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Pharmaceutical Development and Assessment of Montelukast Sodium Fast Dissolving Oral Thin Film Formulation

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ABSTRACT: Montelukast sodium is drug of choice for the treatment of asthma and allergic rhinitis. The aim of this present study was to develop this drug into an oral thin film formulation to overcome the disadvantages associated while consuming the conventional tablet or liquid dosage form of it. By using different polymeric materials such as hydroxypropyl methylcellulose, polyvinyl pyrrolidone and polyvinyl alcohol as a film former either individually or it's combination; polyethylene glycol 400, glycerol as a plasticizer; mannitol, saccharin sodium as a filler and sweetener, the fast-dissolving oral thin films of montelukast sodium were prepared by solvent casting method. Formulated films were evaluated for weight variation, thickness, surface pH, folding endurance, drug assay, content uniformity, disintegration time, moisture uptake, moisture loss, tensile strength and invitro drug release. Based on evaluation studies, the film formulations were shown satisfactory results and out of which, the formulation F14 has the least disintegration time of 24 seconds and drug release of 99.5% with sufficient tensile strength of >1.0 kg/mm^2. The results proven that montelukast sodium could be developed into an efficient drug delivery system in the form of oral thin film by using combination of different film formers to establish synergistic effects for improving its formulation quality parameters in presence of other selected excipients. It was concluded that oral thin films offer a promising alternative for drug delivery to avoid the difficulty of swallowing, as they are easy to administer and disintegrate quickly in the mouth, allowing for rapid absorption of the drug.

KEYWORDS: solvent casting, polymer, compliance, disintegration, dissolution, tensile strength.

I. INTRODUCTION

Oral thin films (OTFs) are one of the novel drug delivery system that has gained considerable attention in recent years due to their advantages over conventional dosage forms. OTFs are thin, flexible, and easily dissolvable films that can be placed in the mouth, where they rapidly disintegrate and release the active pharmaceutical ingredient (API) for systemic absorption.[1] It belongs to solid dosage forms that disintegrate and dissolve rapidly in the oral cavity without the necessity of water.[2] USFDA states that oral thin films as, "a thin, flexible, non-friable polymeric film strip containing one or more dispersed active pharmaceutical ingredients which is intended to be placed on the tongue for rapid disintegration or dissolution in the saliva prior to swallowing for delivery into the gastrointestinal tract". This unique drug delivery system offers several benefits, including improved patient compliance, increased bioavailability, faster onset of action, and reduced side effects.[3] OTFs can be manufactured using a variety of raw materials and techniques, allowing for customization to meet specific patient needs. These technologies offer more effective and better drug absorption for its bioavailability as compared to the typical conventional dosage forms.[4]

Montelukast is a selective leukotriene receptor antagonist widely used in the treatment of asthma and allergic rhinitis. While it is effective in managing these conditions, patients often experience difficulty in swallowing conventional tablets, which can lead to poor adherence to treatment.[5] Oral thin films are a promising drug delivery system that can improve medication compliance by providing a patient-friendly and easy-to-administer as an alternative. Montelukast OTFs expected to disintegrate rapidly in the mouth

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and delivers the drug directly into the systemic circulation via the sublingual and buccal routes as well as into gastrointestinal tract.

The major components of these films are polymers that may be natural or synthetic. The polymeric nature plays a vital role in altering the disintegration time (DT), which affects the drug release as well as mechanical characteristics.[6,7] Polymers used become hydrated in oral mucosa and develop gel-like consistency through which drug is released. Other than polymers, plasticizers and surfactants were incorporated to improve its texture and drug release. Non-volatile and low molecular weight plasticizers were used for the improved flexibility and tensile strength of the films.[8,9] Plasticizers are screened based on the polymer used and its compatibility with the drug. The concentration and type of plasticizer used influences the mechanical strength of the films. Other important additives such as flavouring and sweetening agents are used to improve the palatability for patient acceptance.[10,11] The various formulation development methods of OTFs includes solvent casting, semi solid casting, hot melt extrusion, solid dispersion extrusion, rolling, inkjet printing, continuous inkjet printing, drop on demand printing, flexographic printing, etc.... [12]

The present study was hypothesized to develop montelukast sodium oral thin film using selected polymers and their combinations thereof with other additives. The films should possess optimum tensile strength, fast disintegration in mouth and better drug release characteristics to comply more on patient acceptance. Hence, the developed dosage form and its process of manufacturing will be a promising alternative with additional advantages over conventional tablets for improved absorption of montelukast to enhance its systemic bioavailability and therapeutic effect.

II. MATERIALS AND METHODS

MATERIALS

The drug montelukast sodium (Yarrow Chem Products, Mumbai); and other excipients hydroxypropyl methylcellulose (HPMC) E15, polyvinyl pyrrolidone (PVP) K30 (Yarrow Chem Products); polyvinyl alcohol (PVA), glycerol, crospovidone (Reachem laboratory chemicals); saccharin sodium, mannitol (Loba Chemie Pvt. Ltd); croscarmellose sodium, sodium starch glycolate (Prachin Chemical) and polyethylene glycol (PEG) 400 (Paxmy Speciality Chemicals) were purchased to carry out various experiments for the development of montelukast sodium OTF.

METHODS

Preparation Method of Montelukast Sodium Oral Thin Films

The films were prepared by solvent casting technique using different disintegrants, polymers and other excipients. The aqueous solution of polymer was prepared by dissolving
the required quantity of polymers in water (10ml) into a container. To that aqueous polymeric solution in the container, added the plasticizer, super disintegrants and sweetening agents. In another container, accurately weighed quantity of montelukast sodium was taken and dissolved in ethanol. The prepared drug solution was transferred to the container having polymeric solution slowly with continuous stirring. The uniformly mixed solution was slowly poured to cast on the petri dish and allowed to dry for 120–180 minutes at 55ºC±2ºC. The formed films were carefully removed from the petri dish and cut into the sizes of 2×2 cm^2, equivalent to have a dose of 5mg of montelukast sodium. The dried and sized films were packed individually into an aluminium pouch and sealed.

The quantitative compositions of different formulations prepared were described in table 1(a) and table 1(b). In Table 1(a) the composition of films having different disintegrants at two concentration levels were shown. In Table 1(b) the composition of films having differnt polymers and their combination thereof were shown.

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Table 1(a): Formulation composition of montelukast sodium oral thin film prepared using different super disintegrants

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8
	Quantity in mg							
Drug	79.55	79.55	79.55	79.55	79.55	79.55	79.55	79.55
HPMC	300	300	300	300	300	300	250	200
Sodium Starch Glycolate	21.6	36	0	0	0	0	0	0
Croscarmellose Sodium	0	0	21.6	36	0	0	36	36
Crospovidone	0	0	0	0	21.6	36	0	0
Saccharin Sodium	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
PEG 400	180	180	180	180	180	180	180	180
Glycerol	90	90	90	90	90	90	90	90
Mannitol	45.25	30.85	45.25	30.85	45.25	30.85	80.85	130.85
Total Weight	720	720	720	720	720	720	720	720

Table 1(b): Formulation composition of montelukast sodium oral thin film prepared using combinations of polymers

Formulation Code	F9	F10	F11	F12	F13	F14	F15	F16
	Quantity in mg							
Drug	79.55	79.55	79.55	79.55	79.55	79.55	79.55	79.55
HPMC	250	250	250	250	250	250	250	250
Polyvinyl alcohol	21.6	36	0	0	21.6	21.6	36	36
PVP-K30	0	0	21.6	36	21.6	36	21.6	36
Croscarmellose Sodium	36	36	36	36	36	36	36	36
Saccharin Sodium	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
PEG-400	180	180	180	180	180	180	180	180
Glycerol	90	90	90	90	90	90	90	90
Mannitol	59.25	44.85	59.25	44.85	37.65	23.25	23.25	8.85

III. EVALUATION METHODS OF MONTELUKAST SODIUM ORAL THIN FILM

Drug excipient compatibility study by FT-IR spectroscopy

Using Fourier Transform Infrared (FTIR) spectroscopy, the compatibility of drugs and excipients were studied. Shimadzu 160A, Kyoto-Japan was used to record the FTIR spectrum between the wavelength of 600 and 4000 cm^{-1}, using KBr disc technique. The baseline correlation

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was done using dried potassium bromide and the spectrum of dried mixture of drug with potassium bromide was run followed by drug with various excipients proposed in this research work.

Visual Inspection

The prepared oral films were assessed visually in day light for flexibility, homogeneity, transparency, and surface roughness.[13,14]

Weight Variation

A weight variation test was performed on dried films peeled out from petri plate by using 10 pieces of 2 x 2 cm^2 sized film that were cut from various angles.[15].

Film Thickness

This test is necessary to examine the consistency of the film thickness. Three films were chosen at random, and the thickness of each was measured with a digital vernier calliper. At five different sites, includes four corners and the centre were used to measure the thickness, and then the mean thickness was estimated.[16]

Surface pH

The film's surface pH was determined by soaking it with 10ml of distilled water in a petri dish and then measuring it with a pH metre electrode by touching the film surface and noting the pH value.[17]

Folding Endurance Test

Folding endurance measures the film's capacity to endure repeated bending and folding without cracking or breaking. By folding the films repeatedly in the same spot, folding endurance was measured.[18,19,20]

Invitro Disintegration test

The film was carefully positioned in the USP disintegration apparatus on which disk was placed. The amount of time it took the film to totally break down into tiny particles was recorded. Each formulation underwent the test for 3-6 times, with the maximum value being noted.[21,22]

Uniformity of Drug Content

The orally disintegrating thin films, each measuring 2×2 cm^2 in area were put in a glass beaker with 100mL of USP buffer at pH 6.8, and the mixture was kept in sonication for 20 minutes**.** An aliquot of 2 mL was obtained, and it was diluted to 10 mL with same buffer. From that 10 ml was taken to achieve a theoretical concentration of 10µg/ml. By measuring the absorbance with a UV/VIS spectrophotometer (Shimadzu), the drug content was evaluated using a standard curve. The theoretical value was then compared with the actual amount of medication in the patch to measure percentage of the designated amount.[22]

Invitro Dissolution test

Dissolution is the rate at which a drug material enters a solution per unit of time under typical temperature, solvent content, and liquid/solid interface circumstances. For dissolution testing, USP Method 5 (Paddle over disc) was applied. The patch was placed on watch glass apparatus facing up under the mesh, and the holder placed in the bottom of the vessel. The test was performed using the USP Type 2 dissolution test paddle apparatus (LabIndia DS 8000- Lab India Pvt.Ltd) and samples taken in the normal way.[23]

Tensile Strength

The point at which the strip specimen breaks is the maximum stress applied to the film. Optimum tensile strength is necessary for a film to be stable. A load failure occurs when a weight causes a film to rupture. The applied load at rupture was multiplied by the strip's cross-sectional area to determine the tensile strength.[24]

$$\sigma_{max} = P_{max}/A_0$$

Where, P_{max}= maximum load, A_0= original cross-sectional area.

Universal Testing Machine (WDW-100E - TIME Group Inc.) was used to coduct these experiments.

Moisture uptake

The original weight of the film was determined first and then the percentage moisture uptake of films was calculated by exposing it to an atmosphere with a relative humidity of 75% at room temperature for seven days and then using the following formula:

$$\% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture loss

The original weight of the film was determined first and then the film was placed in a desiccator (including calcium chloride) for three days to determine the percentage moisture loss.[24] The films were removed and weighed again after three days and the moisture loss was calculated using the formula:

$$\% \text{ moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

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Stability Testing

Accelerated stability studies were carried out under common stress conditions like temperature and humidity. Selected film formulations were packed in an aluminium packaging material and stored at 40ºC ± 2ºC & 75% ± 5% RH for 4- 24 weeks in stability chamber (CHM 16S – Remi Equipments Pvt. Ltd.). Then the samples were withdrawn at specified period of time and analysed the stability indicating parameters.[25]

IV. RESULTS AND DISCUSSION

Compatibility Studies

The compatibility study of drug with excipients was conducted and samples were analyzed using FTIR. It was observed that there was no change in absorption peaks in the drug mixture when compared to pure drug montelukast sodium. The drug had not undergone any kind of structural change or chemical reaction with the other excipients used in this development work. Therefore, it was confirmed that there was no chemical interaction of drug with the excipients used in this current experimental study and were compatible with each other.

Figure 1(a) represents FTIR spectra of pure drug montelukast sodium and figure 1(b) represents for the drug mixture, which contains drug and all the excipients including HPMC, PVP, PVA, CCS, mannitol, PEG-400, glycerol and saccharin sodium.

In table 2, the wave length (cm^{-1}) of major peaks observed for the drug and its mixture with excipients were recorded.

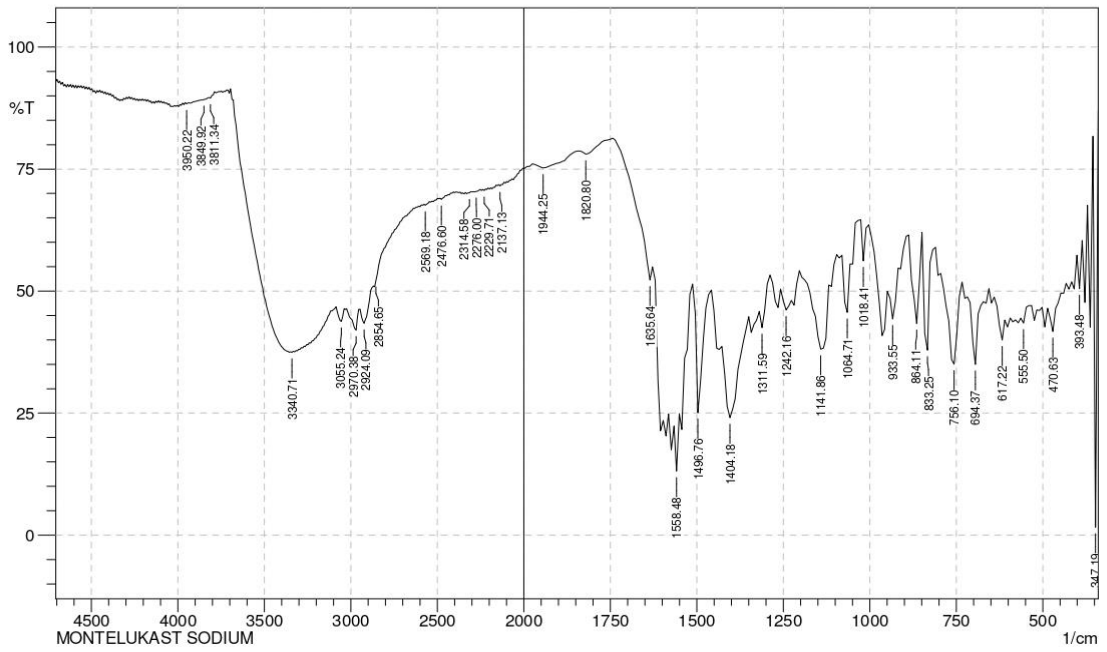

Figure 1(a): FTIR spectra of pure drug Montelukast sodium

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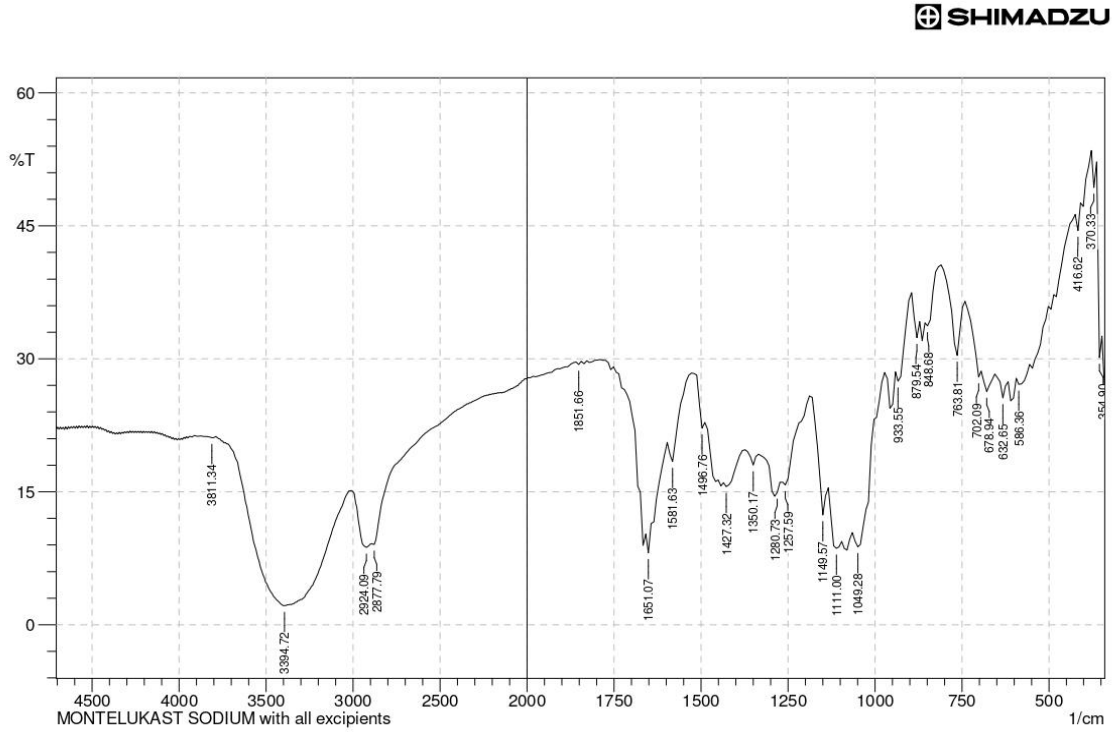

Figure 1(b): FTIR spectra of Montelukast sodium with mixture of all excipients

Table 2: FT-IR spectral wavelength of pure drug Montelukast sodium and it's mixture with all excipients

Visual Inspection

S.No.	Functional group	IR spectral wavelength range (cm^{-1})	Wave length (cm^{-1})	
			Montelukast sodium	Montelukast sodium with all excipients
1	C-Cl Aliphatic	850-550	756.10	848.68
2	C-S Aliphatic	695-675	694.37	678.94
3	C-N Aromatic	1350-1200	1242.16	1280.73
4	C=S Aromatic	1600-1450	1558.48	1581.63
5	C=O Carboxylic	1760-1600	1635.64	1651.07
6	C-H Aliphatic	3000-2850	2970.38	2877.79
7	C-H Aromatic	3100-2900	3055.24	2924.09
8	O-H Stretching	3600-3200	3340.71	3394.72

The formulations F1-F6 were observed to be uniform, transparent, smooth surface and elegant, where the polymer HPMC alone used at above 40% concentration (300 mg). In both the formulations F7 and F8 the films were not formed properly because of reduced concentration of HPMC quantity 250mg and 200mg, respectively were used. Even though the polymer HPMC used at reduced concentration of 35% (250mg) in the remaining all formulations F9-F16, the films were formed properly because of the incorporation of other polymers such as PVA and PVP. Also, the films of formulation F9-F16 were observed to be uniform, transparent, smooth surface and elegant to comply visual inspection.

Weight Variation

A digital weigh balance was used to determine the weight of the prepared films. The films showed weights ranging from 43 mg to 48 mg and the variation observed was within ± 7%. There is no significant variation in the weight of films and hence it complies the weight variation parameter. The results were shown in table 3.

Film Thickness

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The thickness of each film measured at different places (four corners and the centre) of the formulation were ranging from 0.11 to 0.15 mm. The variation observed was 0.13 ± 0.02 mm and hence the variation in thickness was not significant as the films were prepared by manual solvent casting technique. The variation can be further controlled at scle-up level when using validated equipments. The results were shown in table 3.

Surface pH

Films may have less potential to irritate the oral mucosa since the surface pH has been determined to be in the range of 6.35 to 6.75, which falls in normal salivary pH range. These results proven that developed formulations were compatible while the surface of the films contacted the mucosal membrane of mouth in presence of salivary secretion. The results were shown in table 3.

Folding Endurance Test

The folding endurance has been performed by folding a single film repeatedly until it broke. The value of folding endurance was determined by how many times the film could be folded in the same position without breaking. The folding endurance of all formulations was found to be between 259 to 295. As the values exceeds >250, which indicates better compliance for folding endurance test and the results were shown in table 3.

Invitro Disintegration Test

All the films have shown disintegration time (DT) of less than 1 minute. Formulations F1–F6, the films were prepared with different super disintegrants. The formulation F1 and F2 had sodium starch glycolate (SSG) as a super disintegrant and showing DT of 48 seconds at 3% concentration level (F1) and 39 seconds at 5% concentration level (F2). Formulation F3 and F4 had croscarmellose sodium (CCS) as a super disintegrant and showing disintegration time of 43 seconds at 3% concentration (F3) and 35 seconds at 5% concentration (F4). Formulation F5 and F6 showing DT of 52 seconds at 3% concentration (F5) and 41 seconds at 5 % concentration (F6) which has crospovidone (CP) as super disintegrant. Hence, increasing the concentration of disintegrant impart better disintegration. Also, formulation containing CCS at 5% concentration showing reduced DT in compare to other disintegrants used.

Formulations prepared using HPMC alone (F1 – F6) showing disintegration time of 35 seconds to 52 seconds, whereas formulation prepared using combination of polymers (F9 – F16) showing disintegration time of 24 seconds to 33 seconds. PVP alone or PVP at higher concentration in combination with PVA and HPMC (F11, F12, F14 and F16) showing DT of less than 30 seconds. PVP act as better solubilizer and dissolution enhancer. Hence PVP and PVA playing significant role in reduction of disintegration time and film formation. The results were shown in table 3.

Uniformity of Drug Content

The drug content of individual film formation was observed to be between 96.8% - 99.5%. As the assay results showing more than 95% for all the formulations which indicates there is no significant variation in uniformity of drug content among all formulations. The drug was evenly distributed throughout the entire area of film formed by this present solvent casting method. The results were shown in table 3.

Table 3: Weight variation, thickness, surface pH, folding endurance, disintegration time and drug content of montelukast sodium oral thin film formulations.

Formulation code	Weight (mg)	Thickness (mm)	Surface pH	Folding endurance	Disintegration time in sec (max. value)	Drug content (%)
F1	44.5±1.3	0.14±0.01	6.47±0.10	264	48	97.3±1.5
F2	46.2±1.8	0.14±0.01	6.54±0.08	278	39	97.2±2.0
F3	45.0±2.1	0.13±0.02	6.50±0.15	280	43	96.8±1.8
F4	45.4±1.9	0.14±0.01	6.50±0.09	285	35	97.2±2.1
F5	45.7±2.0	0.13±0.02	6.52±0.12	277	52	96.8±1.7
F6	46.1±1.8	0.13±0.01	6.55±0.20	265	41	97.7±2.2
F7	Film not formed properly					
F8	Film not formed properly					
F9	45.2±2.2	0.14±0.01	6.49±0.08	259	32	97.7±1.7

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F10	44.9±1.7	0.14±0.01	6.57±0.10	277	30	98.6±1.4
F11	46.1±1.5	0.13±0.02	6.52±0.11	289	29	97.2±1.6
F12	45.3±2.2	0.14±0.01	6.48±0.09	284	26	99.0±1.1
F13	44.8±1.7	0.14±0.01	6.56±0.12	289	32	97.7±2.0
F14	46.2±1.8	0.13±0.02	6.55±0.15	295	24	99.5±0.8
F15	45.4±2.1	0.13±0.01	6.50±0.13	290	33	98.1±1.0
F16	44.9±1.8	0.14±0.01	6.49±0.09	287	28	98.6±1.2

Invitro Drug Dissolution Test

For formulations F1 – F6, which were prepared using different super disintegrant at two level of concentration showing significant variation in drug release. The average drug release observed was 75.9±2.6% and 78.8±2.4% for formulations prepared using sodium starch glycolate (F1 and F2); 81.6±2.1% and 84.5±1.8% for formulations with croscarmellose sodium (F3 and F4); and 70.1±1.6% and 72.9±2.6% for formulations with crospovidone (for F5 and F6), respectively at concentration level of 3% and 5%. The formulation F3 and F4 prepared using croscarmellose sodium showing higher drug release in compared to other formulations (F1, F2, F5 and F6) prepared using sodium starch glycolate and crospovidone. Croscarmellose sodium is hydrophilic and made of insoluble and fibrous by crosslinking sodium salt of carboxy methyl cellulose. The functionality of CCS as super disintegrant related to its fluid uptake by capillary action and swellability characteristics. Swelling of CCS is due to the hydration of the carboxy methyl group, the degree of substitution determines its functionality. In compare to other disintegrant both the property of wicking and swelling characteristics of CCS in the formulation F3 and F4 attributes increased quantity of solvent uptake and better disintegration of 35 sec. Hence for further formulations croscarmellose sodium was used as disintegrant at concentration level of 5%.

Further to improve the dissolution, formulation trial F7 and F8 were performed using reduced concentration of HPMC polymer, where the HPMC quantity of 250mg and 200mg were used respectively in compare to 300mg of HPMC used in all the previous formulations F1 – F6. Due to reduced concentration of HPMC in this formulation which leads to poor development of films in the petri plate and hence it was necessary to conduct further experiments to improve its film forming ability.

Along with reduction HPMC quantity, other film formers, polyvinyl alcohol and polyvinyl pyrrolidine were used to improve the dissolution rate and film forming ability. The drug release observed was 93.2±1.8% and 90.3±1.4% for formulations prepared using PVA (F9 and 10); and 96.1±0.9% and 98.9±0.7% (F11 and F12) for formulations with PVP, at a concentration level of 3% and 5%, respectively. When using PVP along with HPMC the drug release observed was satisfactory and further film strength needs to be measured. When using PVA along with HPMC as film former the drug release observed was at lower side due to its film characteristics.

Further trials were planned using combination of both PVA and PVP with HPMC and studied its release characteristics. The drug release observed was 96.1±1.1% and 98.9±1.6% (F13 and F14) when using PVP at two concentration level (3% and 5% respectively) along with PVA at lower quantity level of 3%. Further the drug release was 93.2±2.0% and 90.3±1.8% (F15 and F16), when PVP used at two concentration level (3% and 5% respectively) along with PVA at higher quantity level of 5%. Due to higher quantity of PVA the drug release observed was at lower side in both the formulation. Satisfactory drug release was observed when the PVA quantity was at lower concentration and PVP quantity at a higher concentration along with HPMC polymer.

In figure 2, the drug release profile comparison of formulations prepared using different disintegrating agents at two concentration level (F1-F6) were presented.

In figure 3, the drug release profile comparison of formulations prepared using HPMC polymer with PVA or PVP separately at two concentration level (F9-F12) were presented.

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In figure 4, the drug release profile comparison of formulations prepared using combination of HPMC with PVA and PVP (F13-F16) were presented.

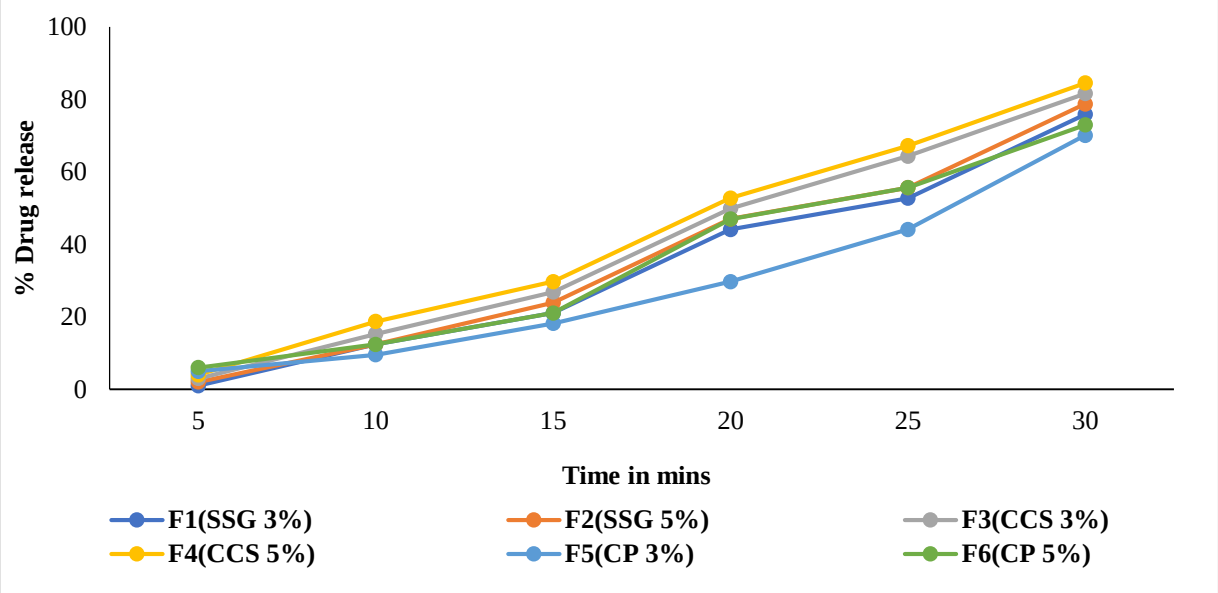

Figure 2: Dissolution profile for formulations having different disintegrants (F1-F6).
Note: SSG- Sodium starch glycolate, CCS- Croscarmellose sodium, CP- Crospovidone

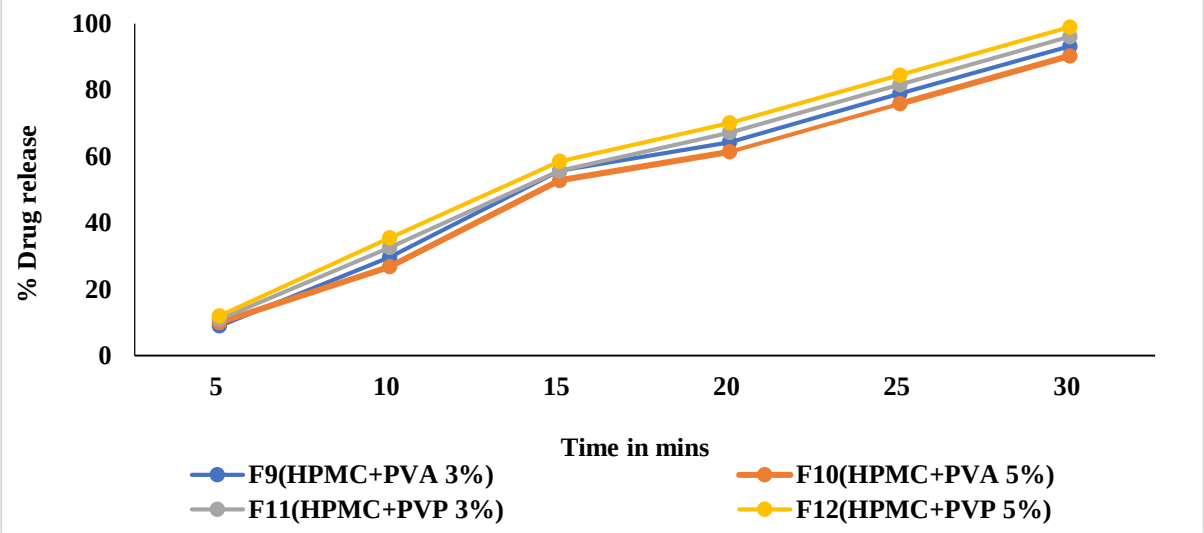

Figure 3: Dissolution profile for formulations having Polyvinyl alcohol (PVA) or Polyvinyl pyrolidine (PVP) with HPMC polymer

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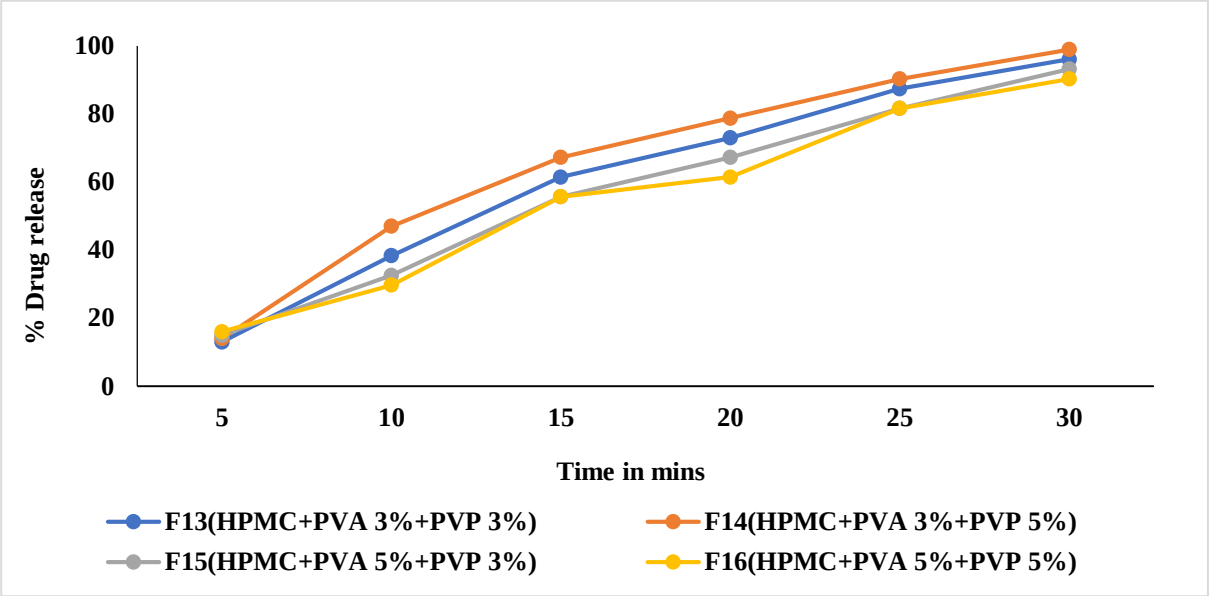

Figure 4: Dissolution profile for formulations with combination of polymers.
Note: PVP-Polyvinyl pyrrolidine, PVA- Polyvinyl alcohol

Tensile Strength

The tensile strength of the film formulations prepared using combination of HPMC polymer with PVA and PVP (F13-F16) were determined by using universal testing machine (UTM). All the formulations F13, F14, F15 and F16 having satisfactory tensile strength of more than 1kg/mm^2 and there were no significant differences in tensile strength. The percentage elongation was observed to be increased in the order of F13(14.29%) < F14(16.67%) < F15(19.35%) < F16(23.33%), respectively. It indicates that higher in elongation was due to increased concentration of the polymer in the film formation.

In table 4, the recorded values of tensile strength and percentage elongation for the formulations (F13-F16) prepared using combinations of polymers were shown.

Table 4: Tensile strength and percentage elongation of montelukast sodium oral thin film

Formulations	Tensile strength Kg/mm^2	Percentage elongation (%)
F13 (HPMC+PVA 3%+PVP 3%)	1.12±0.06	14.29±1.2
F14 (HPMC+PVA 3%+PVP 5%)	1.19±0.05	16.67±0.9
F15 (HPMC+PVA 5%+PVP 3%)	1.26±0.09	19.35±1.4
F16 (HPMC+PVA 5%+PVP 5%)	1.31±0.08	23.33±1.6

Moisture uptake and Moisture loss study

In moisture uptake and moisture loss study of the developed film formulations of montelukast sodium, it was observed that the maximum moisture uptake / moisture loss was less than 5%. The difference between the initial and final weight were not significant which indicates that no films were affected by moisture stress. In table 5 the weight recorded at initial and end of the study were presented for all the formulations prepared.

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Table 5: Moisture uptake and moisture loss study of montelukast sodium oral thin film

Formul-ations	Initial weight (mg)	Moisture uptake study		Moisture loss study	
		Final weight (mg)	% moisture uptake	Final weight (mg)	% moisture loss
F1	44.5±1.3	45.1±1.8	1.35	43.8±0.4	1.57
F2	46.2±1.8	46.8±1.4	1.29	45.6±0.7	1.29
F3	45.0±2.1	45.6±1.2	1.33	43.8±1.1	2.67
F4	45.4±1.9	46.1±0.9	1.54	43.9±1.2	3.30
F5	45.7±2.0	46.4±1.1	1.53	44.0±0.9	3.72
F6	46.1±1.8	47.1±0.8	2.17	45.7±1.6	0.89
F9	45.2±2.2	46.4±1.2	2.65	44.6±0.9	1.33
F10	44.9±1.7	45.7±2.1	1.79	43.5±0.8	3.12
F11	46.1±1.5	46.9±0.6	1.73	44.8±1.4	2.82
F12	45.3±2.2	47.0±0.5	3.75	44.2±1.3	2.43
F13	44.8±1.7	45.6±1.1	1.79	44.2±0.5	1.34
F14	46.2±1.8	46.9±0.4	1.52	45.6±1.5	1.29
F15	45.4±2.1	46.2±0.7	1.76	44.9±0.7	1.10
F16	44.9±1.8	45.8±1.4	2.0	43.9±0.4	2.23

Stability Studies

Selected film formulations (F13, F14, F15 and F16) were stored at accelerated stability condition. The films samples were withdrawn for a period of 12 weeks. Various stability parameters like weight variation, disintegration time, dissolution profile, and percentage drug content were analysed. From the stability analysis results, there was no significant differences observed at the end of testing and hence it was found to be that the films were stable during its storage. In table 6, the testing results at the end of 12^{th} week were presented along with the initial analysis for comparison.

Table 6: Stability study of montelukast sodium films at accelerated stability storage condition of 40^0 C ± 2^0 C / 75% RH ± 5%

Formu-lation	Weight (mg)		Disintegration time max (sec)		Percentage drug release at 30 mins (%)		Percentage drug content (%)	
	Initial	End	Initial	End	Initial	End	Initial	End
F13	44.8±1.7	46.0±1.9	32	35	96.1±1.1	95.2±0.8	97.7±2.0	97.3±1.2
F14	46.2±1.8	45.2±2.1	24	26	99.5±1.4	99.1±1.5	99.5±0.8	99.1±1.0
F15	45.4±2.1	44.8±1.6	33	38	93.2±2.0	92.1±1.7	98.1±1.0	97.7±0.8
F16	44.9±1.8	45.5±2.2	28	31	90.3±1.8	90.1±1.3	98.6±1.2	98.2±1.3

V. CONCLUSION

In this present work oral thin film of montelukast sodium was formulated using HPMC and its combination with other film formers like PVA and PVP. The synergistic effects of combination of film formers were well studied and its significance in film formation, disintegration time and dissolution in the formulation were proven through the experiments. PVP having the ability to improve the hydrophilicity and PVA impart better film characteristics. Solvent casting technique was employed for film preparation, which is simple and scalable method for large scale or industrial manufacturing in future. Developed formulations were characterized using various analytical methods for their physical properties, disintegration, invitro drug release, tensile strength, moisture uptake, moisture loss and stability on storage at accelerated conditions. Formulation F14 containing 5% of CCS as disintegrant and the polymers combination

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HPMC, PVP and PVA at a concentration of 35%, 5% and 3%, respectively showing less disintegration time of 24 seconds, complete drug release of 99.5% in 30 minutes and complies other quality parameters. Wherever PVP was used at 5% concentration in the formulation the disintegration was found to be less than 30 seconds. Hence the polymeric nature and the disintegration mechanism of disintegrants playing an important role in the development of OTF. The results of the current study led to the conclusion that fast-dissolving film formulation could be an alternative promising method and to be utilised as a useful tool to extend the life cycle of an existing conventional montelukast sodium tablets or liquid dosage form. In future the commercial feasibility needs to be assessed by scale up at larger scale level and performing clinical / bioequivalent studies.

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