



Research Article

PREPARATION AND EVALUATION OF MOUTH DISSOLVING FILMS FOR THE DELIVERY OF ALMOTRIPTAN

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ABSTRACT

The aim of the present investigation is to prepare and evaluate mouth dissolving films (MDFs) of Almotriptan (ALMO) and to find out the effect of various formulation variables like film thickness, plasticizers, polymer viscosities and solubilizing agents on physico-mechanical and drug release properties of ALMO. Hydroxyl propyl methyl cellulose (HPMC E3, E5, E15) of different viscosity grades were used as film forming agents, poly ethylene glycol (PEG-400) and glycerol as plasticizers. The developed MDFs were characterized for film thickness, disintegration time, FTIR, DSC, XRD and drug release behavior. The films were homogenous, elegant, transparent and smooth in texture. Photomicrographs, along with DSC and XRD studies confirm no recrystallization of ALMO with in MDFs. *In-vitro* drug release studies indicate that HPMC E15 films attributed to their higher viscosity showed slower ALMO release compared to other formulations. Addition of solubilizing agents (PVP K30 and SLS) to HPMC E3 formulations brought a significant increase in ALMO release rates compared to formulations without them. The formulation F5 showed quicker disintegration (within 8.66sec) and ALMO release rates (complete release was obtained in 80sec) along with good physico-mechanical properties. Accelerated stability studies revealed no significant change in appearance and ALMO content in MDFs indicating that ALMO was stable in MDFs.

Keywords: Almotriptan; Mouth dissolving films; Wet film applicator; Formulation variables.

INTRODUCTION

The patient usability is often used to describe the drug products with characteristics that meet the need of the patient groups. The properties of the pharmaceutical products should be optimized to patient agreeableness. Orally administered pharmaceutical formulations like tablets, chewable formulations have been assessed for their potential patient acceptance features. However, a harmonized approach towards the patient acceptability testing has not yet been fulfilled^{1,2}.

Mouth dissolving films (MDFs) are unique formulations that were introduced in this context for providing an easy and convenient means of drug administration. MDFs are solid dosage forms that disintegrate or dissolve rapidly (<1 minute) when placed in the mouth, without drinking or chewing. It is suggested that drugs go directly to the systemic circulation after buccal or sublingual delivery, resulting in rapid drug absorption and improved bioavailability via avoidance of first-pass metabolism. In addition to simple and easy means of drug administration without the need for water, oral films can provide fast drug action resulting from the swift disintegration and drug release from the dosage forms^{3,4}.

MDFs are thin and flexible layer of polymer with or without a plasticizer⁵. Since they are thin and flexible by their nature, it can be more agreeable by the patient. The thin films is polymeric matrices that meet many prerequisites for being used efficiently as a drug release platform⁶. MDFs have showed the capacities to enhance the onset of drug action and improve the drug efficacy. Compared with the current traditional dosage forms, it emerges

out to be superior in terms of enhanced bioavailability and high patient compliance⁷. The wide availability of polymers and the underlying assumptions in manufacturing technology have made possible to develop a wide range of thin films⁸. Therefore, MDFs are gaining reputation and affirmation in the pharmaceutical area as a novel drug delivery dosage form.

Ideal MDFs need to exhibit desirable features such as sufficient drug loading capacity, fast dissolution rate, and acceptable formulation stability^{9,10}. In the development of MDFs, the main critical issues are represented by the tensile properties required for packaging and handling procedures, dissolution in the oral cavity, stability, and taste¹¹. In the present investigation a systemic study on MDFs has been performed for the development of more desirable formulations of Almotriptan (ALMO) for the effective treatment of migraine.

Migraine is one of the most common and disabling diseases encountered in general practice, although it is often not diagnosed or is not treated optimally¹². A recent study using International Headache Society diagnostic criteria reported a lifetime migraine prevalence of 6% in men and 18% in women, with an increased prevalence approaching the age of 4-0 years that declines thereafter in both sexes¹². An epidemiologic study from the Netherlands found that migraineurs have a median of 12 migraine attacks per year, and 25% have at least 2 attacks per month¹³. ALMO 1-(((3-(2-(Dimethylamino) ethyl) indol-5-yl) methyl) sulfonyl) pyrrolidine a triptan derivative used for the treatment of acute migraine headaches with or without aura in adults. ALMO is well absorbed following oral administration with peak blood concentration reaches between 1-3hours. It under goes first pass

metabolism and oral bioavailability is around 70%. All these properties of ALMO make it a right candidate for delivering through per oral cavity as MDFs. Presently, ALMO is marketed in the form of IR tablets (Axert, Almogran, Almotrex etc.). Keeping in view of the patient compliance and need of the better therapeutic efficacy and since no research work has been done on ALMO MDFs, the present investigation was aimed at preparation and evaluation of ALMO MDFs to ensure quick onset of action.

MATERIALS AND METHODS

Materials

ALMO gift sample from Mylan Laboratories Ltd, Hyderabad, hydroxyl propyl methyl cellulose E3, E5, E15 (Gift sample from Colorcon Pvt. Ltd, India), Methanol (Loba Chemie, Mumbai), Sodium lauryl sulphate (Merck, India), PVP K30 (Dr. Reddy's Laboratories, Hyderabad), Pine apple flavor (Darwin Laboratories, Vijayawada), Aspartame (Darwin Laboratories, Vijayawada). All other reagents of analytical grade were used.

Preparation of Artificial Saliva

Artificial saliva was prepared as follows, using the following ingredients; sodium chloride-0.844g; potassium chloride-1.2g; calcium chloride dihydrate-0.193g; magnesium chloride hexahydrate-0.111g; potassium phosphate dibasic-0.342g¹⁴. These ingredients were added one by one to 500mL of distilled water and then the volume was made up to 1000mL using the same. The pH was adjusted with 0.1N hydrochloric acid to 5.7.

Preparation of ALMO MDFs

Initially, placebo MDFs were prepared using different polymers and plasticizers in order to select the suitable polymer-plasticizer combination that forms MDFs with desired film properties and mechanical strength. After selecting the suitable combinations, ALMO MDFs were prepared as per formula given in Table 1 to a batch size of 5g. ALMO was dissolved in a mixture of solvents (water and methanol) in a beaker and other ingredients were added one by one and finally polymer was added and mixed thoroughly. The mixture was sonicated for 1min to remove any entrapped air bubbles and casted on a glass plate with a wet film applicator set at 30 mil (750µm) and 40 mil (1000µm) thickness and was dried at 40°C for 60min in hot air oven. The dried films were then peeled off from the glass plate, cut into appropriate sizes, and stored in desiccator until use.

Chromatographic Conditions for Analysis of ALMO

RP-HPLC system (Shimadzu) comprising of a Degasser (DGU-20A3), Binary pump (LC-20 AD), an Auto-sampler (SIL-20 AC HT) and a PDA-detector (SPD M20A) was used to develop method for analysis of ALMO. Shimadzu LC solution software was used to collect and process the data. The mobile phase consisting of formic acid (0.02 % v/v): methanol (70:30 %v/v) at flow rate of 1 ml/min in isocratic mode and the eluents were monitored at 227 nm. Separation was achieved on Agilent Eclipse C₁₈ column (150*4.6mm, 5 µm). The developed method was validated as per ICH guidelines and used for the analysis of ALMO.

DSC Studies

Thermograms of ALMO and ALMO MDFs were recorded using differential scanning calorimeter (Shimadzu, DSC-60, Japan). Samples weighing 5 mg were sealed in aluminium pans and

heated from 50-400°C at rate of 10°C per minute. An empty aluminum pan was used as reference.

X-RD Studies

X-RD studies of ALMO and ALMO MDFs were performed using X-Ray Diffractometer (Shimadzu, XRD-7000, Japan) with Cu-Kα radiation at 40 kV and 30 mA. X-Ray diffraction patterns were collected over 2θ range of 10-40° at a scan rate of 4° per min. The position and intensities of diffraction peaks were considered for the identification of ALMO in different samples.

FTIR Studies

FTIR studies were carried out using ATR-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000-500 cm⁻¹ at a resolution of 1.0 cm⁻¹. The powder or film sample was simply placed onto the ATR crystal and the sample spectrum was collected.

Evaluation Parameters for ALMO MDFs

Morphological Properties

Properties such as homogeneity, color, transparency, and surface of ALMO MDFs were tested visually. All the formulations were stored at room temperature (25±3°C) with relative humidity of approximately 65 ± 5% and were tested periodically every month for a period of 6 months. The films were packed in aluminum foil pouches.

Thickness

The thickness was measured with screw gauge at different places of MDFs to evaluate the reproducibility of preparation method. The thickness of film was evaluated using a screw gauge with a range of 0-10mm and revolution 0.001 mm. Anvil of the thickness gauge was turned and the film was inserted after making sure that the pointer was set to zero. The film was held on the anvil and the reading on the dial was noted down.

ALMO Content

Three one cm² films were taken each in a 10 ml volumetric flask and dissolved in 5ml of distilled water and then final volume was made up with distilled water. Samples were suitably diluted with artificial saliva and then analysed using RP-HPLC-PDA method.

Variation of Mass

Mass variation among the different batches of the formulations was calculated by measuring mass of one cm² film cut from different areas of the MDFs. The estimations were carried out in triplicate.

In-vitro Disintegration Studies

In the present investigation *in-vitro* disintegration study was carried out using two independent methods namely, drop method and petri dish method. For both the methods only a small quantity of medium was required so that the natural conditions can be simulated.

Drop Method

The MDFs of 1cm² were placed on a glass slide and placed planar on a petridish and then a drop of distilled water was dropped by a pipette onto the MDFs. The time until the film dissolved and

caused a hole within the film was measured. The estimations were carried out in triplicate.

Petri Dish Method

In this method 2 ml of distilled water was placed in a petridish and a film of 2x2 cm² was placed on the surface of the water and the time required to dissolve the film completely was measured. The estimations were carried out in triplicate.

Tensile Strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks^{15,16}. In the present investigation tensile strength was measured using a Tech Tensiometer-UTM9051 (Dak Systems Inc., Mumbai, India) fitted with a load cell of 500N (50kg) capacity. The data was collected and processed through Test Bench II software. A fixed dimension (length x width = 10 x 2 cm) of film was mounted between pneumatic grips without any loose folds and all the dimensions were entered into the software to calculate the cross-sectional area. Instrument was operated at speed of 5mm/min until the film breaks. The whole experiment was carried out in triplicate.

Percent Elongation

When films change their posture and stretches in size, then the stress applied is referred to strain. Strain is the ratio of deformation of film caused by strain to its original dimensions. The concentration of plasticizer in the formulation is directly proportional to the elongation of the film. In the present investigation percent elongation was computed from the Test Bench II software while conducting the tensile strength experiments. The estimations were carried out in triplicate.

Folding Endurance

Folding endurance provides an overall picture of brittleness of the film. It is determined by repeated folding of the film at the same place till the film breaks. The measurements were carried out in triplicate. The number of times the film is folded without breaking is computed as folding endurance value¹⁷.

In-vitro Drug Release Studies

The *in-vitro* drug release studies were conducted using 500ml of artificial saliva as dissolution medium using USP Type V Dissolution Rate Testing apparatus. A temperature of 37°C and 50 rpm were maintained. Each film of appropriate size (3 x 2.4cm²) equivalent to 5mg dose was cut and placed on a watch glass covered with nylon wire mesh. The watch glass was then dropped into dissolution flask. 5 ml samples were withdrawn at predetermined time intervals 5, 10, 20, 30, 40, 50, 60, 80, 100, 120, 180, 240, 300, 360 sec and every time replaced with 5 ml of fresh dissolution medium. The samples were analysed by RP-

HPLC-PDA method. The experiments were conducted in triplicate.

Stability Studies

Stability studies were carried out on F11 containing 1%w/w ALMO and HPMC E3. MDFs were packed in aluminum pouches, sealed and stored 40°C, 75±5% RH for 6 months. During this time, the MDFs were examined for appearance, weight variation and drug content properties.

RESULTS AND DISCUSSION

Preparation of ALMO MDFs

Initially, different placebo MDFs were prepared with HPMC (E3, E5 and E15), methyl cellulose, sodium alginate, and Na CMC as film formers using PEG 400 and glycerol as plasticizers and observed for their film forming capacities and morphology. Sodium alginate and methyl cellulose showed poor film forming capacities and MDFs prepared were not easily separable from the glass plate upon casting. In contrast, MDFs prepared with Na CMC and HPMC polymers were elegant in appearance with good mechanical properties and hence selected for further development. However, upon drug loading MDFs prepared with Na CMC showed crystallization of ALMO immediately after drying. Moreover, MDFs obtained were brittle with poor mechanical properties. Whereas, MDFs prepared with HPMC polymers were transparent with quick drying rates and good mechanical properties. Therefore, HPMC polymers with three different viscosity grades (E3, E5 and E15) were selected for preparation of ALMO MDFs. Different ALMO MDFs were prepared as per the formulae given in Table 1. A 5g batch size of formulations gave approximately 120 cm² film area.

Morphological Properties

ALMO MDFs were visually tested for homogeneity, transparency, color and smoothness. MDFs prepared with 2% w/w ALMO load were transparent initially but turned opaque within 15 days. This might be due to recrystallization of ALMO within the MDFs. In order to prevent the crystallization of ALMO, PVP K30 as solubilizing agent was added to the formulations at 0.04% level. However, crystallization of ALMO was still observed. Further trials were made by decreasing the ALMO load to 1.25% w/w equivalent to 62.5 mg of ALMO base. With 1.25%w/w ALMO load the films were transparent and no crystallization was observed even at the end of 6 months. Hence, the drug load of 1.5%w/w was selected for further development of MDFs. The photographs of MDFs with different ALMO loads were shown in Fig.1. The morphological characterization of MDFs was further established by visualizing MDFs under binocular microscope (Olympus-CH20i) with magnification 10X. The photomicrographs of MDFs are shown in Fig. 2.

Table 1: Formulae of HPMC-ALMO MDFs

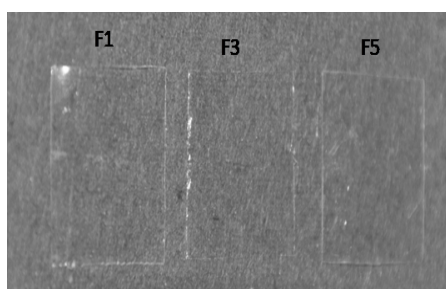
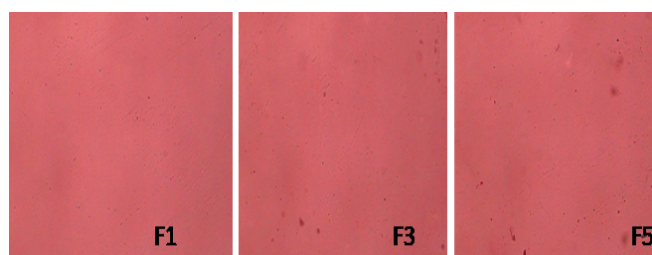
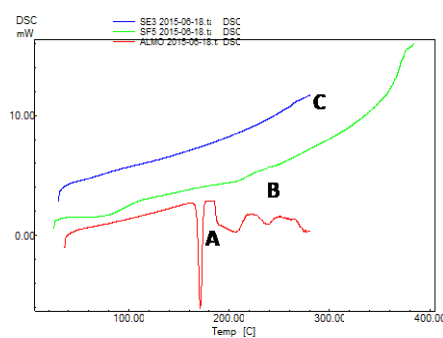
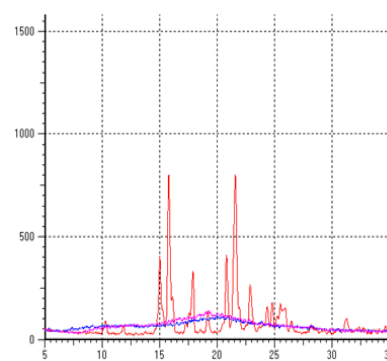
Ingredients (mg)	F1	F2	F3	F4	F5	F6
ALMO #	62.5	62.5	62.5	62.5	62.5	62.5
HPMC E3	375	375	-	-	375	375
HPMC E5	-	-	375	-	-	-
HPMC E15	-	-	-	375	-	-
PEG 400*	25	-	25	25	25	25
GLYCERINE *	-	25	-	-	-	-
SLS	-	-	-	-	-	2
PVP K30	-	-	-	-	2	-
WATER*	1787.5	1787.5	1787.5	1787.5	1785.5	1785.5
METHANOL*	2750	2750	2750	2750	2750	2750

#Maleate salt equivalent to 62.5mg of base; *Amount taken based upon their density

Table 2: Physico-mechanical, Chemical properties of different ALMO MDFs

Formulations	Drug content* (mg/cm ²)	Mass variation* (mg)	Percent elongation*	Folding endurance	Thickness* (µm)	Disintegration time*(sec)	
						Drop method	Petri dish method
F1	0.643±0.030	3.1±0.10	87.02±0.80	105± 2.89	63.33±7.52	9.67 ± 0.577	18.5 ± 0.50
F2	0.603±0.060	3.33±0.152	81.19±0.96	54± 2.08	56.66±6.32	11.33 ± 1.527	20.33 ± 1.154
F3	0.663±0.040	3.63±0.155	90.00±0.27	115 ± 1.53	75.00±14.71	15.66 ± 1.154	25.67 ± 0.577
F4	0.75±0.085	3.96±0.208	96.02±0.80	121± 2.52	112.5±17.72	21.33 ± 2.516	31.83 ± 1.041
F5	0.656±0.040	3.46±0.115	92.15±0.79	129± 2.52	66.66±5.47	8.66 ± 0.577	12.83 ± 1.258
F6	0.653±0.035	3.30 ±0.10	81.45±1.37	98± 2.08	65.00±5.47	9.33 ± 0.577	14.33 ± 0.577

*estimations were carried out in triplicate

**Fig. 1: Photographs of ALMO MDFs with 1.25% load (F1, F3, F4 (coloring agent was not added to show the difference in appearance between crystallized and optimized film)).****Fig. 2: Photomicrographs of A (F1), B (F3), C (F4).****Fig.3: DSC thermograms of ALMO (A), F5 (B), F5 placebo (C)****Fig.4: X-RD spectra of ALMO (---), F5 Placebo (---), and F5 formulation (---)**

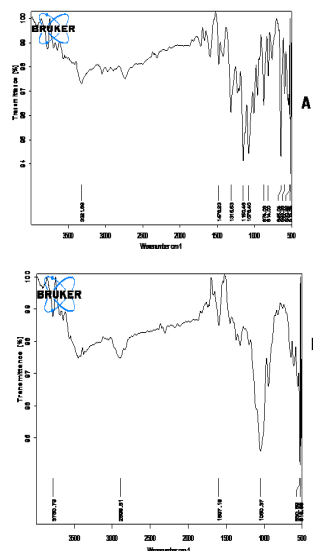


Fig. 5: FTIR spectra of A) ALMO, B) F5 formulation

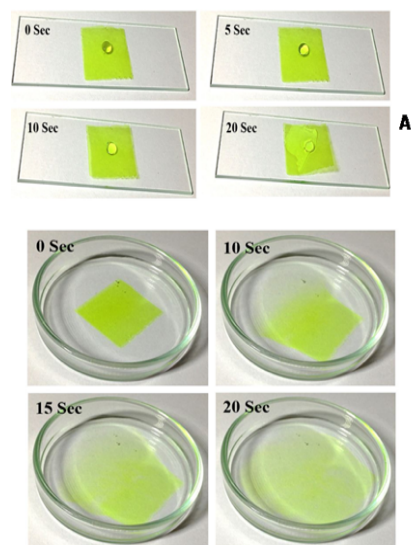
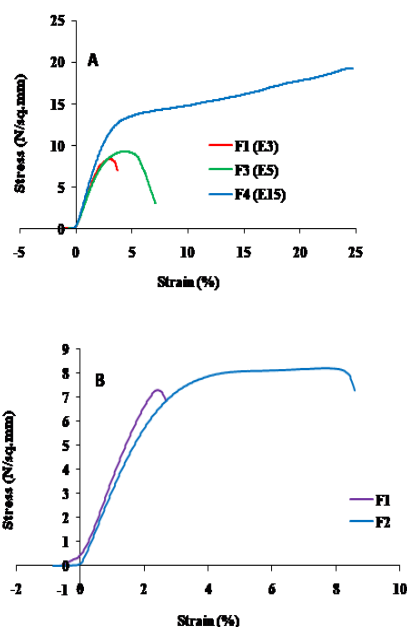
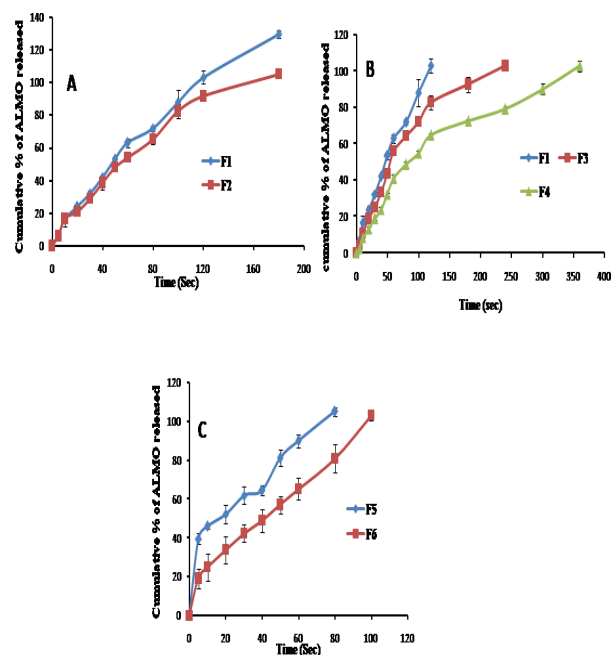
Fig. 6: *In-vitro* disintegration of MDF (F5) by (A) Drop method and (B) Petri dish method

Fig.7: Effect of Film Plasticizers (A) and Polymer viscosities (B) on Tensile strength of ALMO MDFs

Fig. 8: Effect of plasticizers (A), Polymer viscosities (B) and Solubilizing agents (C) on *in-vitro* release of ALMO from MDFs

DSC and X-RD Studies

In order to confirm the absence of ALMO recrystallization within the MDFs, the prepared MDFs were subjected to DSC and X-RD studies. DSC thermograms obtained for ALMO and selected ALMO MDFs (F5 placebo, F5) were shown in Fig.3. Thermogram of ALMO showed sharp endothermic peak at 171.06°C corresponding to the melting point of ALMO indicating that ALMO exists in single crystalline state. Thermograms of ALMO MDFs showed no or weak peaks compared to ALMO, which may be due to molecular dispersion of ALMO within the MDFs. Also no extra peaks were observed in the thermograms indicating the absence of ALMO recrystallization within the films. The X-ray diffractograms of ALMO and F5 placebo, F5 formulations were given in Fig. 4. ALMO showed characteristic peaks at 15.45°, 17.50°, 20.95°, 21.29° and 22.48°2θ. The X-ray

diffractograms of the ALMO MDFs showed weak or no signals when compared to the characteristic peaks of ALMO. This may be due to molecular dispersion of ALMO within the MDFs. Overall, results from DSC and X-RD studies clearly indicates that the ALMO was not in crystalline state in MDFs.

FTIR Studies

The compatibility between ALMO and different excipients used in formulations was studied using FTIR studies. The FTIR spectra of at 1150.48cm⁻¹(aliphatic C-N stretching), 3321.69cm⁻¹(aromatic secondary amine N-H stretching), 645.04cm⁻¹(C-S stretching), 1078.40cm⁻¹(S=O stretching). These characteristic peaks of ALMO were all retained in the MDFs and no shift in major peaks was observed indicating that there is no interaction

between ALMO and excipients in MDF formulations. FTIR spectra of ALMO and F5 formulation were shown in Fig.5.

Film Thickness

Thickness of the MDFs was measured using screw gauge at different places across the whole area of the MDF in order to evaluate the reproducibility of preparation method and formulation. The results were given in Table 2. Around 90% of wet film thickness was lost during drying. Preparation of MDFs with wet film applicator resulted in uniform film thickness throughout the whole area of the MDFs. MDFs of E3 formulations containing PVP and SLS show high thickness values ($66.66 \pm 5.47 \mu\text{m}$ and $65.00 \pm 5.47 \mu\text{m}$ respectively for F5 and F6) compared to the MDFs of E3 formulations without PVP and SLS ($63.33 \pm 7.52 \mu\text{m}$ respectively for F1). Among the two types of plasticizers used, formulations containing glycerol (F2, $56.66 \pm 6.32 \mu\text{m}$) showed slightly higher thickness compared to formulations containing PEG 400 (F1, $63.33 \pm 7.52 \mu\text{m}$). MDFs prepared with HPMC E15 (F4) showed higher thickness ($112.5 \pm 17.72 \mu\text{m}$) compared to MDFs prepared with E5 (F3, $75.00 \pm 14.71 \mu\text{m}$) and E3 (F1, $63.33 \pm 7.52 \mu\text{m}$). Increase in viscosity of polymer as in case with E15 resulted in lesser film area and thereby resulting in higher film thickness.

ALMO Content

Films of one cm^2 were cut from top, middle and bottom areas ($n=3$) of whole MDF and ALMO content was estimated. The results were given in Table 2. The results showed a good uniformity of ALMO within the film, indicating good solubilization of ALMO in MDFs. Formulations with HPMC E15 (F4) showed higher ALMO content ($0.75 \pm 0.085 \text{mg}/\text{cm}^2$) compared to E5 (F3, $0.663 \pm 0.040 \text{mg}/\text{cm}^2$) and E3 (F1, $0.643 \pm 0.030 \text{mg}/\text{cm}^2$). In both cases, decrease in film area resulted in more drug entrapment within the small area of the MDFs resulting in higher ALMO content values. MDFs of E3 formulations with PVP and SLS (F5, F6) shows high drug content ($0.656 \pm 0.040 \text{mg}/\text{cm}^2$ and $0.653 \pm 0.035 \text{mg}/\text{cm}^2$) when compared to MDFs of E3 formulations without PVP and SLS (F1, $0.643 \pm 0.030 \text{mg}/\text{cm}^2$) indicating the solubilization of ALMO by PVP and SLS.

Mass Variation

Mass of 1cm^2 films cut from different batches was recorded on electronic balance (Shimadzu-ATX224) and results are given in Table 2. Same mass was obtained with the three batches of films indicating reproducibility of preparation method and formulation.

In-vitro Disintegration Studies

In the present investigation the effect of film thickness, polymer viscosities and solubilizing agents on *in-vitro* disintegration of MDFs was studied. Studies were carried out using two independent methods drop and petri dish methods to mimic the *in-vivo* conditions. The results were given in Table 2. The results revealed that film thickness, polymer viscosities and solubilizing agents had significant effect on disintegration of MDFs. MDFs with HPMC E3 showed faster disintegrating times (F1, $9.67 \pm 0.577 \text{ sec}$ by drop method) compared to E5 (F3, $15.66 \pm 1.154 \text{ sec}$) and E15 (F4, $21.33 \pm 2.516 \text{ sec}$). Higher film thickness due to higher polymer viscosities as in case with HPMC E15 films resulted in delayed disintegration of MDFs. Significantly faster disintegration times were observed with the addition of PVP K30 and SLS to the formulations (F5, $8.66 \pm 0.577 \text{ sec}$ and F6, $9.33 \pm 0.577 \text{ sec}$ respectively) compared to MDFs without them. The images of MDF (F11) disintegration by drop and petridish methods are shown in Fig. 6A and 6B respectively.

Tensile Strength and Percent Elongation

Tensile strength demonstrates the ability of film to withstand the external forces during the packing and transportation. MDFs should possess moderate tensile strength and high percent elongation. In the present study the tensile strength of MDFs was measured using Mini Tech Tensiometer-UTM9051 and tensile strength profiles were shown in Fig. 7. Formulations prepared with HPMC E15 showed more tensile strength values compared to E5 and E3 films (Fig. 7A) indicating that increase in polymer viscosity increased the tensile strength of films. No significant difference in tensile strength was observed between formulations with PEG 400 and glycerol as plasticizers (Fig. 7B) indicating that plasticizers had no significant impact on the tensile strength of films.

Percent elongation values were computed from the Test Bench II software during tensile strength experiments and results were given in Table 2. Among the polymers used formulations with HPMC E15 showed higher percent elongation (F4, 96.02 ± 0.80) compared to E5 (F3, 90.00 ± 0.27) and E3 (F1, 87.02 ± 0.80) films. Overall, from the results it can be concluded that polymer viscosity and film thickness had significant impact on tensile strength and percent elongation of films.

Folding Endurance

Along with tensile strength, folding endurance demonstrates the resistance of film towards mechanical forces during packing or transport. The number of times film folds without breaking is computed as folding endurance. Folding endurance values were in conjunction with tensile strength profiles with MDFs casted with E3 (F1) showed lesser folding endurance values (Table 2) compared to those with E5 (F3) and E15 (F4), indicating the brittleness of E3 (F1) films.

In-vitro Drug Release Studies

There are no adequate methods reported / published for dissolution testing of dosage forms administered into or within oral cavity in pharmacopoeias. Some dissolution methods are reported for ODTs and chewing gums but not for MDFs. In the present investigation, dissolution of MDFs were carried out using Type 5 dissolution apparatus and 500mL of artificial saliva was used as dissolution medium in order to mimic the *in-vivo* conditions. The effect of various formulation variables like film thickness, plasticizers, polymer viscosities and solubilizing agents on ALMO release from the MDFs was studied and the comparative *in-vitro* release profiles were shown in Fig. 8. Totally 6 different formulations of ALMO were prepared using HPMCE3, HPMCE5, HPMCE15 as film forming polymers with and without SLS and PVPK30. PEG 400, Glycerin are used as plasticizers.

F1 and F2 formulations were prepared with HPMC E3 as polymer for both formulations and PEG 400, Glycerine as plasticizers respectively. The cumulative percent of ALMO released at the end of 5sec is 7.04 ± 1.15 and 5.95 ± 0.721 for F1 and F2 respectively. Complete ALMO release was obtained at 120sec and 180sec for F1 and F2 respectively and the comparative release profiles are shown in Fig 8A. The ALMO release from F1 (E3 and PEG 400) is significantly higher when compared to F2 (E3 and Glycerine).

The cumulative percent of ALMO released at the end of 5 sec is 7.04 ± 1.15 , 4.323 ± 0.468 and 2.35 ± 0.42 for F1, F3, and F4 respectively. Complete ALMO release was obtained at 120, 240 and 360 sec for F1, F3 and F4 respectively and the comparative

profile was shown in Fig 8B. The ALMO release from F1 (only E3) is higher when compared to F3 (only E5), F4 (only E15). Overall, the order of percent ALMO released from MDFs is $F1 > F3 > F4$.

Effect of solubilizing and or wetting agents on ALMO release was also observed. Both the SLS and PVP K30 were added to the formulations at 0.04% level. The cumulative percent of ALMO released at the end of 5sec is 39.66 ± 2.57 and 19.10 ± 4.91 for F5 and F6 respectively. Complete ALMO release was obtained at 80sec and 100sec for F5 and F6 formulations respectively and the comparative profile was shown in Fig 8B. The ALMO release from F5 (E3 and PVP) is significantly higher when compared to F6 (E3 and SLS).

Overall, PEG 400 was selected as suitable plasticizer because F1 shows higher dissolution properties when compared to F2. HPMC E3 formulations (F1, F5, F6) with and without PVP K30 and SLS shows superior dissolution properties when compared to HPMC E5 (F3) and HPMC E15 (F4) formulations. This may be due to low viscosity of the E3 polymer than the E5 and E15 polymers. MDFs with PVP and SLS gave superior dissolution properties when compared to MDFs without PVP and SLS. MDFs with PVP (F5) gave higher dissolution properties when compared to SLS formulations (F6). The comparative release profiles for MDFs with and without PVP and SLS are given in Fig 8C.

Drug Release Kinetics

For better understanding of the release profiles obtained with ALMO MDFs, the drug release data obtained at different time points was fitted into kinetic models such as First order and Higuchi models^{18,19}. The first order release rate constant ' k ' (sec^{-1}) values and correlation coefficient (R^2) values are calculated from dissolution data (0-40 sec) of ALMO MDFs. When compared to F2 (E3 and Glycerine) the ' k ' value was higher for F1 (E3 and PEG). A 1.3 fold increase in ' k ' value for F1 formulation was observed when compared to F2. When compared to F1 (only E3) the ' k ' values were lower for F3 (only E5) and F4 (only E15). Overall, the ' k ' values were in the order of $F1 > F3 > F4$. A 1.3 and 1.7 folds increase in ' k ' values for F1 formulation when compared to F3 and F4 formulations was observed.

When compared to F1 (only E3) the ' k ' values were significantly higher for F5 and F6 formulations containing PVP and SLS respectively. A 1.66 and 1.16 folds increase in ' k ' values for F5 and F6 formulations when compared to F1 was observed. Overall, MDFs of ALMO with PVP and SLS gave higher ' k ' values when compared to MDFs of ALMO without PVP and SLS. Among 6 formulations, the ' k ' value was significantly higher for F5 when compared to other formulations. The Higuchi square root model of all the formulations showed higher correlation coefficient values (0.921-0.995) indicating diffusion is the release mechanism.

Stability Studies

Stability studies were carried out for F5 formulation containing 1.5 % w/w ALMO with HPMC E3 and PVP K30. MDFs were stored at 40°C with relative humidity of approximately 75±5% for 6 months. The appearance, weight variation and ALMO content of the MDFs were examined. The appearance of MDFs remained unchanged throughout the studies and no crystallization was observed. There is no statistically significant change in weight of MDFs. MDFs showed 96-103% of ALMO content after 6 months, indicating that the ALMO was stable in MDFs.

CONCLUSION

From this investigation, it can be concluded that ALMO can be successfully formulated into MDFs at 1.25% drug loadings with wet film applicator ensured the reproducibility of the preparation method. MDFs prepared with HPMC E3, E5 and E15 as film forming polymers possessed good physico-mechanical and dissolution properties. Among the 6 formulations, the F5 (7.5% w/w HPMC E3 as film former and 0.04% w/w PVP K30) gave higher *in-vitro* ALMO release (105.03 ± 2.05 at the end of 80 seconds). The developed ALMO MDFs may provide quick onset of action with improved oral bioavailability and enhanced patient compliance with good therapeutic efficacy when compared to the current marketed formulations i.e. IR tablets.

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