



Design and Evaluation of Melt in Mouth Films of Almotriptan

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ABSTRACT

The present study was aimed to formulate and evaluate melt in mouth films of almotriptan using polymers pullulan, carragennan, xanthan gum and guar gum as the film forming agents. Almotriptan is 5-HT_{1B} and 5-HT_{1D} antagonist, used in the management of migraine. Glycerol was incorporated as plasticizer to improve flexibility of films. Sorbitol as sweetener. Sodium starch glycolate used as a disintegrant. An attempt was made to prepare melt in mouth films of almotriptan with the purpose of developing a dosage form for quick onset of action, which will be beneficial in managing severe condition of migraine attack, aiding in enhancement of bioavailability and easy for administration. The films were prepared by solvent casting method. They were evaluated for physicochemical characterization such as uniformity of weight, thickness, folding endurance, uniformity of drug content, surface pH, percentage elongation and tensile strength all of which showed satisfactory results. The formulations were also subjected for *in vitro* disintegration and *in vitro* drug release. Melt in mouth films of almotriptan containing single polymer pullulan (FA1) showed best results, in terms of tensile strength (1.2 ± 0.288), percentage elongation ($15.1 \pm 0.288\%$), folding endurance (>300), *in-vitro* disintegration time ($10.3 \pm 0.58\text{sec.}$), surface pH (6.20 ± 0.001 pH), thickness (0.1032 ± 0.001 3mm) and percentage content uniformity (99.9 ± 0.021). Satisfactory dissolution profile was obtained with maximum release of 96% of drug within 120 sec. The stability studies showed that there was no appreciable change in parameters when stored at three different temperatures.

Keywords: Almotriptan, Melt in Mouth Films, Rapid disintegration, Solvent Casting.

INTRODUCTION

Among the different routes of administration, the oral route of administration continues to be most preferred route due to various advantages including ease of administration, avoidance of pain, versatility and most importantly patient compliance.¹ These dosages are administered in the form of pills, granules, powders and liquids. Generally, a pill is designed for swallowing intact or chewing to deliver a precise dose of medication to patients. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure. However, some patients, particularly pediatric and geriatric patients, have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of throat choking.² In order to assist these patients, several fast dissolving drug delivery systems have been developed. Fast dissolving drug delivery systems can be manufactured by a variety of technologies, including direct compression, wet granulation and freeze-drying. Some make use of different disintegrating mechanisms, such as high level of disintegrating or effervescent agents, which cause the dosages to disintegrate rapidly in the mouth. Most of the existing fast dissolving drug delivery systems are in the form of tablets and are designed to dissolve or disintegrate in the patient's mouth within a few seconds or minutes without the need of water or chew. But even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. The most common complaint was tablet size, followed by surface form and

taste.³ Hence, Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets/capsules to modified release tablets/capsules to oral disintegrating tablet (ODT) to the recent development of oral strip (OS), a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity.⁴

A migraine headache is thought to be caused by widened blood vessel exerting pressure on the brain. In migraine, patients experience one or more short lived attacks of intense headache, usually at the same time every day and often at night and are usually of sufficient severity to disturb or prevent daily activities. Almotriptan is a serotonin 5-HT₁ receptor agonist "triptan". It mainly acts by narrowing the blood vessel in the brain and thereby reducing pressure and pain in the brain. It is available in 12.5 mg and 6.25mg in most countries. Almotriptan relieves nausea, vomiting, photophobia (light hypersensitivity) and phonophobia (sound hypersensitivity) associated with migraine attacks pain. Thus for an anti migraine drug like almotriptan, a quick release dosage form will be very suitable, so that at times of severe attacks the film can be conveniently be consumed by the patient without the help of water, for an immediate action. Also, since the drug starts getting absorbed from the oral cavity itself, the bioavailability may be expected to increase. Hence, it was thought worthwhile to formulate quick release film type of dosage form for almotriptan.

MATERIALS AND METHODS

Almotriptan was a gift sample from Mylan inc Hyderabad. Pullulan was obtained from Hayashibara co. Ltd, xanthan gum and carrageenan was obtained from HiMedia Laboratories Pvt. Ltd, Mumbai. All the other chemicals used were of analytical grade.

Formulation of Melt in Mouth Films of Almotriptan

Weighed quantities of polymers (soaked in distill water if necessary) were dissolved in separate volumes of distilled water with constant stirring. The dissolved polymers were mixed together and deaerated. To this blend of polymer, aqueous solution of drug almotriptan, glycerol as plasticizer, sodium starch glycolate as disintegrant and

sorbitol as sweetener were added and mixed to get a homogeneous solution and volume was made up to 10ml. The casting solution (10 ml) was poured into glass moulds of area 16cm² and kept for drying at 50°C for 8 h. After drying films were removed with the help of sharp blade and kept in desiccator for 24 h. Cut the films into square dimension of 4 cm², so that each film contained about 6.25 mg of drug. These films were kept in desiccator at relative humidity 30-35% for 2 days for further drying, wrapped in aluminum foil and packed in self-sealing covers and stored in desiccator till further studies. Formulation composition of almotriptan melt in mouth films reported in Table 1.

Table 1: Formulation compositions of almotriptan melt in mouth films

Formulation Code	Pullulan (mg)	Carrageenan (mg)	Xanthan Gum (mg)	Guar Gum (mg)	Drug (mg)	Glycerol (mg)	Sorbitol (mg)	SSG (mg)
FA1	500	-	-	-	25	150	30	10
FA2	700	-	-	-	25	150	30	10
FA3	1000	-	-	-	25	150	30	10
FB1	-	500	-	-	25	150	30	10
FB2	250	250	-	-	25	150	30	10
FB3	400	100	-	-	25	150	30	10
FC1	-	-	500	-	25	150	30	10
FC2	250	-	250	-	25	150	30	10
FC3	400	-	100	-	25	150	30	10
FD1	-	-	-	500	25	150	30	10
FD2	250	-	-	250	25	150	30	10
FD3	400	-	-	100	25	150	30	10
FE1	200	100	100	100	25	150	30	10
FE2	100	100	100	200	25	150	30	10
FE3	100	100	200	100	25	150	30	10

Characterization of Melt in Mouth Films

Compatibility Studies by I.R Spectral Analysis

FTIR spectra matching approach was used for detection of any possible chemical interaction between the drugs and polymers. IR spectra of certain medicated films and the corresponding physical mixtures as well as the untreated drug were done at a range of 4000-600 cm⁻¹ using KBr disk method (Alpha-T, Bruker). The samples were ground, mixed thoroughly with KBr and compressed at a pressure of 15tons /cm². The spectra obtained were compared and interpreted for the functional group peaks.

Physical Appearance

All the films were visually inspected for color, flexibility, homogeneity and smoothness.

Uniformity of Weight and Film Thickness Test

The individual weight of 10 samples of each formulation was determined and the average weight was calculated.⁵

The thickness of the film can be measured by micrometer screw gauge at 5 different strategic locations. This is helpful in determination of uniformity in the thickness of the film.^{6,7}

Surface pH

The surface pH of the film was determined in order to investigate the possibility of any side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the oral cavity. The film to be tested was placed in Petri dish and was moistened with 1 ml of distilled water and kept for 30 sec. The pH was noted after bringing the electrode of pH meter in contact with the surface of the formulation and allowing it to equilibrate for 1 minute.⁸

Folding Endurance

The flexibility of patches can be measured in terms of what is known as folding endurance. Folding endurance of the patches was determined by repeatedly folding a

small strip of the patch at the same place till it broke. The number of times the patch could be folded at the same place, without breaking gives the value of folding endurance.

Drug Content

Drug content uniformity was determined by dissolving the film of area 4 cm² in simulated saliva solution (pH 6.75) in a 100 ml volumetric flask. The absorbance of the solution was measured using UV-VIS spectrophotometer (Shimadzu UV 1800) at a wavelength of 283 nm and drug content was determined.⁷

Measurement of Tensile Strength and Percentage Elongation

Tensile test was performed to assess the strength and elasticity of optimized film formulation. The elongation to break is the strain on a material when it breaks and it gives an indication of toughness and stretch ability prior to breakage. The instrument, which was designed in our laboratory, as per literature specification was used for the measurement of tensile strength. The strips were clamped at the static end and were attached to the movable rod on railing with the help of a clip. The weights were gradually added to the pan to increase the pull force until the film was cut. The elongation was determined simultaneously by noting the distance travelled by the pointer, before break of the film, on the graph paper. The weight required to break the film was noted as the break force. The tensile strength was calculated using Allen's formula. a, b, L are the width, thickness and length of the films. ΔL is the elongation at break.

$$\text{Tensile strength} = \frac{\text{Breakforce}}{a \times b} \times \frac{1 + \Delta L}{L}$$

$$\% \text{Elongation at break} = \frac{\text{Increase in length}}{\text{Original length}} \times 100$$

In vitro Disintegration Time

In vitro disintegration test was performed by placing the film in a glass beaker of 25ml simulated salivary buffer (pH 6.75) with constant stirring. The disintegration time was the time when the film starts to break or disintegrates.⁹

In vitro Dissolution Studies

The *In vitro* dissolution studies of melt in mouth films of almotriptan was carried out in a beaker containing 50 ml of the simulated salivary fluid (pH 6.75) as a dissolution medium, maintained at 37 ± 0.5°C. The medium was stirred at 100 rpm. Aliquots (3ml) of the dissolution medium were withdrawn at 15, 30, 45, 60, 75, 90, 105 and 120 s intervals and the same amount was replaced with the fresh medium. Absorbance was measured spectro photo meterically, at a wavelength of 283 nm after appropriate dilutions.⁹

Drug Release Kinetic Studies

Different mathematical models are applied for describing the kinetics of the drug release process from any system; the most suited being the one which best fits the experimental results. The *in vitro* drug release kinetic analysis is done by the software "PCP Dissolution Version 2.08". Kinetics of almotriptan release from formulations was determined by finding the best fit of the dissolution data (drug-released fraction against time) to distinct models: zero-order, first-order and Higuchi.

Stability Studies

Stability of a formulation can be defined as the time from date on manufacture of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. The stability studies of the formulated fast dissolving films were carried out on prepared films kept at different temperature. The film was packed in aluminum foil and stored in a desiccators for stability studies at 2±8°C (45% RH), 25±30°C (60% RH), and 45±50°C (75% RH) for a period of 45 days. The films were observed for physical appearance, surface pH, folding endurance, drug content and maximum drug release at the end of 45 days was noted.¹⁰

RESULTS AND DISCUSSION

Compatibility studies by I.R spectral analysis

IR studies were carried out for pure drug, pullulan, carrageenan, xanthan gum, guar gum and the formulated films FA, FB, FC, FD, and FE. The IR spectrum of pure drug almotriptan showed a prominent peak at 1119 cm⁻¹ due to C=O stretching of carboxylate group, C – Cvibration was observed at 851 and at 779 a peak was observed due to C – C₁ stretch. C – H deformation was seen at 622. From these spectra's it was observed that there was no significant change in the original peak of the drug and the polymers when compared with spectra of formulated films and this indicates that there was no interaction between drug and polymers.

Characterization of Melt in Mouth Films

Physicochemical Parameters

Physical appearance

Physical appearance of the films was evaluated; all the films were easily removable from the mould, flexible and without any recrystallization.

Uniformity of weight

The individual weight of 10 samples of each type formulation was determined and the average weight was calculated. It was observed that weight of the entire film sample in each formulation was uniform. In the case of formulation FA the weight ranged from 84-144 mg, FB ranged from 78 - 80 mg, FC ranged from 71-77mg, FD ranged from 66 - 84 mg, and FE ranged from 77- 82 mg.



The results of weight variation were represented in Table 2.

Film thickness

Thickness of each film of all formulation was found to be uniform. Thickness ranged from 0.103 mm to 0.285mm. As the concentration of carrageenan, xanthan gum and guar gum increased, the thickness of the films also increased. The results of film thickness were represented in Table 2.

Surface pH

As an acidic or alkaline pH may cause irritation to the mucosa, an attempt was made to keep the surface pH as close to neutral as possible, by the proper selection of the polymers for developing the films. The surface pH of formulations was found to be in the range of 6.2 to 7.01, as shown in Table 2. The surface pH for all the formulations was well within range of neutral pH and not cause irritation in the oral cavity and ultimately achieves patient compliance.

Folding endurance

It was found that all the formulations showed good folding endurance, that is greater than 300, except for FA1 which was brittle (<300). Result revealed that all the films are flexible.

Estimation of drug content of the films

The drug content was estimated as per the procedure mentioned in the methodology. The amount of drug present in the films was found to be uniform for all the formulation and drug content was found to be ranged between 94-102 %.

Tensile strength measurement

The strength and elasticity of the film was reflected by the parameters like tensile strength (TS) and elongation at break (E/B). In formulation FA3, containing pullulan in high concentration exhibited least tensile strength of $0.906 \pm 0.0016 \text{ Kg/mm}^2$ and least percentage elongation $5.3 \pm 0.57\%$. Hence the formulation FA3 was found to be brittle. When the pullulan concentration was decreased, the tensile strength value increased from 0.906 ± 0.001 to $1.2 \pm 0.015 \text{ Kg/mm}^2$ and percentage elongation increased from $5.3 \pm 0.57\%$ to $15.1 \pm 0.288\%$ as seen in FA1 formulation. As concentration of the polymer pullulan increased, the brittleness also increased and as the concentration of pullulan decreased, the films had sufficient strength and found flexible to handle. The tensile strength and percentage elongation of FB1 was $1.58 \pm 0.015 \text{ Kg/mm}^2$ and $60.5 \pm 0.5\%$ respectively; FB1 contained carrageenan as the single polymer and found to be elastic. FB2 formulation contained pullulan and carrageenan in same concentration, its tensile strength and percentage elongation was $1.451 \pm 0.044 \text{ Kg/mm}^2$ and $45.1 \pm 0.58\%$ respectively and which was less than FB1. In FB3 formulation, concentration of pullulan was high, the tensile strength was 1.289 ± 0.011 and percentage

elongation was $22.3 \pm 0.58\%$ which was less than FB1 and FB2, and showed satisfactory toughness and flexibility which is stated to provide better patient compliance as they are less likely to cause contact irritation unlike an unduly elastic film. Similar observations were obtained in case of FC and FD formulations. In the formulation, containing all the polymers in different combination (FE1, FE2, FE3) the results obtained were satisfactory, among them FE1 was considered to be the best, showing tensile strength of $1.275 \pm 0.077 \text{ Kg/mm}^2$ and 20 ± 0.115 percentage elongation. Hence we concluded that tensile strength is influenced by the type of polymer used as well as its concentration. The results for all formulations are reported in Table 2.

In vitro disintegration time

The disintegration time is the time when the film start to break or disintegrate. It is seen that formulation FA1 (10 ± 0.58 sec) containing single polymer pullulan disintegrated fast when compared to the rest of the formulations. The formulation FA1 was the thinnest film among all fifteen formulations and it leads to fast disintegration. The formulation FB1 and FB2 (32 ± 1.52 , 33 ± 1 sec) showed the least disintegration time, due to higher concentration of carrageenan in them. This may also be related to its thickness, since FB1 and FB2 showed highest thickness 0.285 ± 0.0053 and 0.275 ± 0.0018 mm respectively. The observation made here can be correlated with the study done by Choudhary *et al*¹. According to his study disintegration time of the films was influenced by thickness of films. The results for all formulations are given in Table 2.

In vitro Drug Release Studies

An ideal melt in mouth film or strip comprises of water soluble and/or water swellable film forming polymer due to which the film or strip dissolves instantaneously when placed on the tongue in the oral cavity, thus rapid drug release is obtained. *In vitro* drug release from film depends on several factors, such as the manufacturing process, the type of excipient, drug solubility and concentration, polymer concentration and pH of the dissolution medium.

From the dissolution profile of various formulation prepared it is observed that the formulation containing single polymer pullulan (FA1 and FA2) showed good release rate; as the time required for wetting and dissolving the drug molecules present in the polymer matrices was decreased and disintegration and dissolution was increased.

The formulations containing single polymers like carrageenan, xanthan gum and guar gum (FB1, FC1, and FD1) showed less drug release when compared to their formulation in combination with pullulan. The release of drug at the end of 120sec, for FB1, FC1, and FD1 showed 58%, 68% and 65% respectively. This may be due to the gelling nature of these natural gums, which delayed the drug release from the film. The formulations FB2, FC2,

FD2 showed comparatively better release than their formulations containing single polymer (FB1, FC1, and FD1), showing drug release of 62.3%, 82.7% and 76.1% respectively. The formulation FB3, FC3, FD3 showed good drug release (77.7%, 92%, and 87.8%). These films

contained pullulan in high concentration, which increased wettability and penetration of water into the film matrices and hence increased diffusion of the drug, which was responsible for the fast drug release from the films.

Table 2: Uniformity of weight, thickness, surface pH, tensile strength and percentage elongation and disintegration time of the films

Formulation Code	Weight (mg)*	Thickness (mm)*	Surface pH#	Tensile strength* Kg/mm ²	% Elongation*	*Disintegration Time (sec)
FA1	84±1.25	0.1032±0.0013	6.25±0.001	1.2±0.015	15.1±0.288	10.3±0.58
FA2	104.3±1.05	0.126±0.0015	6.2 ±.005	1.05±0.037	10.5±0.57	14.5±0.53
FA3	144.1±1.00	0.203±0.0022	6.5±0.008	0.906±.0016	5.3±0.57	24.6±1.15
FB1	80.35±0.67	0.285±0.0018	6.23±0.007	1.58±.015	60.5±0.5	32±1.52
FB2	78.7±1.63	0.275±0.0053	6.45±0.054	1.451±.044	45.1±0.28	33.01±1
FB3	71.9±0.87	0.203±0.0048	6.8±.001	1.289±0.011	22.3±0.58	19.4±0.529
FC1	77.9±0.73	0.260±0.0016	7.12±.002	1.48±0.038	51.8±1.04	23.23±0.68
FC2	74±0.66	0.193±0.0014	6.28±0.005	1.35±0.068	45.8±.29	15.3±0.527
FC3	71.8±0.63	0.182±0.0016	6.96±0.009	1.24±0.091	40.1±0.1	12.10.173
FD1	84.8±0.62	0.271±0.0032	6.79±0.003	1.593±0.094	65±0.25	31.01±1
FD2	68.3±1.25	0.235±0.003	6.89±0.002	1.428±.062	61±0.58	21.02±1
FD3	66.1±1.37	0.230±0.0032	7.10±0.006	1.31±0.072	54.2±0.12	15.6±1
FE1	82.5±0.707	0.216±0.0035	7.05±.0014	1.275±0.077	20±0.115	11.6±0.56
FE2	77.1±0.994	0.242±0.0019	6.89±.0025	1.30±0.09	41.3±0.17	17.3±1.15
FE3	81.6±0.516	0.230±0.0018	6.58±.0056	1.32±0.071	69±0.55	14.3±0.577

*Each value is the mean 6 determinations ± SD; n = 3 determination

The films, which were prepared using combination of all polymers (FE1, FE2, and FE3), showed very good drug release. This indicated that good release from the formulation was obtained when all the polymers were used in optimum concentration. In all the fifteen formulations prepared, the formulations containing single polymer pullulan showed the best release i.e. formulation FA1, followed by the formulation prepared using combination of the entire polymer which was in correlation with the study done by Kulkarani et al.¹² Among the formulation prepared using xanthan gum and guar gum, formulation containing xanthan gum showed better drug release. The least release was seen with the formulation containing carrageenan as polymer. In case of formulation FA; FA1 showed better release than FA2 and FA3. FA1 contains least concentration of pullulan when compared to FA2 and FA3. FB1 contained carrageenan alone as the polymer were as in FB2 contained equal concentration of pullulan and carrageenan, which showed comparatively better release than FB1, formulation FB3 had higher concentration of pullulan than carrageenan and showed better release than FB1 and FB2. Similar observation can be made in case of FC and FD formulations. When it comes to FE formulation, which contained all polymers in different combination, FE1 showed the best result than FE3 and FE2. From the data, it is evident that using all the

polymers in optimum concentration, the drug release can be improved.

Among the fifteen formulations prepared, formulation FA1, FE1, FC3, FA2 and FD3 were found to be best formulations in terms of drug release. The order of drug release in each set of formulation is given as;

FA1>FA2>FA3; FB3>FB2>FB1; FC3>FC2>FC1; FD3>FD2>FD1; FE1>FE3<FE2

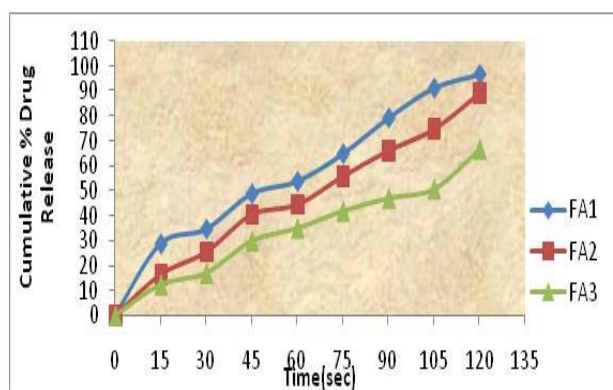


Figure 1: *In vitro* drug release profile of formulation containing pullulan as the polymer.

Drug Release Kinetic Studies

In order to determine the release mechanism that provides the best description to the pattern of drug release, the *in vitro* release data were fitted to zero order,

first order, and Higuchi matrix. The release data were also kinetically analyzed using the Korsmeyer–Peppas model. The release exponent (n) describing the mechanism of drug release from the matrices was calculated by regression analysis using the following equation.

$$M_t / M_\infty = K t_n$$

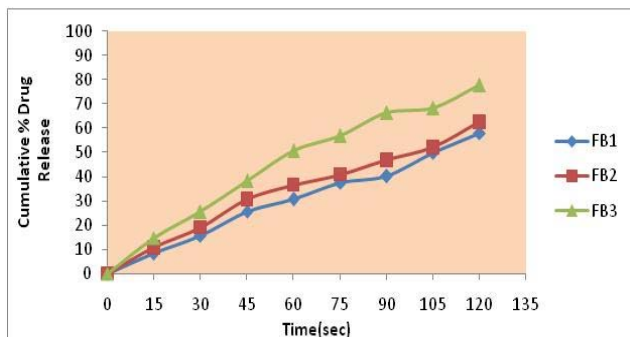


Figure 2: *In vitro* drug release profile of formulation with pullulan and carrageenan as the polymer

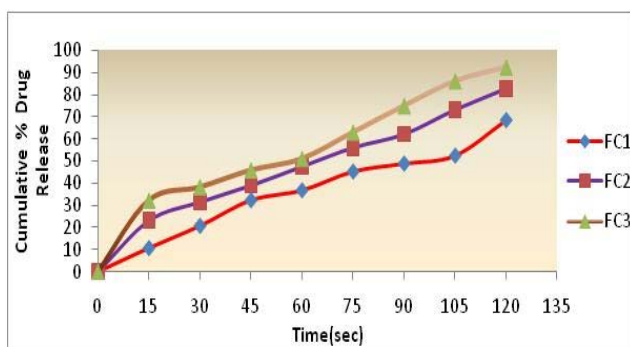


Figure 3: *In vitro* drug release profile of formulation containing pullulan and xanthan gum as polymer

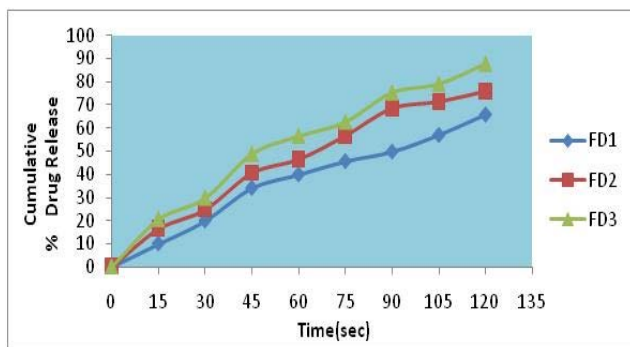


Figure 4: *In vitro* drug release profile of formulation containing pullulan and guar gum as polymer

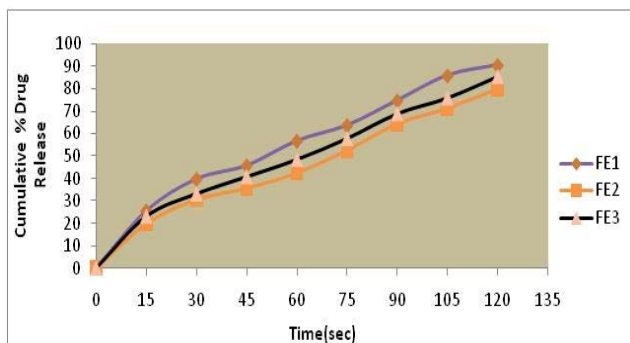


Figure 5: *In vitro* drug release profile of formulation

containing pullulan, carrageenan, xanthan gum and guar gum as polymers.

Where M_t/M_∞ is the fraction of drug released (using values of M/M_∞ within the range 0.10–0.60) at time t and K is a constant incorporating the structural and geometric characteristics of the release device. A value of $n = 0.5$ indicates case I (Fickian) diffusion, $0.5 < n < 1$ indicates anomalous (non-Fickian) diffusion, and $n = 1$ indicates case II transport (Zero order release), $n > 1$ indicates Super case II transport.

It was observed that formulations FB2, FB3, FC2, FC3, FD1, FD2, FD3, FE1 and FE3 followed first order, whereas FA1, FA2, FA3, FB1, FC1, FE2 followed zero order. From the values of release exponent “n” obtained by applying peppas equation, it is observed that the mechanism of drug release was Non Fickian diffusion ($0.5 > n$) for all the formulations, n value ranged from 0.512 to 0.918 which indicated that, type of release is anomalous transport. Apart from that, the R^2 values of Higuchi matrix model for most of the formulations were more than 0.95 indicating that diffusion of drug from the swelled polymer followed the matrix diffusion process.

Stability Studies

Stability studies were carried out for 45 days as per ICH guidelines at $2^\circ\text{C} \pm 3^\circ\text{C}$, $25^\circ\text{C} \pm 2^\circ\text{C}$ (60% RH) and $45^\circ\text{C} \pm 2^\circ\text{C}$ (75% RH). The films were observed for physical change, percentage drug content, surface pH, folding endurance and percentage drug release. Melt in mouth films of almotriptan was found to be physically and chemically stable and showed no significant change in terms of physical characteristics, surface pH, folding endurance, percentage drug content and percentage drug release. It is evident from the stability study that all the films are stable under normal shelf-conditions.

CONCLUSION

Melt in mouth films are the most advanced form of oral solid dosage form due to more flexibility and comfort. In the present study an attempt was made to formulate melt in mouth films of almotriptan, which offers a suitable and practical approach in serving the desired objective of faster disintegration and dissolution characteristics with increased bioavailability. Based on the encouraging results, the almotriptan melt in mouth films can be considered suitable for clinical use in the treatment of migraine, where rapid onset of action is desirable along with convenience of administration. The method of preparation is found to be simple and requires minimum excipients, thus making the product cost-effective. Further, these findings may help the industry to scale up for commercial production.

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