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Preparation and *In Vitro* Evaluation of Mouth Dissolving Films Containing Rizatriptan

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ABSTRACT

The present investigation deals with the formulation of mouth dissolving oral films of Rizatriptan which is used for the treatment of migraine. Rapidly dissolving films have acquired great importance in present scenario because of exclusive properties. The films of Rizatriptan were carried out using different grades of HPMCE3, E6, and E15, maltodextrin DE6, xanthan gum and other polymers by solvent casting method. The prepared films were evaluated for film thickness, folding Endurance, Surface pH, morphological properties, %drug content and content uniformity, tensile strength, percent elongation, *in vitro* disintegration time and *in vitro* dissolution studies. The optimized formulation F24 prepared using HPMC E15 showed minimum disintegration time (9 sec), highest dissolution rate i.e. 99.6% of drug within 8 min and satisfactory physicochemical properties. The optimized film was evaluated for its bioavailability compared with pure drug as reference standard. Statistical analysis declare that no significant difference between the bioavailability parameters C_{max} , T_{max} , $AUC_{0-\infty}$ and AUC_{0-t} of the test film (F24) and the reference product (Pure drug) indicated that they exhibited comparable plasma level-time profiles. These results revealed that the mouth dissolving film containing Rizatriptan is considered to be effectively useful for the treatment of migraine where quick onset of action is expected.

Keywords: Rizatriptan, mouth dissolving films, *in vivo* studies, solvent casting method.

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INTRODUCTION

Oral drug delivery is the largest and oldest segment of the total drug delivery market. It is the fastest growing and most preferred route for drug administration¹ the peroral application is an effective and inexpensive way for drugs that can be absorbed in the gastrointestinal tract. The conventional dosage forms given by this route including tablets and capsules suffers from patient non-compliance due to difficulty in swallowing associated with their use. Moreover, the delay in onset of action by this route also calls for a delivery system which could provide a rapid onset and a quick relief². For the last two decades there has been an enhanced demand for more patient-compliant dosage forms. The demand for their technology also increased drastically. A film or strip can be defined as a dosage form that employs a water-dissolving polymer, which allows the dosage form to quickly hydrate, adhere, and dissolve when placed on the tongue to provide rapid local or systemic drug delivery. Drug release may be either quick i.e. within seconds or slower to take few minutes by varying the rate of dissolution of the films³.

Mouth dissolving oral films offers an attractive route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well supplied vascular and lymphatic drainage, also large surface area of absorption, easy ingestion & swallowing, pain avoidance make the oral mucosa a very attractive and feasible site for systemic drug delivery⁴. The delivery system consist of a very thin oral strip, which is simply based on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto site of application. It then disintegrates and dissolves to release the medication⁵. Rapidly dissolving dosage forms are also called as quick dissolving delivery systems, quick disintegrating, mouth dissolve dosage forms or melt-in-mouth dosage forms. A fast dissolving film is a novel approach to get quick onset of action and to get immediate relief of the symptoms. Hence, fast dissolving films are the best formulations as they are soluble in saliva with in 1 minute releasing the drug and inactive ingredients⁶. Bioavailability of drug in film dosage form is greater than the convectional dosage form⁷.

Migraine is a chronic, episodic, neurological disorder, which usually begins in childhood, adolescence or early adult life, characterized by unilateral headache often accompanied by nausea and vomiting⁸, gastrointestinal disturbance and extreme sensitivity to light and sound⁹.

Rizatriptan is a 5-HT_{1D} (5-hydroxy tryptamine 1D)-receptor agonist, used in the treatment of migraine and cluster headache. Rizatriptan is the first member of a new class of antimigraine compounds that act as a specific and selective 5-hydroxytryptamine-1 receptor agonist¹⁰. The

lower bioavailability of Rizatriptan is primarily because of pre systemic first-pass metabolism and partly because of incomplete absorption¹¹.

In the present study an attempt was made to prepare oral dissolving films of Rizatriptan with the dose of 10mg in order to improve the bioavailability, quick on set of action and patient compliance with hydroxy propyl methyl cellulose, maltodextrin DE6, propylene glycol, xanthan gum, citric acid, aspartame and vanillin. The *In vivo* performance of the optimized formulation was also demonstrated using rabbits as an animal model.

MATERIALS AND METHOD

Materials:

Rizatriptan was generous gift from Matrix laboratories, Hyderabad, India. Hydroxy propyl methyl cellulose of E3, E6 & E15 was obtained from Nectar life sciences, Hyderabad. Maltodextrin DE6, xanthan gum and aspartame was obtained from MSN labs, Hyderabad. Propylene glycol, vanillin, citric acid and amaranth were obtained from SD FINE CHEM LTD, Mumbai. Methanol, acetonitrile and milliQ water are of HPLC grade. All other chemicals used were of analytical grade.

Methods:

Preparation of Rizatriptan Oral Films

The Fast Dissolving Oral Films of Rizatriptan using polymers were prepared by solvent casting method. Hydroxypropylmethyl cellulose (HPMC) with different grades like HPMC E3, E6, and E15 is known for its good film forming properties and has excellent acceptability. Maltodextrin DE6 as film modifier, it acts as film-forming agent, solubilizer and imparts sweetness to the formulation. Propylene glycol as plasticizer, Xanthan gum as stabilizing agent, Citric acid as saliva stimulating agent, Aspartame as sweetening agent and Vanilla was used as a flavouring agent. The aqueous dispersion was prepared by dissolving HPMC, maltodextrin in distilled water maintained at 70°C. The suspension was used after 24 h to remove all the air bubbles entrapped. The active ingredient was added in the required quantity. The solution was poured on petri plate and then kept for drying at 75°C for first 30 min and then it was decreased to 45°C for next 24 h. The resultant film was cut into the dimension of 2 cm X 2 cm in size, in which 2.5 mg of Rizatriptan was included¹².The formulation was carried out using three different polymers, Hypromellose E3, E6 and E15 and the resulting films were evaluated for physicochemical properties.

Composition Of Rizatriptan Fdofs Using Various Grades Of HPMC (E3, E6, E15)

Table 1: Formulation Trials Using HPMC E3

Ingredients (mg)	F1	F2	F3	F4	F5
Rizatriptan	10	10	10	10	10
HPMC E3	500	450	400	400	300
Maltodextrin	50	100	125	125	125
Xanthan gum	10	10	8	5	5
Propylene glycol	80	90	90	100	100
Aspartame	20	20	20	20	20
Citric acid	10	10	10	10	10
Vanilla	q. s				
Amaranth	q. s				
Water(ml)	q. s				

Table 2: Formulation Trials Using HPMC E6

Ingredients (mg)	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Rizatriptan	10	10	10	10	10	10	10	10	10	10
HPMC E6	500	450	450	400	400	400	350	350	250	250
Maltodextrin	50	100	150	150	175	200	200	200	200	250
Xanthan gum	10	10	10	10	8	8	8	5	5	5
Propylene glycol	100	120	120	160	140	140	140	140	140	140
Aspartame	20	20	20	20	20	20	20	20	20	20
Citric acid	10	10	10	10	10	10	10	10	10	10
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				
Water(ml)	q. s	q. s	q. s	q. s	q. s	q. s				

Table 3: Formulation Trials Using HPMC E15

Ingredients(mg)	F 16	F17	F18	F19	F20	F21	F22	F23	F24	F25
Rizatriptan	10	10	10	10	10	10	10	10	10	10
HPMC E15	500	500	400	400	400	350	350	280	240	200
Maltodextrin	50	100	150	175	200	200	180	180	250	250
Xanthan gum	10	10	10	10	8	8	8	5	5	5
Propylene glycol	120	140	160	140	140	140	140	140	140	140
Aspartame	20	20	20	20	20	20	20	20	20	20
Citric acid	10	10	10	10	10	10	10	10	10	10
Vanilla	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
Water(ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

EVALUATION OF MOUTH DISSOLVING FILMS:

Physical characterization of MDFs:

Physical characterization of MDFs 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 parameters like film thickness, weight variation, folding endurance, surface pH, tensile strength, percent elongation, disintegration time, dissolution time and % drug content. The film surface pH was measured by placing the film on petri dish was moistened with small qty of distilled water and place the electrode of the pH meter in contact with the surface of the film.

For evaluation of film weight and thickness, films were taken and weighed individually on a digital balance and the film thickness was measured using Digital Vernier caliper (Mitutoyo) at six different places and the average value was calculated. Folding endurance of patch was determined by repeatedly folding a small strip of film (2cm X 2cm) at the same place till number of times the film could be folded at the same place without breaking was recorded as the folding endurance value. Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. 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. The percent elongation 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, when it is pulled under standard conditions of stress just before the point of break is known as percent elongation. %Drug content was estimated by dissolving a sample strip of film (2cm X 2cm) in 100 ml of phosphate buffer pH 6.8 and the absorbance of solutions was noted using spectrophotometer at 283 nm. The disintegration test was carried out by taking six 2cm X 2cm films, these films were placed in the disintegration apparatus maintaining the temperature at $37\pm 2^{\circ}\text{C}$ and the time taken for disintegration of the films was noted. The *In vitro* dissolution studies were carried out for the films using dissolution apparatus. The values of all the evaluation parameters are given in **Table 4, 5**.

Drug Excipient Interaction Studies

Drug excipient interaction studies were studied by using Shimadzu - IR Affinity 1 Spectrophotometer to confirm possible interaction between the polymer and drug. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons. Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. The analysis was performed by heating the 2-3mg samples on aluminium crimp pans at a rate of $10^{\circ}\text{C}/\text{min}$ in a nitrogen atmosphere.

Stability studies

The stability study of the Rizatriptan formulated 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 °C / 75 % RH for the best formulations for 2 months. The patches were characterized for the drug content and other parameters during the stability study period ¹³.

RESULTS AND DISCUSSION

Evaluation of Fast Dissolving Films

Physical characterization of FDOFs

Formulations (F1-F5) prepared using HPMC E3 were 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, tack property and ease of handling/peeling.

Physical characterization of FDOFs was carried out by visual inspection and the following observations were made. All the prepared films were evenly coloured and no migration of colour was observed. The increased thickness of film is attributed to the increase in the amount of HPMC. Formulation F7, F8, F9, F10 and F18 were found to be brittle in nature. Formulation F6, F12, F14 and F19 films were tacky and difficult to handle.

Evaluation of Physical Parameters

Table 4: Evaluation of Fast Dissolving Oral Film Formulation Batches (HPMC E6) F6-F15

Formulation code	Weight variation(mg)	Thickness (mm)	Folding endurance (count)	Surface pH
F6	37.10±2.1	0.14±0.01	22±3	6.71±0.05
F7	39.68±1.7	0.15±0.02	63±1	6.88±0.01
F8	40.34±1.9	0.14±0.01	77±3	6.77±0.00
F9	39.26±1.2	0.14±0.01	82±4	6.87±0.01
F10	40.67±0.5	0.14±0.03	85±1	6.93±0.02
F11	42.34±1.9	0.13±0.01	92±2	6.74±0.02
F12	41.38±0.3	0.09±0.02	83±3	6.89±0.02
F13	39.01±2.1	0.09±0.01	113±1	6.90±0.02
F14	35.67±1.6	0.05±0.03	21±2	6.86±0.03
F15	35.34±0.9	0.04±0.01	22±1	6.71±0.05

Table 5: Evaluation of Mouth Dissolving Film Formulation Batches (HPMC E6) F16-F25

Formulation code	Weight variation(mg)	Thickness (mm)	Folding endurance (count)	Surface pH
F16	37.00±1.6	0.15±0.01	31±2	6.88±0.01
F17	41.77±1.5	0.15±0.02	63±4	6.77±0.00
F18	39.35±0.9	0.15±0.00	75±3	6.87±0.01
F19	40.01±0.4	0.15±0.01	76±1	6.90±0.02
F20	43.32±1.6	0.14±0.01	89±3	6.76±0.02
F21	40.68±1.5	0.12±0.01	91±4	6.76±0.01
F22	39.67±1.8	0.09±0.01	106 ±1	6.82±0.01
F23	37.02±0.3	0.07±0.02	123±2	6.80±0.02

F24	36.34±2.4	0.05±0.01	31±3	6.86±0.03
F25	36.00±2.0	0.04±0.01	32±2	6.76±0.02

The prepared films were evaluated for the following parameters:

Surface pH of all mouth dissolving films prepared by using different polymers was found to be in the range of 6.09 to 6.81 pH, 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. The weight variation of the formulations was in the range of 60.5±0.5 to 71.2±0.5 mm, which was acceptable. The results showed that as the concentration of polymer increases weight of film also increases. Thickness of mouth dissolving film depends on the concentration of polymer. All the mouth dissolving formulations of different polymers are show thickness value in the range of 0.04±0.01 to 0.15 ± 0.02 mm. The optimized film (F24) has thickness of 90±2 µm. A result of thickness measurement showed that as the concentration of polymer increases, thickness of mouth dissolving film also increases. 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 100±2 to 112±1 (**Table 4**). The optimized film (F24) has folding endurance value of 112±1, which was desirable. The % drug content and content uniformity was performed for all the fast dissolving oral films and found to contain 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 96.4±0.5 to 101.2±0.9 % (**Table 4**) for three different cuts from each film. The optimized formulation (F24) %drug content was found to be 100.1±0.2. 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. The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters, tensile strength and percent elongation at break. Tensile strength and percent elongation of all prepared formulation is shown in **Table 4**. Results revealed that optimized formulation (F24) showed better tensile strength (9.5 g/cm²) and moderate % elongation.

In vitro disintegration studies

The disintegrating time of all the formulations using Rizatriptan ranges from 9 to 31sec. *In vitro* disintegrating time for mouth dissolving film using HPMC E6 was ranges from 18 to 31sec, the results were depicted in figure 2 and the disintegrating time for the films made by the polymer HPMC E15 was ranges from 9 to 18 shown in figure 3. The disintegration time of optimized

formulation (F24) was found to be 9 sec, when compared with innovator product (Table 6) Marketed Product (30 sec) which was very less and desirable for quick onset of action.

***In vitro* drug release studies**

Cumulative % drug release was calculated on the basis of drug content of Rizatriptan present in the respective film. The results obtained in the *in vitro* drug release for the formulations were tabulated in table. The graphs from F5 to F17 are depicted in Figure 4 and the graphs of formulation F20 to F25 are shown in Figure 5. The formulations F5, F9, F10, F11, F20, F21 & F22 show drug release up to 89% at the end of 8 min. Rapid drug dissolutions were observed in F15, F16 and F17 which release 98.6 and 96.1 respectively. The optimized formulation (F24) shows highest percent of drug release 99.45 by the end of 8 min, the initial release of the optimized formulation was more when compared with Marketed product therefore the onset of action was very quick compare with the innovator product **Figure 1 and 2.**

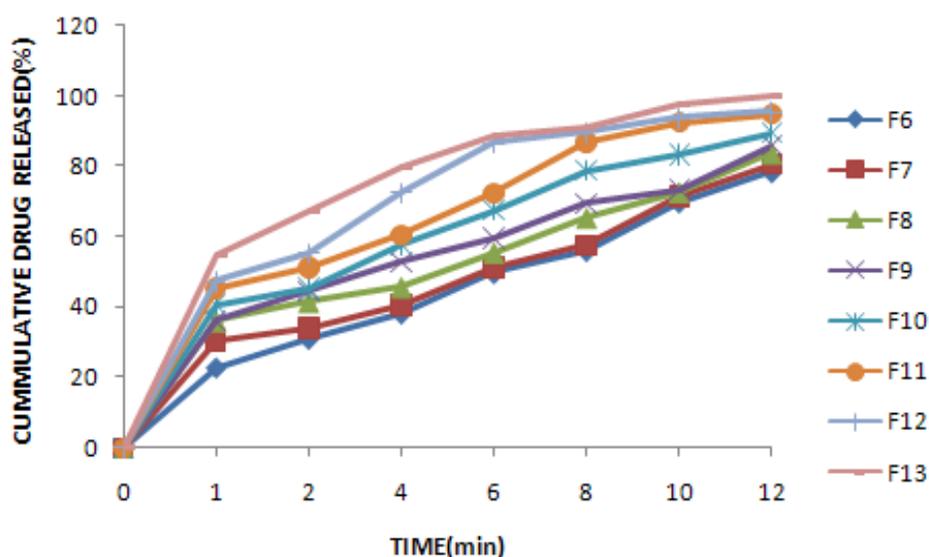


Figure 1: Invitro drug release profiles of Rizatriptan FDOF formulations(F6 to F13)

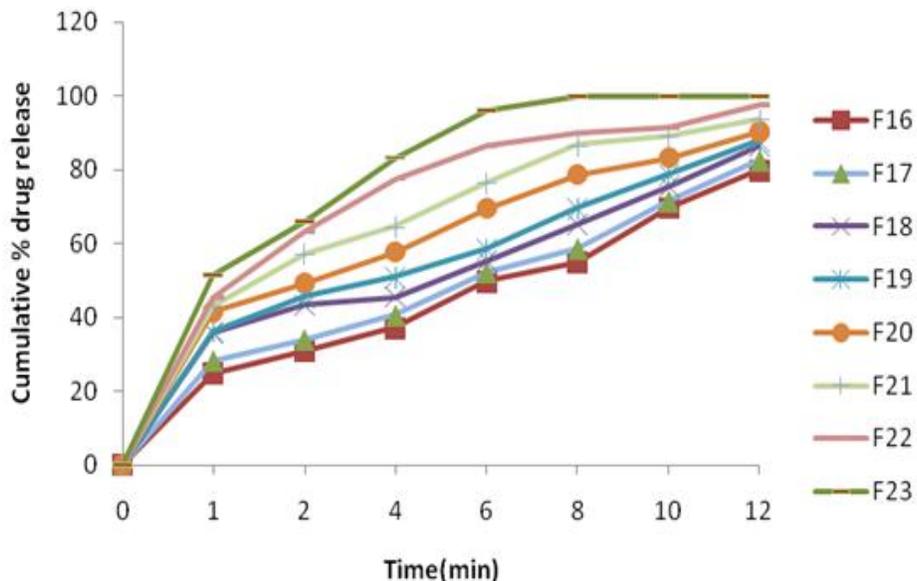


Figure 2: Invitro drug release profiles of Rizatriptan FDOF formulations (F16 to F23)

Drug Excipient Interaction Studies

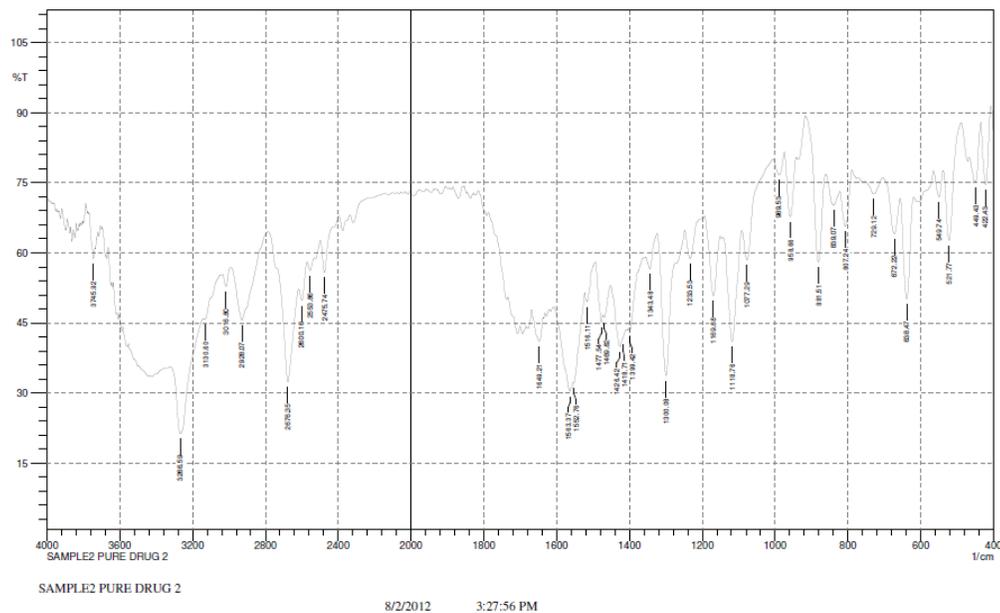


Figure 3: (Pure drug) Rizatriptan

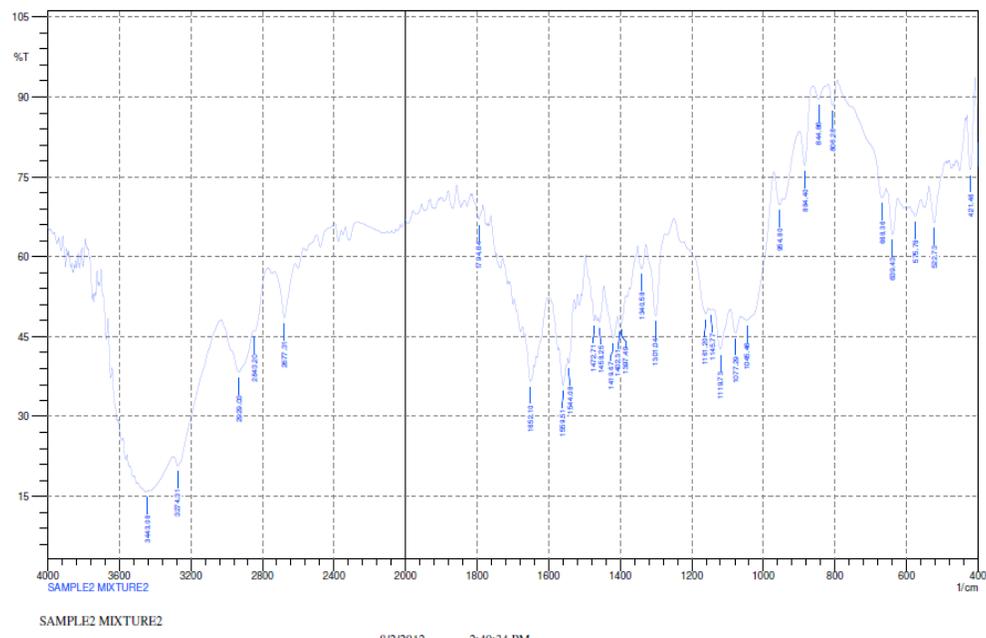


Figure 4: Drug+HPMCE15+Maltodextrin

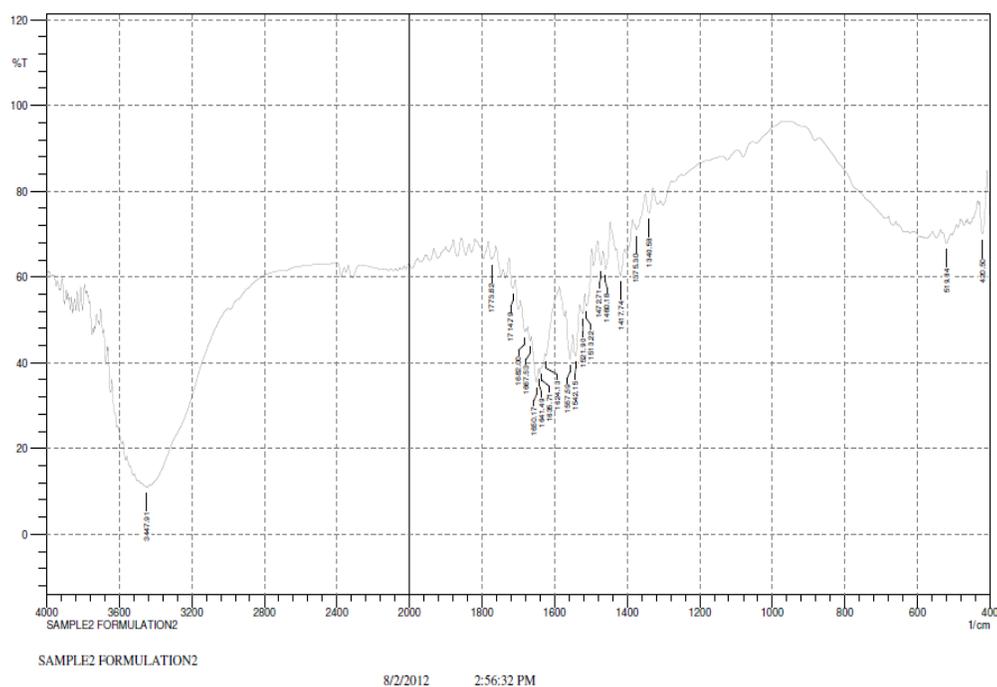


Figure 5: Optimized formulation (F24)

Interpretation of FTIR Data

The FTIR spectra of pure Rizatriptan **figure 3** displayed bands at 3450 cm^{-1} due to N-H stretch, at 1736 cm^{-1} due to C=O stretching, at 1651 cm^{-1} due to heterocyclic C=C stretching. The spectra also showed bands at 1370 cm^{-1} due to C-H bending. The FTIR spectrum of film containing Rizatriptan exhibited characteristic bands consistent with the molecular structure of Rizatriptan such as bands at 3456 cm^{-1} due to N-H stretch, at 1736 cm^{-1} due to C=O stretching, at 1650 cm^{-1} due to

heterocyclic C=C stretching, at 1370 cm^{-1} due to C-H bending. Thus, the presence of characteristic absorption bands of Rizatriptan and the film containing Rizatriptan suggest that there is no interaction takes place between the drug and excipients used in the formulation.

Drug Excipient Compatibility Studies by DSC

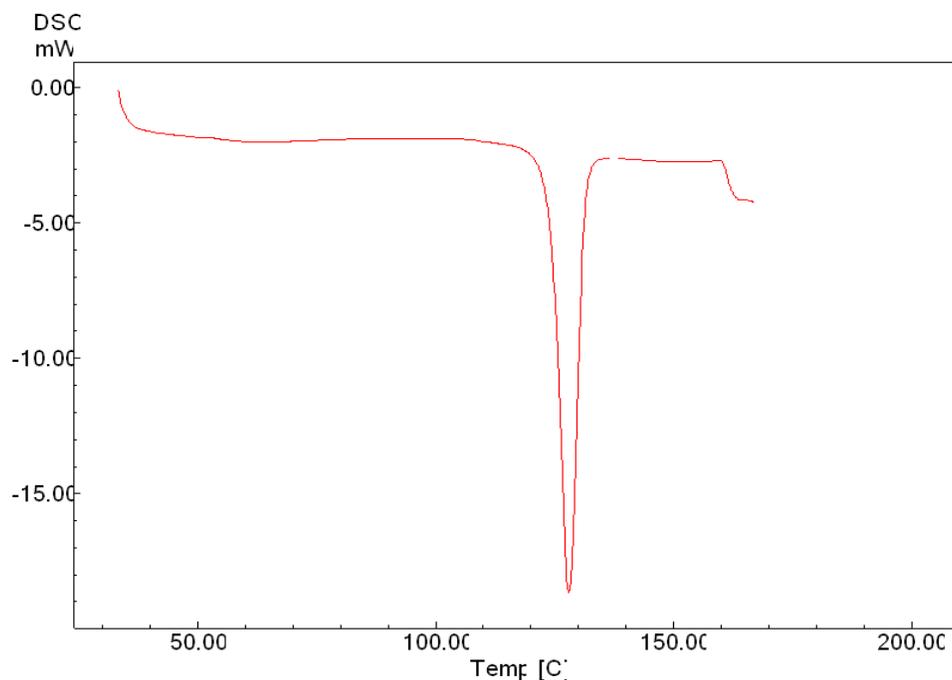


Figure 6: DSC Thermogram of Rizatriptan - Pure Drug

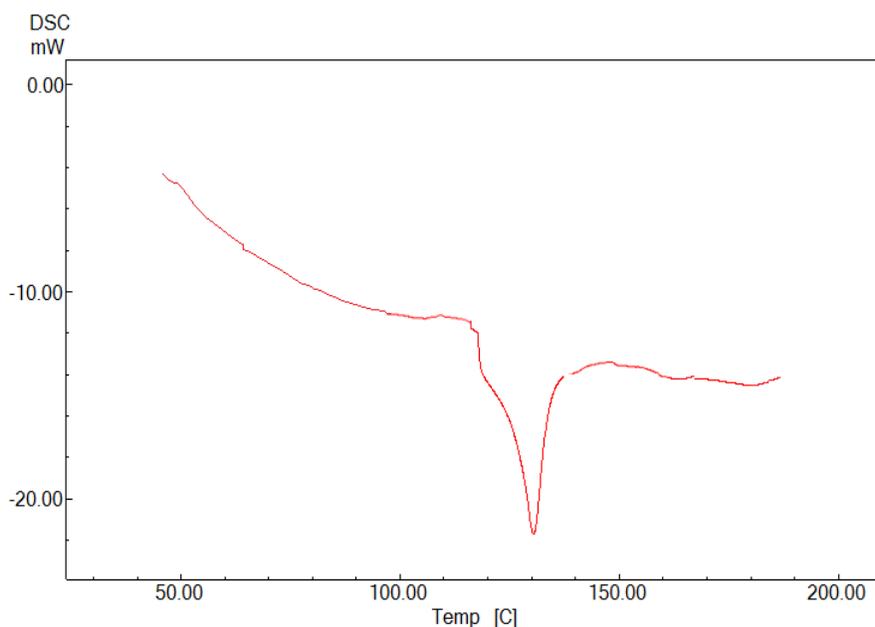


Figure 7: Rizatriptan Optimized Formulation (F24)

DSC thermograms revealed that there is no considerable change observed in melting endotherm of pure drug (137.79) figure 6 and drug in optimized formulation (139.36) figure 7. It indicates that there is no interaction takes place between drug and other excipients used in the formulation.

Stability Studies for (F24) optimized formulation

F24 formulation was selected for stability studies on the basis of high cumulative % drug release and also results of *in vitro* disintegration time. Stability studies were conducted under different conditions according to ICH guidelines. From these results it was concluded that, formulations F23 is stable and retained their original properties with minor differences. The results of disintegration time, drug content and transparency are shown in the Table 6, which indicates no alteration after storage.

Table 6: Accelerated stability testing data of optimized formulation (F24) kept for stability at 40 °C /75 %RH

Retest Time For F24	Disintegration Time (sec)	Percent Drug Content/ Assay (%)	Transparency
1 Week	9±4	100.1±0.2	Transparent
2 Weeks	10±2	100.2±0.2	Transparent
1 Month	10±2	99.1±0.2	Transparent
2 Months	10±2	99.0±0.2	Transparent

SUMMARY AND CONCLUSION

In this work, systemic efforts were made to prepare mouth dissolving films of Rizatriptan (8 mg/2cm X 2 cm film) by using solvent casting method with different concentrations of HPMC-E3, E6 and E15, maltodextrin and xanthan gum. The bitter taste of the drug was masked by aspartame and vanilla flavour. Among the prepared formulations F24 showed minimum disintegration time 9 sec and the release of drug from F24 was found to be 99.6% within 8 min. Based on the satisfactory physicochemical properties like tensile strength, folding endurance, thickness, disintegration results and dissolution studies of F24, it was concluded that F24 finalized as optimized formulation. The initial release of the optimized formulation (F24) was more when compared with innovator product, therefore the onset of action was very quick compare with the innovator product. DSC and FTIR data revealed that no interactions takes place between the drug and polymers used in the optimized formulation. *In vitro* evaluation of the films confirmed their potential as an innovative dosage form to improve delivery of Rizatriptan. Therefore, the mouth 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.

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