pleasant taste.
2. The drug to be incorporated should have low dose up to 40 mg.
3. The drugs with smaller and moderate molecular weight are preferable.
4. The drug should have good stability and
5. It should be partially unionized at the pH of oral cavity.
6. It should have the ability to permeate oral mucosal tissue.

**MATERIALS AND METHODS**

Montelukast Sodium was received as gift sample from Mylon laboratories (Nasik, Sinner). The Pullulan was purchase from Kumar organic Pvt Ltd, Bangalore, PEG-400 was purchase from SD fine chem Mumbai, Glycerin was Purchase from SD fine chem Mumbai, Aspartame was taken from department of Pharmaceutics of Smt. S. S. Patil College of Pharmacy, Chopda.

**Characterization of Drug and Excipients**

**1. Fourier Transformation Infrared Spectroscopy (FTIR)**

FTIR spectra of pure montelukast sodium and physical mixture of drug and excipients were recorded on Shimadzu Corporation, (Tokyo, Japan) Model-1601 PC. Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average

scans collected in the region 400- 4000 cm-1 at spectral resolution of 2 cm-2 and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

**2. Differential Scanning Calorimetry (DSC)**

Thermal properties of the pure montelukast sodium and the physical mixture of drug and excipients were analyzed by Shimadzu DSC-60, Shimadzu Limited Japan. The samples were heated in a hermetically sealed aluminium pan. Heat runs for each sample were set from 30 to 350°C at a heating rate of 10°C/ min, using nitrogen as blanket gas.

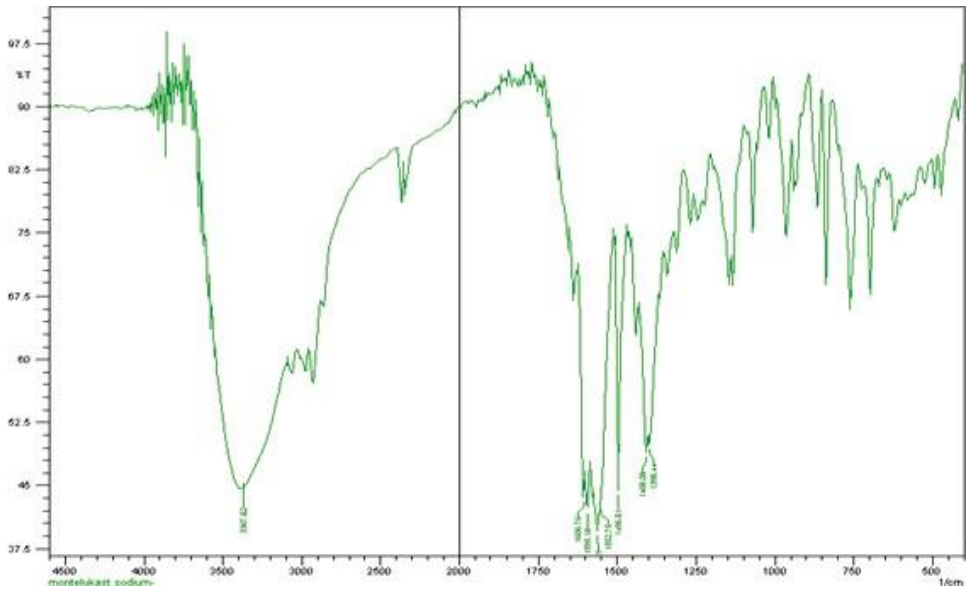

**Figure 1:** IR spectrum of montelukast sodium

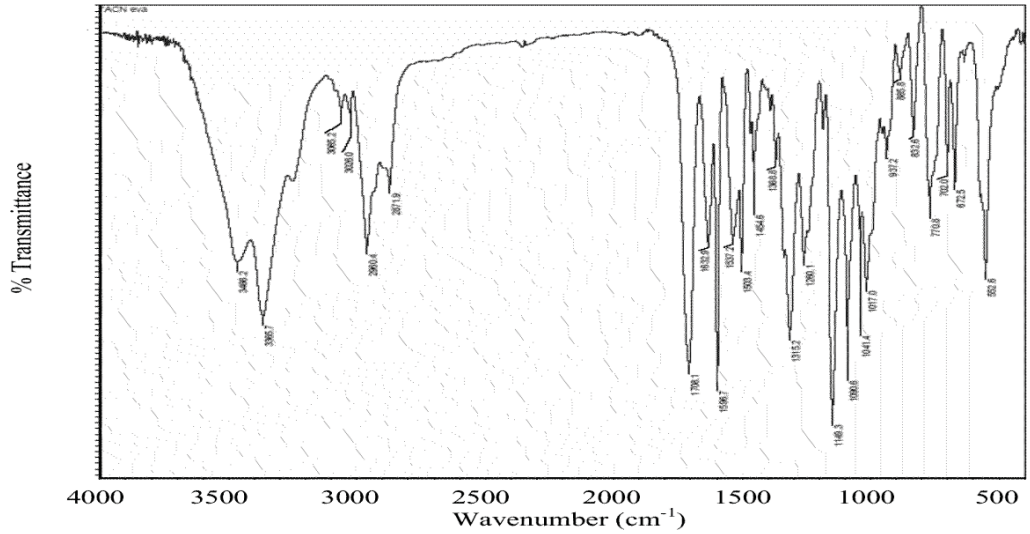


**Figure 2:** FT-IR spectra of pullulan

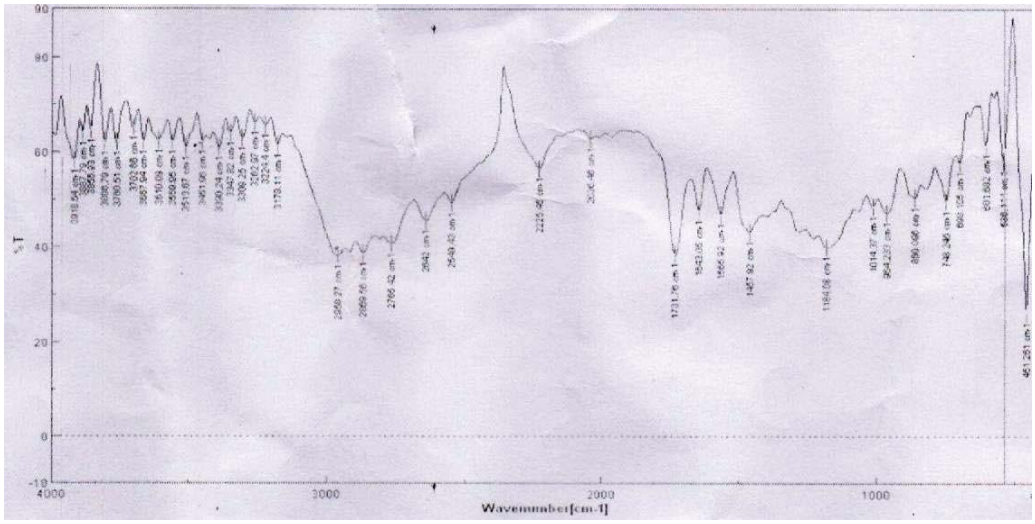


**Figure 3:** FT-IR-spectra of sodium CMC

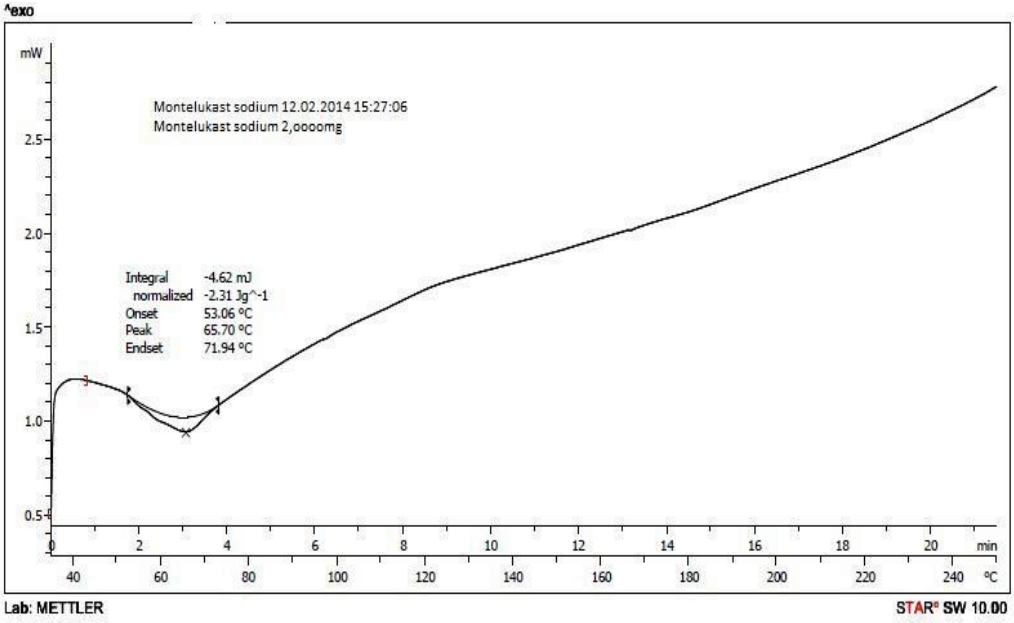


**Figure 4:** DSC spectra of montelukast sodium

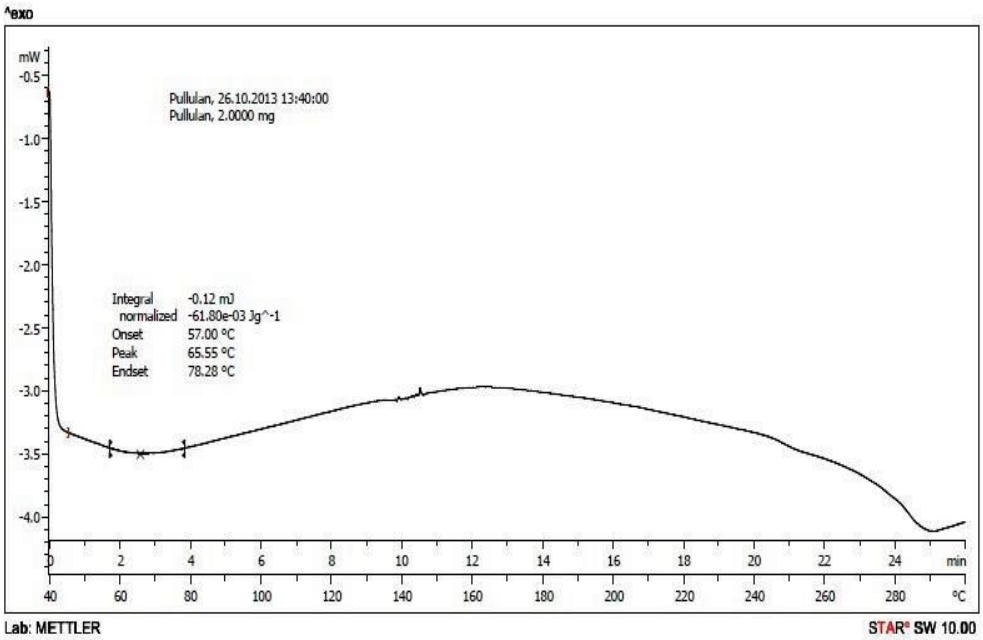


**Figure 5**: DSC spectra of pullulan

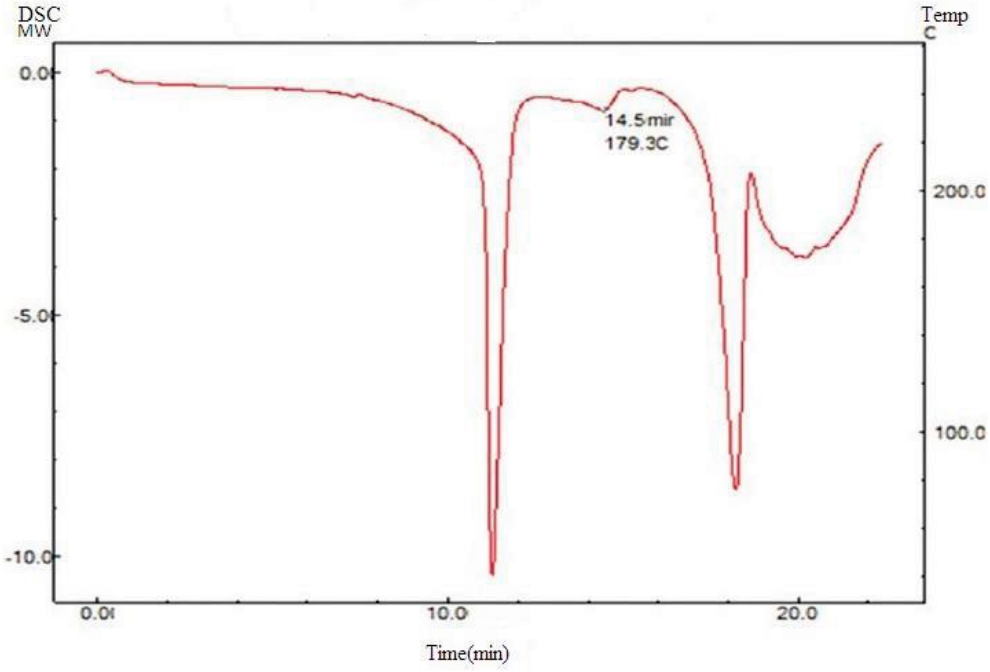


**Figure 6:** DSC Spectra of Sodim CMC

**Preparation of Montelukast Sodium Oral Thin Films**

The oral thin films of Montelukast sodium (MTS) were prepared in laboratory using pullulan by solvent casting method. pullulan is known for its good film forming properties and has excellent acceptability. Hence, for the fabrication of films, propylene glycol was used as a plasticizer, glycerin as humectant and mannitol was used as a sweetener. The required quantity of MTS was dissolved in 10 ml of distilled water containing pululan to form polymeric dispersion. Briefly, propylene glycol, glycerin, aspartame and various polyhydric alcohols were dissolved in 5 ml of 50% v/v ethanol. Alcoholic solution and the polymeric dispersion were mixed to obtain a homogeneous dispersion and 20 ml of the dispersion was cast onto each polypropylene petriplate. The composition of various films is shown in Table 1.

The dispersion was dried at 40–45°C. The films were carefully removed from petri plates and stored in an air tight glass bottle. The films were evaluated for imperfections and cuts, peel ability without rupturing, folding and cracking endurance and surface roughness.

**Table 1: Different Formulation of Oral Thin Film Montelukast Sodium**

| Ingredients | MF1 | MF2 | MF3 |
|---|---|---|---|
| Montelukast Sodium | 10 | 10 | 10 |
| Pullulan Gum | 80 | - | 40 |
| Sodium CMC | - | 80 | 40 |
| Ethanol (ml) | 1 | 1 | 1 |
| Glycerol (ml) | 0.02 | 0.02 | 0.02 |
| PEG 400 (ml) | 0.02 | 0.02 | 0.02 |
| Monitol (5%w/v) | 0.5 | 0.5 | 0.5 |
| Methanol (ml) | Qs | Qs | Qs |
| Water (up to 10 ml) | 10 | 10 | 10 |

**Evaluation of Mouth Dissolving Film**

The film was evaluated for weight variation, mouth dissolving time, taste, surface pH, uniformity of thickness, weight, folding endurance, drug content uniformity, *in-vitro* release, percent moisture loss (PML), percent moisture absorption (PMA), swelling percentage, stability and bioequivalence.

**1. Film Weight Variation**
For evaluation of film weight and thickness films were taken and weighed individually on a digital balance.

**2. Thickness**
The film thickness was measured using Digital Vernier Caliper (Aerospace) at six different places and the average value was calculated.

**3. Folding Endurance**
Folding endurance of the film was determined by repeatedly folding one film at the same place till it broke. Number of times the film could be folded at the same place without breaking gave the value of the folding endurance. This evaluation was done for three films.

**4. Percentage Moisture Absorption (PMA)**
The PMA test was carried out to check the physical stability of the mouth dissolving film at high humid conditions. Three films were taken, weighed accurately and placed in a desiccator containing saturated solution of aluminium chloride, keeping the humidity inside the desiccators at 79.5 %.

**5. Appearance**
The prepared film was transparent with smooth surfaces and odorless as shown in Figure 7 with background of black paper


MONTs film Using Pullulan gum (Black Paper Background)

MONTs film Using sodium CMC (Black Paper Background )

**Figure7:** Images of oral thin film of montelukast sodium

**6. Disintegration Time**
The disintegration for orally disintegrating tablets describes in centre for drug evaluation and research guidance can be applied to fast dispersible oral strips. Although no official guidance is available for oral fast disintegrating film/strips, this may be used as a qualitative guideline for quality control test or at development stage. But for the present work disintegration was measured by taking the 25 of 0.1N HCl in 50 ml beaker and individual film is dipped into that solution and disintegration time was recorded.

**7. Drug Content**
For determination of drug content Montelukast sodium mouth dispersible film equivalent to dose of 10 mg was dissolved in 50 ml of 0.1N HCl. The solution was sonicated for 10 min and then filtered through Whatmann filter paper no. 41, to separate out the insoluble excipients. 1 ml of filtrate was diluted to 100 ml with HCl 0.1N. The absorbance of resultant solution was measured using U.V. spectrophotometer at 287 nm and drug content was calculated. All above evaluation parameter result are shown in Table 2.

**Table 2: Evaluation of Oral Thin Film of Montelukast Sodium**

| Batches | Thickness (mm) | Weight (mg) | Folding Endurance | Surface pH | %Drug Content | *In-vitro* Disintegration Time (Sec) |
|---|---|---|---|---|---|---|
| **F1** | 0. 18±0.00 | 0.16±.005 | 140±15.67 | 6.53±03 | 99.8±.003 | 37.7±1.52 |
| **F2** | 0. 20±0.05 | 0.15±.007 | 106±9.29 | 6.49±05 | 95.6±.007 | 40.8±2.00 |
| **F3** | 0.19±0.10 | 0.17±.003 | 110±10.12 | 6.78±06 | 98.3±09 | 45.3±1.56 |

**8. Compatibility**

The possible interaction between Montelukast sodium with excipients was studied by differential calorimeter (DSC).There was no considerable change in DSC endothermic values, compared to pure Montelukast sodium and with the excipients (Pullulan). Peak value for combination was obtained at 152.30°C. A pure drug shows peak value at 152.24°C. Hence it shows that there was no interaction between drug and excipients. The additional peak was observed at 287°C, from literature it was peak found due to pullulan degradation between 250-280°C.

**9. *In-vitro* Dissolution study**

The *in-vitro* release of drug from all formulations was determined using USP apparatus type II (Paddle method). The following conditions were followed to study the *invitro* dissolution study of Montelucast mouth dispersible film. USP dissolution apparatus: Type II (Paddle method),

volume of dissolution medium: 900 ml, speed: 50 rpm, Temperature: 37±0.5°C, Dissolution medium: 0.1N HCl, Sampling interval: 1 min. The drug release is shown in Table 3. Quantity of sample withdrawn: 5 ml were withdrawn at 1min interval for 3 min. The volume withdrawn was replaced by fresh volume dissolution medium. The filtered samples were analysed by UV visible spectrophotometer at 287.00 nm and absorbance was noted. Cumulative percent drug release was calculated.

**Table 3: Drug Release Pattern**

| Time(min) | F1 | F2 | F3 |
|---|---|---|---|
| **0** | 0.000 | 0.000 | 0.000 |
| **1** | 82.177 | 83.803 | 79.083 |
| **2** | 98.253 | 97.387 | 96.461 |
| **3** | 99.866 | 98.078 | 97.090 |

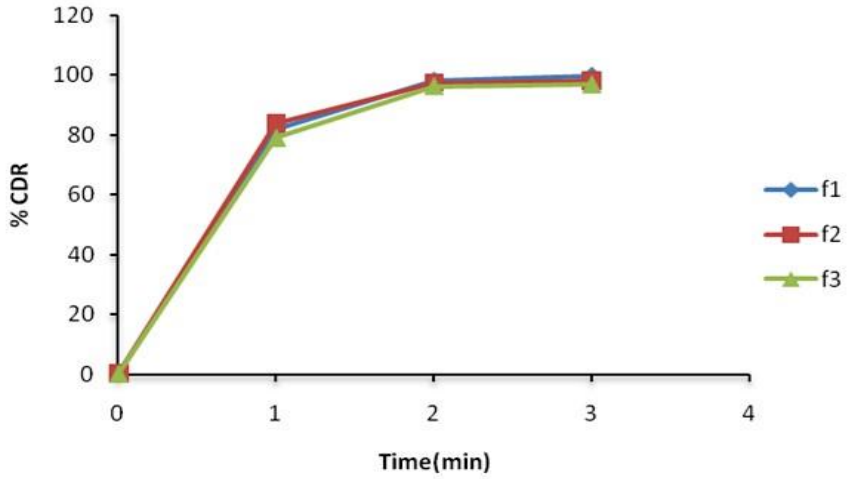


**Figure 8:** *In-vitro* dissolution profile of montelukast sodium

**RESULT**

In present work, montelukast sodium was selected for this investigation as novel drug dosage form for pediatric, geriatrics and also for general population to improve bioavailability by preventing first pass metabolism, rapid onset of action. The main objective of study was to formulate and evaluate fast dissolving oral film of montelukast sodium by using polymer pullulan gum, sodium CMC and plasticizer glycerin by solvent casting method. Pullulan was found to be compatible with montelukast sodium, which was confirmed by FTIR spectroscopy. All formulations (F1 toF3) were evaluated for weight variation, thickness, drug content, disintegration time. Results of folding endurance, % elongation and tensile strength proved by texture analyser that when concentration of plasticizer and polymer are increased the flexibility of film also increases. From all evaluation parameter it was found that batch F1 show good physical appearance, texture and flexibility. Hence F1 batch can be selected as best batch. Results of In-vitro drug release study reveals that batch F1 shows maximum drug release (99.8± 0.003%) within 60 seconds.

**CONCLUSION**

The present study reveals the use of fast dissolving film prepared by solvent casting technique using montelukast sodium as a model drug. The technique used was found advantageous compared to other method especially when cost, equipment requirements and processing comfort is concerned. The prepared montelukast loaded can be used in emergency condition of severe asthmatic attacks. It could find a better application for patient compliance and occurrence especially in children. The comparison study by using pullulan and sodium CMC as film forming polymer was performed. There was considerable reduction in film strength and increase in percent elongation of film with increase in glycerol content. The result showed that film containing pullulan with 5% glycerol showed better disintegration, dissolution and folding endurance when compared with film containing sodium CMC. Hence, the film containing pullulan was used for further optimization where the optimized batch depicted disintegration time of less than 46 sec, complete drug release within 3 min, percent elongation as 61.24 cm % and folding endurance more than 140.

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