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Research Article

Fast dissolving oral films of almotriptan malate: Preparation and in vitro/in vivo evaluation

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Abstract

Almotriptan malate is a second generation triptan used in acute treatment of migraine attacks. Present work aimed at preparing quick onset of action which is beneficial in migraine disease, aiding in the enhancement of bioavailabity and is very convenient for administration without the problem of swallowing and using water. The film were prepared by using different grades of HPMC E3, E6, and E15, maltodextrin DE6 and other polymers by solvent casting method. They were evaluated for physical characteristics such as thickness, uniformity of weight, folding endurance, drug content, surface pH, percentage elongation and tensile strength and results were found to be satisfactory. The formulations were subjected to disintegration and in-vitro drug release test. The in vitro disintegration time of the optimized formulation F15 was 10 sec and drug release was found to be very fast i.e. 98.8% of within 10min. In vivo studies confirmed that their potential as an innovative dosage form to improve the bioavailability and considered to be potentially useful for the treatment of migraine where quick onset of action is desirable.

Keywords: Almotriptan malate, fast dissolving oral films, disintegration time, HPMC, bioavailability

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1. Introduction

The ultimate goal of any drug delivery system is the successful delivery of the drug, in which almost 90% of the drugs are administered to the body for the treatment of various disorders and diseases as it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance [1,2,3].

About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphagia patients turned the manufacturer to the parenterals and liquid orals. But the liquid orals have the problem of accurate dosing mainly and parenterals are painful drug delivery, so most patient incompliance. Each pharmaceutical company wants to formulate the novel oral dosage form which has the higher bioavailability, quick action and most patient compliance [4].Many pharmaceutical companies have directed their research activity in reformulating existing drugs into new dosage forms. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity [5, 6].

Fast dissolving drug delivery system is easy to administer and provides better patient compliance in the elderly, pediatric, mentally retarded, nauseated and uncooperative paients [7].This delivery system consists of the solid dosage forms that dissolve quickly i.e. within a matter of seconds in the oral cavity without the administration of water. The delivery system consists of a very thin oral strip which is simply placed on the patient's tongue or any other oral mucosal tissue and instantly gets wetted by saliva [8].The film rapidly hydrates onto the site of application. It then rapidly dissolves and disintegrates to release the medication for oro-mucosal absorption. Fast dissolving oral thin films are widely accepted by

patients and also to the caregiver for their ease-of-delivery, portability and accurate dosing [9]. They also provide quick onset of action within few seconds as the oro-mucosal absorption of drug occurs directly from the site of administration to the systemic circulation avoiding first pass metabolism to produce the desired effect [10].
Rapidly dissolving films (RDF) were initially introduced in the market as breath fresheners and personal care products such as dental care strips and soap strips. However, these dosage forms are introduced in the United States and European pharmaceutical markets for therapeutic benefits. The first of the kind of oral strips (OS) were developed by the major pharmaceutical company Pfizer who named it as Listerine® pocket packs™ and were used for mouth freshening [11].

Migraine is a common, chronic disorder with episodic attacks [12].It affects 10-20% of the population during the most productive periods of their working lives; women are affected up to four times more often than men [13].
Almotriptan malate is a second generation triptan used in acute treatment of migraine attacks in adults with a history of migraine with or without aura, which has been shown to have efficacy comparable to sumatriptan with an improved tolerability profile [14].

Conventional available Almotriptan malate tablets are not suitable where quick onset of action is required for the disease like migraine attack. There is a need to develop rapidly dissolving dosage form to provide the patients with the most convenient mode of administration, particularly one that disintegrates and dissolves/ disperses in saliva and can be administered without need of water. Fast dissolving oral films are useful in patients such as paediatric, geriatric, bedridden, or developmentally disable who may face difficulty in swallowing conventional tablets. So the patients would be benefited from acute treatment by using proposed drug delivery system. Thus, a fast dissolving film is a unique solid oral dosage form and has valuable advantages. The present study is aim to formulate and characterize the fast dissolving oral films of Almotriptan malate by solvent casting method for rapid onset of action in the management of migraine attack and also to improve the bioavailability of the drug.

2. Materials and methods

Almotriptan malate was generous gift sample from MSN labs, Hyderabad, India. Hydroxy Propyl Methyl Cellulose (HPMC E3, E6 & E15) was gifted by Nectar life sciences, Hyderabad, Maltodextrin DE6, Xanthan gum and Aspartame was obtained from Matrix Labs, Hyderabad, Propylene glycol, Vanillin, Citric acid Amaranth from SD FINE CHEM. LTD, Mumbai. Methanol, Acetonitrile and MilliQ water are of HPLC grade. All other chemicals used were of analytical grade.

Determination of dose of Almotriptan Malate

Amount of drug required per film =8.75mg of Almotriptan Malate equivalent to 6.25mg of Almotriptan
Therefore, 4 films require 35mg of drug
Area of the petridish (πr^2) ==3.14*4.5*4.5=63.5cm^2
6 films of 4 cm^2 each i.e. (2cm*2cm) can be obtained freely per petridish
Area not required is the one remaining after cutting the films from the centre of petridish. This is obtained as
Area considered= Sum of the areas of number of films taken= 4 cm^2*6=24 cm^2
Amount of drug in area considered=52.5mg
Area not considered= Total area of petridish-Area considered= 63.5-24= 39.5 cm^2
4 cm^2 film contains 8.75mg of drug therefore 39.5 cm^2 contains 86.6mg of drug
Amount of drug in area not considered=86.6mg
Therefore,
Total drug dose = (Amount of drug in area considered) + (Amount of drug in Area not considered) = 52.5+86.6= 139.1
Therefore, an approximate amount of 139.1mg drug was considered per petridish.

Preparation of Almotriptan Malate oral films

It was aimed to prepare fast dissolving oral films of Almotriptan malate with the dose of 6.25mg per 4 cm^2 film. Film forming polymers hypromellose different grades and maltodextrin were weighed accurately, added to a small amount of water in a small beaker, covered with an aluminium foil and soaked for 24 hours to ensure complete hydration. Xanthan gum was added on next day in small amounts and the solution was stirred on a magnetic stirrer at 75rpm for first half an hour and later 50rpm for 1.5 hours. Then, propylene glycol was added and stirring was continued for 30 minutes at 50rpm. Almotriptan malate, aspartame, citric acid, vanillin and amaranth were dissolved in sufficient quantity of water and added to the

polymer mixture. This film forming solution was then stirred well to obtain a homogenous solution. Dry and clean petridish was selected and the solution was poured into it. Drying was carried out at 45°C in a hot air oven for 6 hours. The petridish was then removed and left aside to cool down to room temperature. The film was then peeled carefully using surgical scalpel by making a small incision in the film on one side of the petridish. Small films of 4 cm^2 were cut from one big film and packed primarily in aluminium foil and secondarily in a self- sealing polythene bag to ensure least moisture penetration and the resulting films were evaluated [15].The composition of Almotriptan malate fast dissolving oral films with different HPMC grades are shown in Table 1, 2 &3

Evaluation of Almotriptan Malate fast dissolving oral films:

Physical characterization of FDOFs:

Physical characterization of FDOFs can be carried out by visual inspection for characteristics such as colour, thickness, brittleness, peeling ability, transparency, surface smoothness, tack property and film forming capacity.

The prepared films were subjected for in vitro evaluation tests like Thickness, Folding Endurance, Surface pH, Morphological properties, %Drug content and content uniformity, Tensile strength, Percent elongation, In vitro Disintegration time, In vitro Dissolution studies and in vivo studies on rabbits.

Surface pH

The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 30s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done [16].

Weight variation and thickness

For evaluation of film weight and thickness films were taken and weighed individually on a digital balance. The film thickness was measured using Digital Vernier caliper (Mitutoyo) at six different places and the average value was calculated [17].

Folding endurance

The folding endurance is expressed as the number of folds (number of times the film is folded at the same place) required to break the specimen or to develop visible cracks. This also gives an indication of brittleness of the film. A strip of 2.5 cm × 2.5 cm was subjected to folding endurance by folding the patch at the same place repeatedly several times until a visible crack was observed, and the values were reported [18].

% Drug content & Drug content uniformity

Three films (4 cm^2 of each) were transferred in to separate graduated flasks containing 100 ml of phosphate buffer pH 6.8 and continuously stirred for 2 hrs. The solutions were filtered, suitably diluted and analyzed at 227 nm and the drug content was calculated [19].

Percent Elongation

This mechanical property was evaluated using the Instron universal testing instrument (Model F. 4026, Instron Ltd., Japan) with a 5 kg load cell. The percentage increase in the length of a film (L_2), when it is pulled under standard conditions of stress just before the point of break is known as percent elongation. The initial length of a film is L_1, the increase in length is (L_2-L_1). It is measured in terms of percentage. Percent elongation and tensile strength was carried for only 4 best formulations.

$$\text{Percent elongation} = \frac{(L_2 - L_1)}{L_1 \times \text{Cross sectional area}} \times 100$$

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. Film strip of dimension 5 × 2 cm^2 and free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 3 cm apart. A cardboard was attached on the surface of the clamp via a double sided tape to prevent the film from being cut by the grooves of the clamp. During measurement, the strips were pulled at the bottom clamp by adding weights in pan till the film breaks. The force was measured when the films broke. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below [20].

Table 1: Formulation trials of Almotriptan malate using HPMC E3

Ingredients	F1	F2	F3	F4	F5	F6
Almotriptan malate (mg)	139.1	139.1	139.1	139.1	139.1	139.1
HPMC E3 (mg)	350	375	400	425	450	475
Maltodextrin	275	250	260	250	240	230
Propylene Glycol	80	90	100	110	120	130
Xanthangum(mg)	10	10	10	8	8	8
Aspartame (mg)	20	20	20	20	20	20
Citric acid (mg)	10	10	10	10	10	10
Water (ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Vanilla	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Amaranth	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 2: Formulation trials of Almotriptan malate using HPMC E6

Ingredients	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17
Almotriptan malate (mg)	139.1	139.1	139.1	139.1	139.1	139.1	139.1	139.1	139.1	139.1	139.1
HPMC E6 (mg)	300	310	320	330	340	350	360	370	380	390	400
Maltodextrin	270	260	250	240	230	220	210	200	190	180	170
Propylene Glycol	80	80	100	100	120	140	140	100	140	120	120
Xanthangum(mg)	10	10	10	8	8	8	10	10	10	8	8
Aspartame (mg)	20	20	20	20	20	20	20	20	20	20	20
Citric acid (mg)	10	10	10	10	10	10	10	10	10	10	10
Water (ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Vanilla	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Amaranth	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 3: Formulation trials of Almotriptan malate using HPMC E15

Ingredients	F18	F19	F20	F21	F22	F23	F24	F25
Almotriptan malate (mg)	139.1	139.1	139.1	139.1	139.1	139.1	139.1	139.1
HPMC E15(mg)	200	210	220	230	240	250	260	270
Maltodextrin	180	170	160	150	140	130	120	110
Propylene Glycol	80	80	100	100	120	140	140	160
Xanthangum (mg)	10	10	10	10	8	8	8	8
Aspartame (mg)	20	20	20	20	20	20	20	20
Citric acid (mg)	10	10	10	10	10	10	10	10
Water (ml)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Vanilla	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Amaranth	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

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$$\text{Tensile strengt} = \frac{\text{Load at Failure}}{\text{Strip thickness X Strip Width}}$$

In vitro disintegration studies

Disintegration test was performed to ensure the disintegration of the film in phosphate buffer pH 6.8. One film from each formulation was introduced into one tube of disintegration apparatus IP. A disc was added into the tube. The assembly was suspended in a beaker containing phosphate buffer pH 6.8 and the apparatus was operated until the film disintegrated [18].

In vitro dissolution studies

The phosphate buffer pH 6.8 was taken as the dissolution medium to determine the drug release. The dissolution profile of quick release films of Almotriptan malate was carried out in USP basket type apparatus containing 300 ml of the phosphate buffer pH 6.8. The film was placed in the basket, maintained at 37 ± 0.5°C and the agitation speed was 50 rpm. Aliquots (5 ml) of the dissolution medium were withdrawn at 1, 2, 4, 6, 8, 10 and 12 minutes time intervals and the same amount was replaced with the fresh medium. Samples were

analyzed spectrophotometrically at 227 nm and the cumulative percentage of drug release was calculated [21].

Drug Excipient Compatibility Studies

The drug excipient compatibility studies were carried out by Fourier Transmission Infrared Spectroscopy (FTIR) method and Differential Scanning Colorimetry (DSC) method.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectrum of the samples was prepared using KBr disks by means of hydraulic pellet press at pressure of seven to ten tons.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. The DSC thermograms were recorded for pure drug, HPMC E15, Maltodextrin, Drug and HPMC mixture and optimized formulation. Accurately weighed samples were placed on aluminium plate, sealed with aluminium lids and heated at a constant rate of 5ºC /min, over a temperature range of 0 to 250ºC.

Stability studies

The stability study of the optimized fast-dissolving films was carried out under different conditions according to ICH guidelines. The film was packed in the aluminium foil and stored in a stability chamber for stability studies. Accelerated Stability studies were carried out at 40 ^{0}C / 75 % RH for the best formulations for 6 months. The patches were characterized for the drug content and other parameters during the stability study period [18].

Pharmacokinetic study:

Animal Preparation:

Twelve New Zealand white rabbits of either sex were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature 25^{0}C, RH 45% and 12 h alternate light and dark cycle with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee **(IAEC NO: P35/VCP/IAEC/2015/DBP/AE12/Rabbits).**

***In vivo* Study design:**

The rabbits were fasted overnight before administration of the formulations (ODF contain Almotriptan Malate 6.25mg) and Innovator (AXERT ODT 6.25 mg). The rabbits were randomly divided into two groups each group contains six animals. The group A rabbits were anaesthetized with intravenous injection of pentobarbital in a dose of 25mg/kg then positioned on table with the lower jaw supported in a horizontal position and the ODF was carefully placed on the rabbit tongue. The innovator was administered orally to group B with equivalent to animal body weight.

Blood samples for pharmacokinetic analysis were obtained at different time intervals 0, 0.25, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00 & 24.00 h after dosing. Blood samples were collected in heparinised tubes and were centrifuged for 10min at 3,000 rpm at room temperature.

Preparation of plasma samples for HPLC analysis:

Rabbit plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5 ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1 ml of acetonitrile by vortexing for 1 min. After centrifugation (5000 – 6000 rpm for 10 min), the acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature. Samples were reconstituted in 200 µ1 of 70 % of acetonitrile and 30% water was injected for HPLC analysis.

For HPLC C18 column (ODS-UG-5, 250 ×4.6 mm, 5µ) and the mobile phase consisting of methanol, acetonitrile and THF in the ratio of 46:50:04 (v/v/v) at a flow rate of 1 ml/min with UV detection at 269 nm.

Pharmacokinetic Analysis:

The pharmacokinetic parameters, peak plasma concentrations (C_{max}) and time to reach peak concentration (t_{max}) were directly obtained from concentration time data. In the present study, AUC_{0-t} refers to the AUC from 0 to 24 hrs, which was determined by linear trapezoidal rule and $AUC_{0-\alpha}$ refers to the AUC from time at zero hours to infinity.

The $AUC_{0-\alpha}$ was calculated using the formula AUC_{0-t} + [C_{last}/K] where C_{last} is the concentration in µg/ml

at the last time point and K is the elimination rate constant.

Various pharmacokinetic parameters like area under the curve [AUC], elimination half life (t½). Volume of distribution (V_d), total clearance (Cl_T) and mean residence time for each subject using a non compartmental pharmacokinetic programme. The pharmacokinetic parameters were performed by a non compartmental analysis using Win Nonlin 3.3® pharmacokinetic software (Pharsight Mountain View, CA USA). All values are expressed as the mean ±SD. Statistical analysis was performed with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with $p<0.05$ was considered statistically significant.

3. Results and Discussion

Preparation of Almotriptan Malate oral films

It was aimed to prepare fast dissolving oral films of Almotriptan malate with the dose of 6.25mg per 4 cm^2 film. Total 25 formulations were prepared using three different polymers, HPMC E3, HPMC E6 and HPMC E15 and the resulting films were shown In Figure 1

Fig. 1: Almotriptan Malate films

Physical Characterization of films:

Physical characterization of FDOFs was carried out by visual inspection and the following results were observed.

The films were evenly colored and no migration of colour was observed. The increased thickness of

Table 4: Preliminary evaluation of FDOF'S

Code and properties	Film forming property	Tack property	Ease of handling
F1	Poor	Non-tacky	Brittle, difficult to peel
F2	Poor	Non-tacky	Brittle, difficult to peel
F3	Poor	Tacky	Very thin, difficult to peel
F4	Average	Tacky	Slightly thick, Brittle
F5	Average	Tacky	Slightly Brittle
F6	Average	Tacky	Thin, brittle, difficult to peel
F7	Average	Tacky	Thick
F8	Average	Tacky	Thick
F9	Average	Non-tacky	Thick and brittle
F10	Poor	Non-tacky	Brittle
F11	Average	Non-tacky	Thick and brittle
F12	Good	Non-tacky	Thin and soft
F13	Good	Non-tacky	Opaque, easy to peel
F14	Good	Non-tacky	Slightly opaque
F15	Excellent	Non-tacky	Thin, flexible and easy to peel
F16	Good	Non-tacky	Easy to peel
F17	Good	Tacky	Soft, easy to peel
F18	Good	Non-tacky	Slightly opaque
F19	Poor	Non-tacky	Brittle
F20	Good	Tacky	Thick, easy to peel
F21	Good	Non-tacky	Opaque, easy to peel
F22	Excellent	Non-tacky	Thin, flexible and easy to peel
F23	Good	Tacky	Thick, easy to peel
F24	Excellent	Non-tacky	Thin, and easy to peel
F25	Good	Non-tacky	Easy to peel

film is attributed to the increase in the amount of HPMC. F1, F2, F4, F5, F6, F9, F10, F11 and F19 were found to brittle in nature due to insufficient amount of plasticizer added to the formulation. F1to F3 and F6 are difficult to peel whereas others separated easily.

F4, F7, F8, F9, F11, F23 were found to be thick. F15, F22 & F24 were found to be excellent in film forming property, non-tacky, thin, flexible and easy to peel. The films obtained from all the formulations had smooth surface on either side. Formulations prepared using HPMC E3 was not evaluated for physical parameters and other tests as they fail to satisfy the preliminary characteristics of films due to their poor film forming ability (Table 4).

Evaluation of fast dissolving oral films of Almotriptan malate

Thickness & Weight variation

Thickness of all mouth dissolving films was measured with Digital Vernier caliper (Mitutoyo). All the mouth dissolving formulations of different

Table 5: Physical evaluation of fast dissolving oral films of Almotriptan malate

Code	Thickness(µm)	Weight Variation(mg)	Folding Endurance (count)	Surface pH	% Drug content	In Vitro Disintegration time (sec)
F6	74±1	56.12±0.3	42±1	6.56±0.4	96.8±0.24	35±2
F7	75±1	53.24±0.4	53±2	6.82±0.1	84.68±0.14	32±2
F8	72±1	57.4±0.1	60±2	6.84±0.1	92.45±0.45	30±2
F9	80±3	55.22±0.1	63±1	6.65±0.4	86.5±0.7	27±2
F10	82±1	59.64±0.2	58±4	6.79±0.2	95.6±0.15	25±2
F11	74±1	61.3±0.2	62±1	6.85±0.1	92.54±0.6	23±2
F12	88±1	63.65±0.3	64±2	6.75±0.5	96.56±1.2	20±2
F13	79±1	62.1±0.3	59±2	6.68±0.4	92.4±0.3	18±2
F14	88±0	64.2±0.12	64±2	6.93±0.1	90.3±1.9	16±2
F15	87±2	83.5±0.5	110±2	6.87±0.2	99.5±0.8	10±2
F16	86±2	80.5±0.4	110±2	6.87±0.2	98.5±0.8	12±2
F17	80±2	71.5±0.6	105±2	6.75±0.1	83.4±0.5	17±2
F18	91±2	62.1±0.2	95±2	6.89±0.1	91.4±0.5	28±2
F19	79±2	65.69±0.3	115±3	6.67±0.1	89.5±0.45	26±2
F20	88±0	79.2±0.5	111±5	6.64±0.2	96.7±1.2	22±2
F21	87±1	62.3±0.5	99±1	6.72±0.5	95.2±0.2	18±2
F22	84±0	65.6±0.4	106±2	6.88±0.2	93.5±0.01	12±2
F23	86±2	73.5±0.4	104±2	6.54±0.3	92.5±0.6	15±2
F24	84±2	76.2±0.4	115±3	6.78±0.1	96.56±0.3	12±2
F25	88±2	82.5±0.5	115±2	6.87±0.2	97.5±0.8	14±2

polymers are show thickness value in the range of 0.04±0.01 to 0.15 ± 0.02 mm (Table). The optimized film has thickness of 0.07±0.02. A result of thickness measurement showed that as the concentration of polymer increases, thickness of mouth dissolving film also increases. A result showed that as the concentration of polymer increases weight of film also increases. The weight variation of the formulations was in the range of 35.33±0.9 to 41.67±1.5mm, which was acceptable. Thickness of mouth dissolving film depends on the concentration of polymer.

Folding endurance

Folding endurance gives an indication of brittleness of the film. It was shown that as the concentration of polymer and plasticizer increases, folding Endurance of mouth dissolving film increases. The folding endurance value of the prepared films ranged from 20±2 to 123±2 (Table 5). The optimized film (F23) has folding endurance value of 123±2, which was desirable.

Surface pH

Surface pH of all mouth dissolving films prepared by using different polymers was found to be in the range of 6.7 to 6.9 pH (Table 5), which was close to the neutral pH, which indicated that films may have less potential to irritate the sublingual mucosa, and hence, more acceptable by the patients.

%Drug content

All the fast dissolving oral films were found to contain an almost uniform quantity of the drug, as per content uniformity studies indicating reproducibility of the technique. Drug content in the films was evaluated and the values were found to be between 95.78±1.4 to 100.5±0.2. % (Table 5) for three different cuts from each film. As per the USP requirements, the films found to meet the criteria for content uniformity. No significant difference in the drug content among the films indicated good content uniformity.

In vitro disintegration studies

The disintegrating time of all the formulations was ranges from 10±2± to 38±2 sec. *In vitro* disintegrating time for mouth dissolving film using HPMC E6 was ranges from 14±2 to 38±2 sec, the results were depicted in table and the disintegrating time for the films made by the polymer HPMC E15 was ranges from10±2 to 32±2 shown in table. The disintegration time of optimized formulation (F15) was found to be 10 sec, which was very less and desirable for quick onset of action (Table 5 & Figure 2 & 3).

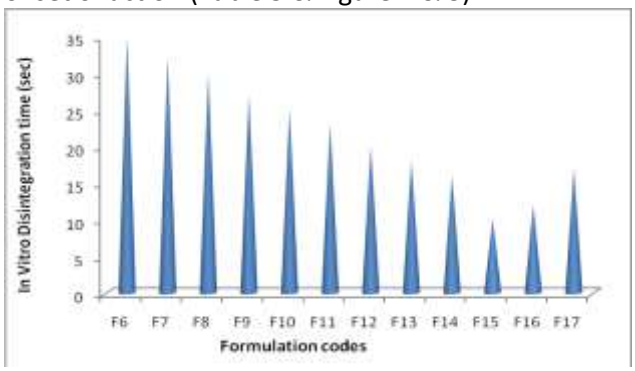


Fig. 2: *In vitro* disintegration time of HPMC E6 formulations

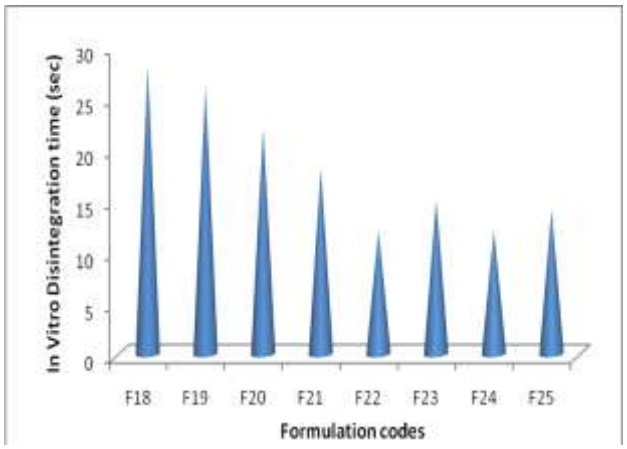


Fig. 3: *in vitro* disintegration time of HPMC E15 formulations

Tensile strength and Percent Elongation:

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters, tensile strength and elongation at break. Tensile strength and percent elongation of all prepared formulation is shown in Table 6, found to be within the limits. Results revealed that optimized formulation (F15) showed better tensile strength (11.2 g/cm^2) and moderate % elongation (9.2).

***In vitro* dissolution studies:**

In-vitro drug dissolution study of formulation batches F6 to F13

The cumulative % drug release for the formulations F6 to F25 are tabulated in Table and Figure. The graphs are depicted in Figure. Formulation F6, F7, F8, F9 and F10 shows drug release up to 77.4, 80.1, 85.3, 90.2, 92.5 and 93.5 respectively at the end of 12 min. The optimized formulation (F15) shows highest percent of drug release 98.8 by the end of 10 min (Table 7, 8, 9 and Figure 4, 5, 6). The cumulative % drug release studies of optimized formulation F15 was

compared with the marketed AXERT ODT (6.25mg) and the drug release of F15 and innovator was found to be 98.8 and 67.6 respectively after 10min, which shown in Table 10 and Figure 7.

Table 6: Tensile Strength and Percent Elongation

Formulation code	Tensile Strength (g /cm^2)	Percent Elongation (%)
F15	11.2	9.2
F16	10.6	8.4
F22	9.7	8.5
F24	10.7	9.0

Table 7: Cumulative % Drug Release for HPMC E6

Time (mins)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	15±1.6	22.4±1.1	18.6±1.5	29.6±1.6	26.8±1.8	30.8±2.1
2	29.2±1.3	35.4±1.4	28.6±1.33	36.5±1.1	34.6±1.6	45.9±1.5
4	36.2±1.2	42.3±1.9	32.5±1.05	48.6±1.7	38.6±1.7	59.5±1.3
6	52.7±1.0	52.6±1.5	56.8±1.43	52.6±1.8	40.1±1.05	69.3±1.7
8	65.2±1.8	68.2±1.7	69.3±1.1	62.9±1.5	73.6±1.8	80.9±1.5
10	73.4±1.2	75.3±1.05	78.6±1.25	85.6±1.1	89.6±1.5	92.6±1.43
12	77.4±1.8	80.1±1.6	85.3±1.8	90.2±1.3	92.5±2.1	93.5±1.6

Table 8: Cumulative % Drug Release for HPMC E6

Time (mins)	F13	F14	F15	F16	F17	F18
0	0	0	0	0	0	0
1	24.8±3.21	16.6±3.04	30.6±1.64	20.6±1.62	23.8±1.8	24.8±1.25
2	32.6±1.3	28.6±1.4	46.9±1.51	26.9±1.1	32.6±3.21	40.9±1.84
4	39.6±1.5	33.6±1.88	58.6±1.05	35.6±1.33	48.5±2.04	58.5±1.3
6	45.6±1.2	45.6±1.4.6	76.3±1.43	49.6±1.7	54.1±2.05	64.3±3.04
8	54.6±1.8	53.8±2.1	90.9±1.1	65.9±1.25	68.6±1.8	72.9±1.25
10	69.8±1.0	71.5±1.5	98.8±1.25	74.6±1.05	79.6±1.2	82.6±1.43
12	79.8±1.18	83.9±1.64	----	86.2±2.3	82.5±2.10	92.5±1.25

Table 9: Cumulative % Drug Release for HPMC E15

Time (mins)	F19	F20	F21	F22	F23	F24	F25
0	0	0	0	0	0	0	0
1	38.54±1.24	30.5±1.4	45.7±1.13	23.9±1.5	27.8±1.4	28.6±2.56	34.9±1.6
2	49.6±1.64	45.9±1.27	56.8±1.15	36.4±1.12	38.7±1.9	35.9±1.14	47.1±1.9
4	64.8±088	52.1±1.5	65.4±2.09	52.9±2.2	42.6±1.7	46.8±1.1	56.5±1.4
6	78.5±1.6	66.58±1.8	4.23±1.16	65.4±1.14	54.8±0.8	59.7±1.3	67.8±1.1
8	80.3±1.06	74.6±2.08	85.4±3.06	77.9±1.8	63.9±1.5	65.7±1.5	72.9±1.6
10	86.4±1.14	83.5±2.71	90.7±1.23	87.9±1.1	75.4±1.1	87.1±1.06	85.9±1.6
12	95.8±1.52	87.7±1.24	94.5±1.75	96.1±1.3	89.3±1.2	95.4±1.13	96.1±1.8

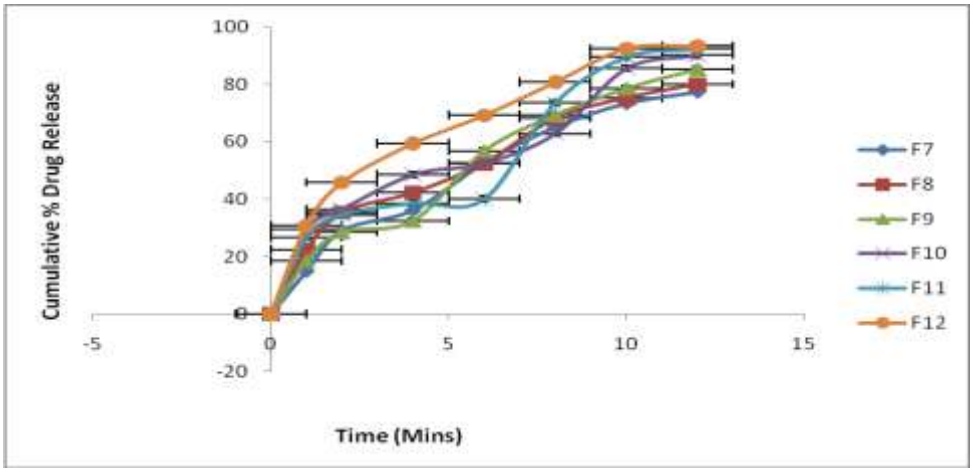


Fig. 4: Cumulative % Drug release for HPMC E6 (formulation F7-F12)

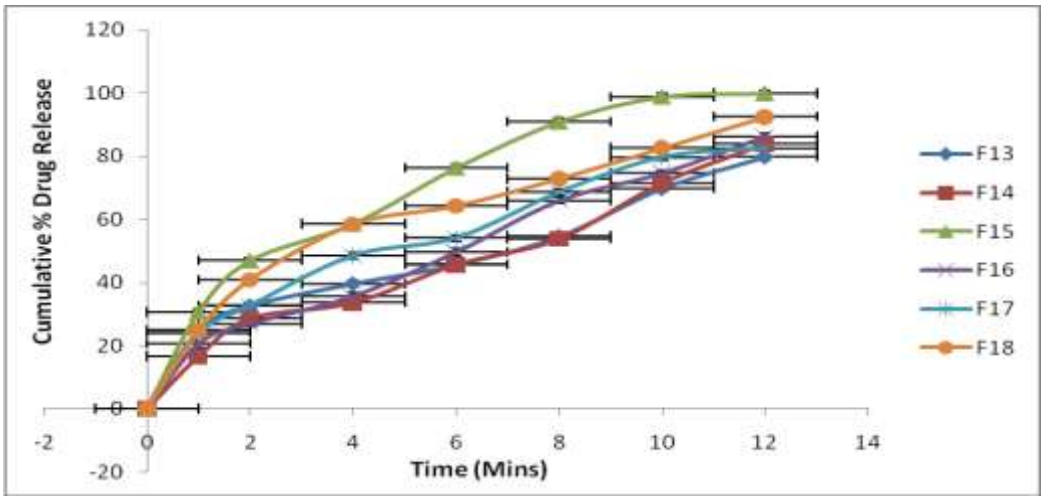


Fig. 5: Cumulative % drug release for HPMC E6 (Formulation F13-F18)

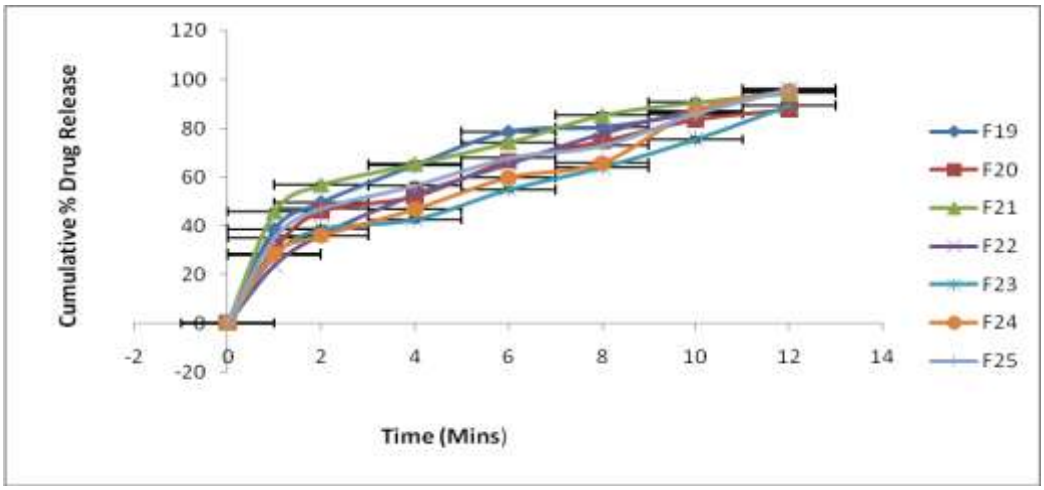


Fig. 6: Cumulative % drug release for HPMC E15 (formulation F19-F25)

Table 10: Comparison of cumulative % drug release of F15 with Innovator Product (AXERT-ODT)

TIME (Min)	0	1	2	4	6	8	10	12
F15	0	30.6±1.64	46.9±1.51	58.6±1.05	76.3±1.43	90.9±1.1	98.8±1.25	----
AXERT ODT (6.25mg)	0	11.6±1.9	18.9±2.65	28.9±1.2	39.8±1.47	52.9±1.8	67.6±1.23	76.8±1.5

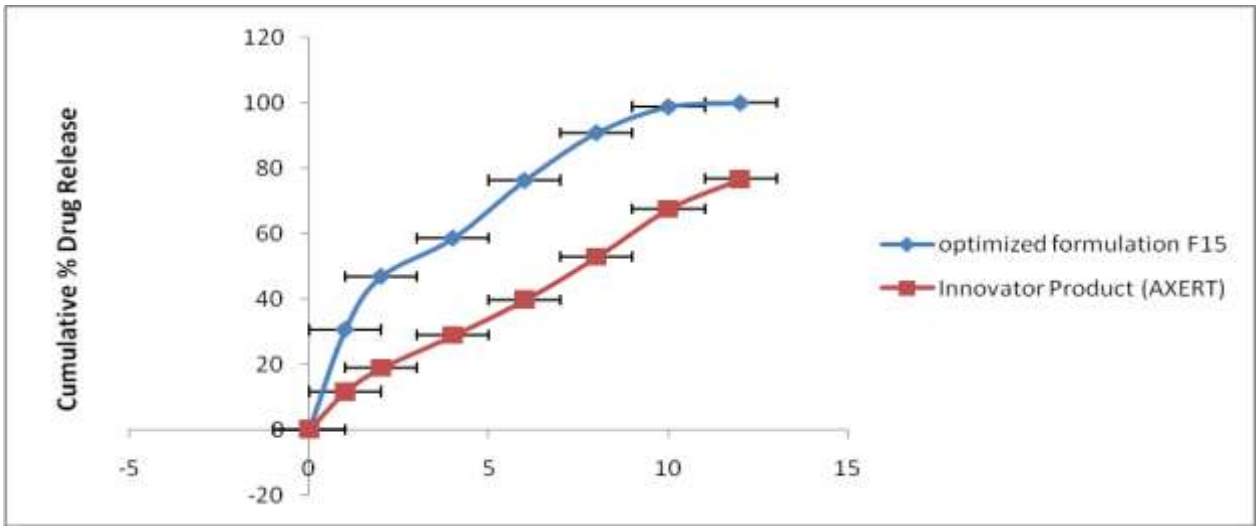


Fig. 7: Comparison of cumulative drug release of F15 with innovator product (AXERT- oral disintegrating tablet)
Drug excipient interactions studies by FTIR

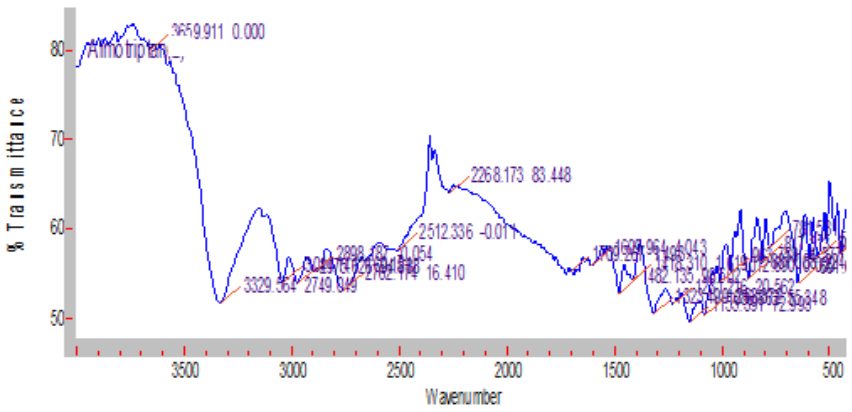


Fig. 8: FTIR Spectroscopy of Almotriptan Malate pure drug

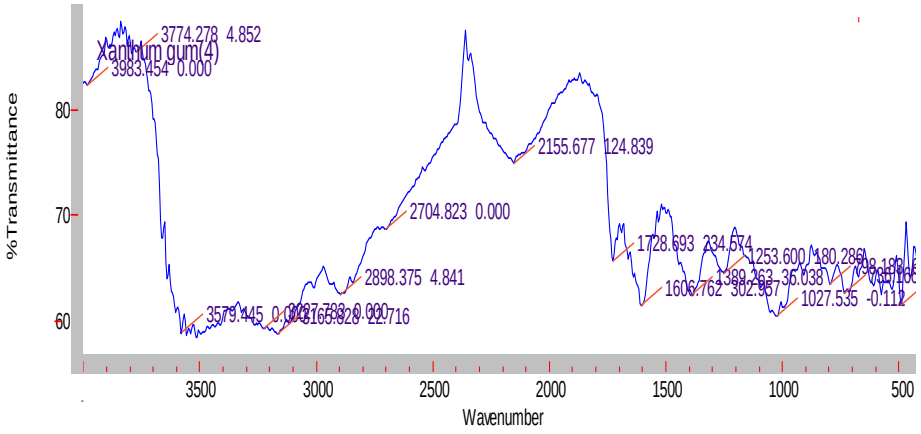


Fig. 9: FTIR Spectroscopy of Almotriptan Malate+ Xanthan gum+ HPMCE6

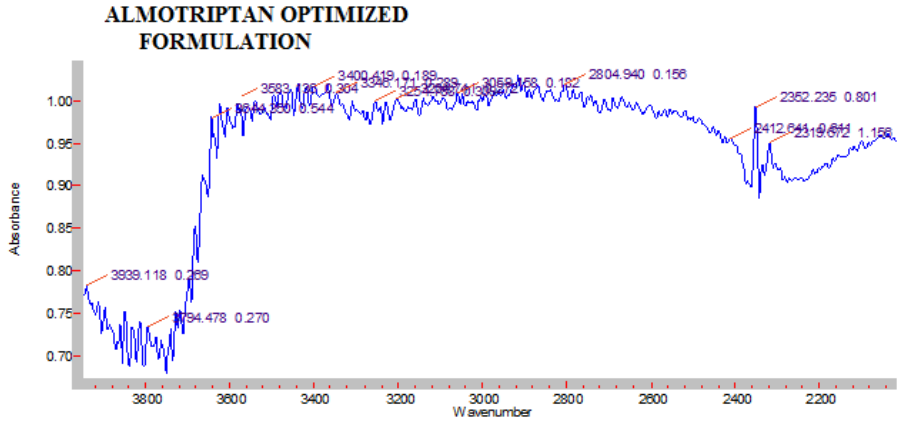


Fig. 10: FTIR Spectroscopy of Almotriptan Malate optimized formulation F15

Interpretation of FTIR Data:

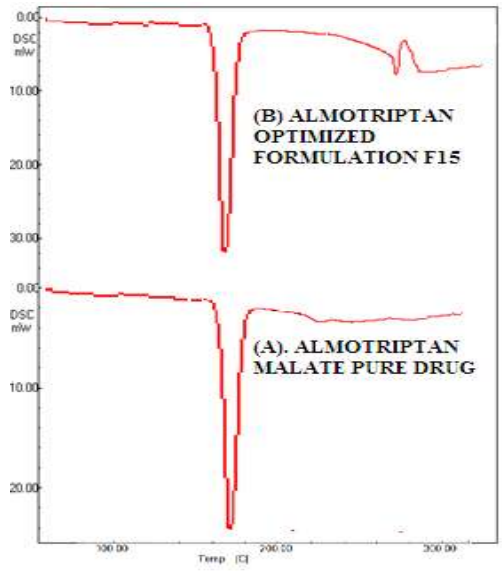
FT-IR spectrums are mainly used to determine if there is any interaction between the drug and any of the excipient used. The FTIR spectra of pure Almotriptan malate (**Figure 8**) displayed bands at 1281cm^{-1} due to C-N stretch, at 3659 cm^{-1} due to O-H stretching, at 1629 cm^{-1} due to heterocyclic C=C stretching. The spectra also showed bands at 3329 cm^{-1} due to N-H bending. The FTIR spectrum of the physical mixture was shown in **Figure 9.** The FTIR spectrum of optimized formulation F15 (**Figure 10**) exhibited characteristic bands consistent with the molecular structure of Almotriptan such as bands at 1289 cm^{-1} due to C-N stretch, at 3651 cm^{-1} due to O-H stretching, at 1623 cm^{-1} due to heterocyclic C=C stretching, at 3346 cm^{-1} due to N-H bending. Thus, the presence of characteristic absorption bands of Almotriptan and the films containing Almotriptan suggest that there was no interaction between the drug and excipients used in the formulation.

Interpretation of DSC Data:

DSC thermograms revealed that there is no considerable change observed in melting endotherm of pure drug (170.79) and drug in optimized formulation (168.36) (Figure 11). It indicates that there is no interaction takes place between drug and other excipients used in the formulation.

Stability Studies for optimized formulation (F15):

Optimized formulation (F15) was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for 6 months according to ICH guidelines. From these results it was concluded that, optimized formulation is stable and retained their original properties with minor differences which depicted in Table 11.

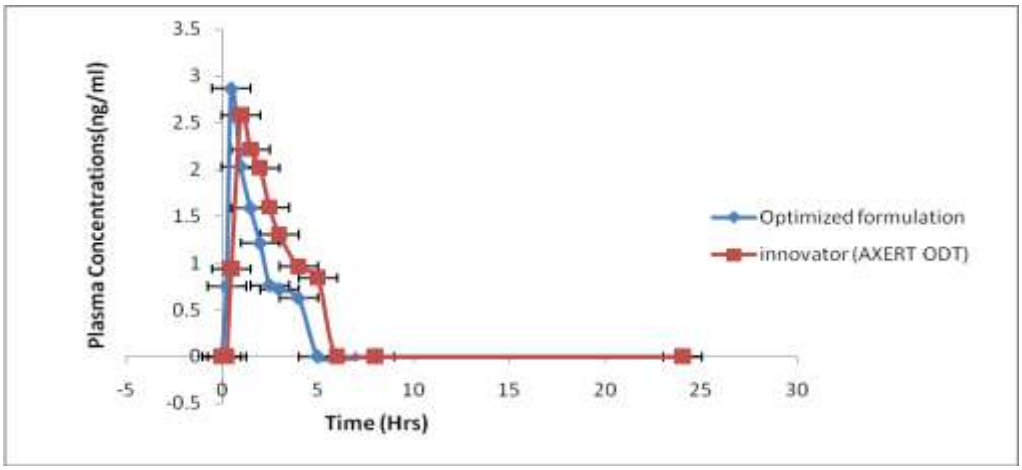


Drug excipient compatibility studies by DSC

Fig. 11: DSC thermogram of Almotriptan pure drug (A) and optimized formulatin F15 (B)

Table 11: Physico-chemical characteristics of optimized formulation (F15) stored at 40 ±2ºC /75 ±5%RH

Retest Time For Optimized formulation	Disintegrating Time (sec)	Percent Drug Content / Assay (%)	*In-vitro* drug release profile (%)	Transparency
0 days	11±2	98.13±0.14	98.14	Transparent
1 month	12±0	98.06±0.12	97.68	Transparent
3 months	12±2	97.54±0.26	96.23	Transparent
6 months	12±5	97.47±0.11	95.56	Transparent



Pharmacokinetic studies

Fig. 12: Plasma concentrations at different time intervals of Almotriptan Malate Optimized formulation F15 (ng/ml) and innovator (AXERT ODT 6.25mg)

Table 12: Comparison of pharmacokinetic parameters of Almotriptan Malate between the film and innovator (AXERT ODT 6.25mg) in Rabbits (mean ± SD, n = 6).

Parameters	Optimized formulation F15 (6.25mg)	Innovator product (AXERT ODT 6.25mg)
Cmax (ng/ml)	2.865±0.1	2.5812±0.1
AUC0-t (ng hr/ml)	21.55135±46.74	20.8695±48.16
AUC0-inf (ng hr/ml)	21.9935±38.14	21.0675±48.16
Tmax (hr)	0.5±0.5	1.0±0.1
t1/2 (hr)	1.453 ± 0.519	2.474 ± 0.01
Kel (hr^{-1})	1.436 ± 0.18	1.576 ± 0.93

Bioavailability parameters:

The Drug release from Almotriptan Malate optimized formulation was almost similar to that from commercial formulation which was selected. Mean plasma concentration profiles of Almotriptan Malate optimized formulation and commercial formulation are presented in **Figure 12.** Both the formulations exhibited as immediate release in *vivo*. As compared to the innovator, prepared film was showed quick release. All the pharmacokinetics parameters displayed in **Table 12**. Mean time to reach peak drug concentration (T_{max}) was 0.5±0.5h and 1.0±0.1h for the optimized and commercial formulations, respectively, while mean maximum drug concentration (C_{max}) was 2.865±0.1ng/ml and 2.5812±0.1ng/ml, respectively. The values for C_{max}, T_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were found to be comparable, indicating that their immediate release patterns were similar. *In vivo* studies confirmed that their potential as an innovative dosage form to improve the bioavailability and considered to be potentially useful for the treatment of migraine where quick onset of action is desirable.

SUMMARY AND CONCLUSION

In the present work twenty five formulations of Almotriptan Malate fast dissolving oral films were formulated by solvent casting method with different concentrations of HPMC-E3, E6 and E15. Formulations with HPMC E3 were not evaluated for physical parameters due to their poor film forming ability, tack property and ease of handling or peeling. The bitter taste of the drug was masked by Aspartame and Vanilla flavour.

Formulations with HPMC E6 and E15 were evaluated for their physical characteristics, thickness, folding endurance, tensile strength, disintegration time, drug content uniformity and drug release characteristics and found to be within the limits.

Dissolution studies were performed for FDOF'S excluding batches that showed poor film forming property. Among all the formulations, F15 showed minimum disintegration time 10 sec and drug release was found to very fast i.e. 98.8% within 10 min when compared to the other formulations. Based on the physicochemical properties F15 was finalized as optimized formulation. DSC and FTIR data revealed that no interactions takes place between the drug and polymers used in the optimized formulation. The in vitro dissolution profiles of marketed product (AXERT ODT) and optimized formulation (F15) was compared and found to be the drug released was 76.8% within 12min from the marketed product, whereas from optimized formulation (F15) the drug release was 98.8% within 10min. Therefore it can be a good alternative to conventional Almotriptan malate tablets for immediate action.

In vivo study exhibited both optimized formulation and innovator shown comparable drug -plasma level- time profiles *in vivo* evaluation of the films confirmed their potential as an innovative dosage form to improve delivery of Almotriptan Malate. Therefore, the oral dissolving film is considered to be potentially useful for the treatment of migraine where quick on set of action, improved patient compliance and comfort is expected.

References

[1] Bhowmik, D., Chiranjib, B., Krishnakanth, P., & Chandra, R.M. (2009). Fast dissolving tablet: an overview. J Chem Pharm Res, 1, 163–177.

[2] Raju, S., Reddy, P.S., Kumar, V.A., Deepthi, A,. Reddy, K.S., Reddy P.V.M. (2011). Flash release oral films of metoclopramide hydrochloride for pediatric use: formulation and *in vitro* evaluation. J Chem Pharm Res, 3 (4), 636–646.

[3] Verma, P., Thakur, A.S., Deshmukh, K., A.K. Jha, Verma, S. (2010). Routes of drug administration. Int J Pharm Studies Res, 1 (1), 54–59.

[4] Galey, W.R., Lonsdale, H.K., Nacht, S. (1976). Clinical the in vitro permeability of skin and buccal mucosa to selected drugs and tritiated water. J. Investigative Dermatol, 67(6), 713-717.

[5] Crama, A., Breitkreutzb, J., Desset-Brèthesc, S., Nunnd, T., Tuleuf, C. (2009). Challenges of developing palatable oral pediatric formulations. Int J Pharm, 365, 1-3.

[6] Florence, A.T. (2008). Neglected diseases, neglected technologies, neglected patients. Int J Pharm. 350, 1-2.

[7] Choudhary, D.R., Patel, V., Patel, H., Kundawala, J.A. (2011). Exploration of film forming properties of film formers used in the formulation of rapid dissolving films. Int J Chemtech Res, 3 (2). 531–533.

[8] Priya, Y.D., Chowdary, Y.A., Murthy, T.E.G.K., Seshagiri, B. (2011). Approaches for taste masking of bitter drugs: a Review. J Adv Drug Res, 1 (2), 58–67.

[9] Bhyan, B., Jangra, S., Kaur, M., Singh, H. (2011). Orally fast dissolving innovation in formulation and technology. Int J Pharm Sci Rev Res, 9 (2), 50–57.

[10] Reema, P., Richard, GZ. (2007). Dissolvable film. US 2007/0042023 A1, 1–8.

[11] Rajni, B., Pravin, P., Sushil K., Sandeep A. (2013). orally dissolving strips: A new approach to oral drug delivery system. Int J Pharm Investig, 3(2), 67–76.

[12] Sheryl, R. H., Marcelo, E. B., Richard, B. L. (2006). Chronic disorders with episodic manifestations: focus on epilepsy and migraine. Lancet Neurol, 5, 148–157.

[13] Lipton, R.B, Bigal, M.E. (2005). The epidemiology of migraine. Am J Med, 1(18), S3-10.

[14] Deleu, D., Hanssens, Y. (2000). Current and emerging second-generation triptans in acute migraine therapy: A comparative review, J Clinical Pharmacol, 40, 687-700.

[15] Kunte, S., Tandale, P. (2010). fast dissolving strips: A novel approach for the delivery of Verapamil. J Pharm Bioallied Sci, 2(4), 325-328.

[16] Kumar, G.V., Krishna, R.V., William, G.J., Konde, A. (2005). Formulation and evaluation of buccal films of salbutamol sulphate. Indian J Pharm Sci, 67:160–164.

[17] Mona, N., Mayank, N., Vikram, C. (2012). Formulation and evaluation of mouth dissolving film of antipsychotic drug aripiprazole. Der Pharmacia Lettre, 4(4), 1221-1227.

[18] Prabhakara, P., Ravi, M., Marina, K., Vijaynarayana, K., Ullas Souza, D., Harish, N.M., Shastry, C.S. (2011). Formulation and evaluation of fast dissolving films of levocitirizine dihydrochloride. Int J Pharm Inves, 1(2), 99–104.

[19] Nafee, N.A., Boraie, M.A., Ismail, F.A., Mortada, L.M. (2003). Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. Acta Pharm, 53, 199–212.

[20] Mashru, R.C, Sutariya, V.B., Sankalia, M.G., Parikh, P.P. (2005). Development and evaluation of fast dissolving film of salbutamol sulphate. Drug Dev Ind Pharm, 31, 25–34.

[21] Hiroyoshi, S., Kazumi, T., Misao, N., Katsuhiko, M., Tadao, T., Hirotaka, Y., Naoki, I., Kazuyuki, H., Mayumi, Y., Yasutomi, K., Yoshinori, I. (2009). Preparation of a fast dissolving oral thin film containing dexamethasone: A possible application to antiemesis during cancer chemotherapy. Eur J Pharm Biopharm, 73(3), 361-365.