CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://zenodo.org/records/10417215

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND CHARACTERIZATION OF RIZATRIPTAN LOADED MOUTH DISSOLVING FILMS

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Abstract:
The most common type of headache is a migraine, which can range in severity from mild to severe and is exacerbated by any regular physical activity. Patients have trouble swallowing solid dosage forms like tablets and hard gelatin capsules, particularly those who are younger or older. Oral thin films that dissolve in the mouth are one such newly created dosage form. When in contact with saliva, the thin oral strip made of hydrophilic polymer dissolves quickly. Thus, aim of this study is formulation and evaluation of mouth dissolving film of rizatriptan. The formulation and evaluation of tablet was performed according to standard methods. In total 16 formulations were prepared. All were observed to be Homogenous, transparent, colorless, both sides smooth. The thickness of formulation ranged from 68.22 ± 4.08 to 108.27 ± 4.08mm. The variation in mg ranged from 3.85 ± 0.204mg to 4.45 ± 0.108mg. The tensile strength extends from 3.12 ± 0.07 to 14.82 ± 0.26. The % elongation varied from 40.19 ± 0.96 to 97.64 ± 1.40. The folding endurance ranged from 31±35 to 115±29.63. The least disintegration time was observed for formulation F11 which is 7.65 ± 0.58 seconds while maximum disintegration time of 65.32 ±1.50 seconds was noted for 65.32 ± 1.50The formulation F11 was proved to be ideal among all. The drug release data of RIZ F11 (n=3) was then noted. The drug percent release in 5 seconds was estimated to be 13.84 ± 1.57. The regression value for first order spot was calculated to be 0.969. The Mean 'k' (sec^{-1}) (0-40 sec). The formulation F11 (1% w/w RIZ with HPMC E3 and PVP K 30), were subjected to stability tests." The MDFs were sealed in aluminum pouches and kept for 6 months at 40 degrees Celsius and 75 percent relative humidity. No crystallization was seen in the MDFs, and their appearance did not alter during the course of the research. The weight variation at sixth month was noted to be 98-100%. The RIZ content at sixth month was determined to be 96-103%.

Keywords: *Migraine, Rizatriptan, Mouth dissolving film (MDF), Fast dissolving drug delivery systems (FDDDS)*

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Please cite this article in press Anshita Gupta et al., ***Formulation And Characterization Of Rizatriptan Loaded Mouth Dissolving Films,*** *Indo Am. J. P. Sci, 2023; 10 (12).*

INTRODUCTION:

The prevalent chronic headache condition known as migraine is typified by recurrent, pulsating episodes that last anywhere from four to seventy-two hours. The most common type of headache is a migraine, which can range in severity from mild to severe and is exacerbated by any regular physical activity. In addition to being linked to symptoms like nausea, vomiting, photophobia, phonophobia, and increased sensitivity of central pain neurons that process information from extracranial skin and muscle as well as intracranial structures, migraines are also caused by the activation of meningeal perivascular pain fibres (Haan *et al*., 2007; Natoli *et al*., 2010).

For the patient, the oral route is the most convenient. However, some patients have trouble swallowing solid dosage forms like tablets and hard gelatin capsules, particularly those who are younger or older. They are unable to take these dosage forms because they are afraid they will choke. Several fast dissolving drug delivery systems (FDDDS) were created in order to get around this. The buccal route circumvents the hepatic first pass metabolism, making it the most widely used method of drug administration. Pharmaceutical companies are currently conducting research to reformulate current medications into novel dosage forms (Arunachalam *et al*., 2010; Arya *et al*., 2010).

Oral thin films that dissolve in the mouth are one such newly created dosage form. When in contact with saliva, the thin oral strip made of hydrophilic polymer dissolves quickly. Without drinking or chewing, they can quickly dissolve (in a matter of seconds) to release the medication. The mucosa's high blood supply enrichment allows for rapid drug absorption and bioavailability. Bypassing first pass metabolism produces the instant bioavailability. Therefore, they are typically made for medications with high first pass metabolisms in order to increase bioavailability (Dixit and Puthli, 2009; Estemalik and Tepper, 2013).

The medication rizatriptan is used to treat migraine headaches, which are characterized by intense, throbbing headaches that can occasionally be accompanied by light and sound sensitivity and nausea. Rizatriptan belongs to a group of drugs known as selective agonists of serotonin receptors. It functions by constricting blood vessels in the brain, obstructing the brain's transmission of pain signals, and preventing the release of specific endogenous substances that trigger pain, nausea, and additional migraine symptoms. Rizatriptan doesn't lessen your frequency of headaches or stop migraine attacks (Láinez *et al*., 2006; Dahlof *et al*., 1999). Keeping in view the advantages of mouth dissolving film this study will deal with formulation and characterization of rizatriptan loaded mouth dissolving films.

MATERIALS AND METHODS:

Chemicals and reagents

Rizatriptan was obtained as gift sample from pharmaceutical industry, Sodium chloride, Potassium chloride, Calcium chloride dehydrate, Magnesium chloride hexahydrate, Potassium phosphate dibasic, water etc were obtained from S.D. Fine chemicals.

Preparation of MDFs:

As a first step, dummy MDFs were made out of a variety of polymers and plasticizers in order to find the optimal mixture for producing films with the appropriate mechanical strength and visual look. RIZ was produced in batches of 5g using the formulas provided in Tables, based on the results of the placebo tests. The RIZ were dissolved in a solvent combination (water and methanol) in a separate beaker, and then plasticizers and other components were added while stirring constantly. The last step was to add the polymer to each beaker and stir it well. A wet film applicator (Paul N. Gardner Company Inc, USA) was used to cast the mixture onto a glass plate at thicknesses of 30mil (750m) and 40mil (1000m) after being sonicated for 2 minutes to eliminate air bubbles. The films were dried in a hot air oven at 40 degrees Celsius for 60 minutes (Panchal *et al*., 2012). After the films dried, they were removed from the glass plate, wrapped in foil, and placed in a desiccator until needed. The wet film applicator utilized in this investigation is seen below.

Table 1: Formulae of HPMC-RIZ MDFs

Ingredients(mg)	%w/w	F1	F1(A) (40 mil)	F2	F2 (A) (40 mil)	F3	F4	F5	F6	F7
RIZ #	2	100	100	100	100	100	100	-	-	-
	1.25	-	-	-	-	-	-	62.5	62.5	62.5
	1	-	-	-	-	-	-	-	-	-
HPMC E3	7.5	375	375	375	375	375	375	375	-	-
HPMC E5	7.5	-	-	-	-	-	-	-	375	375
HPMC E15	7.5	-	-		-	-	-	-	-	-
PEG 400 ^	0.5	25	25	-	-	25	-	-	25	25
GLYCEROL*	0.5	-	-	25	25	-	25	25	-	-
PVP K30	0.04	-	-	-	-	2	2	-	-	2
SLS	0.04	-	-	-	-	-	-	-	-	-
WATER	35 @	1750	1750	1750	1750	-	-	-	-	-
	34.96&	-	-	-	-	1748	1748	-	-	-
	33.75£	-	-	-	-	-	-	1787.5	1787.5	-
	33.71¥	-	-	-	-	-	-	-	-	1783.5
	36~	-	-	-	-	-	-	-	-	-
	33.96>	-	-	-	-	-	-	-	-	-
Pineapple flavour	10	10	10	10	10	10	10	10	10	10
Aspartame	10	10	10	10	10	10	10	10	10	10
Methanol $	55	2750	2750	2750	2750	2750	2750	2750	2750	2750

#Benzoate salt to 100mg of base; * 0.0198mL; $2.75mL; ^0.0223mL; @1.75mL; &1.748mL; ¥ 1.7855mL; £ 1.7875mL; ~1.8mL;>1.798mL

Table 2: Formulae of HPMC-RIZ MDFs (Contd…)

Ingredients(mg)	%w/w	F8	F9	F10	F11	F12	F13	F14	F15	F16
RIZ #	2	-	-	-	-	-	-	-	-	-
	1.25	62.5	62.5	-	-	-	-	-	-	-
	1	-	-	50	50	50	50	50	50	50
HPMC E3	7.5	-	-	375	375	375	-	-	-	-
HPMC E5	7.5	375	-	-	-	-	375	375	375	-
HPMC E15	7.5	-	375	-	-	-	-	-	-	375
PEG 400 ^	0.5	25	25	25	25	25	25	25	25	25
GLYCEROL*	0.5	-	-	-	-	-	-	-	-	-
PVP K30	0.04		-	-	2	-	-	2	-	-
SLS	0.04	2	-	-	-	2	-	-	2	-
WATER	35 @	-	-	-	-	-	-	-	-	-
	34.96&	-	-	-	-	-	-	-	-	-
	33.75£	-	1787.5	-	-	-	-	-	-	-
	33.71¥	1783.5	-	-	-	-	-	-	-	-
	36~	-	-	1800	-	-	1800	-	-	1800
	33.96>	-	-	-	1798	1789	-	1798	1798	-
Pineapple flavour	10	10	10	10	10	10	10	10	10	10
Aspartame	10	10	10	10	10	10	10	10	10	10
Methanol $	55	2750	2750	2750	2750	2750	2750	2750	2750	2750

Table 3: Formulae of Sodium CMC-RIZ MDFs

Ingredients (mg)	%w/w	F17
RIZ[#]	1.25	62.5
Sodium CMC	2	100
PEG 400^	1	50
WATER [*]	36.75	1837.5
METHANOL[$]	59	2950

Evaluation of prepared MDFS:
Detailed analyses of the following attributes were performed on the produced RIZ MDFs.

Morphological Properties:
RIZ MDFs were evaluated visually for qualities such uniformity, color, clarity, and surface. All formulations were kept in a temperature- and humidity-controlled environment (25 2°C, 65 5%, respectively) and evaluated every month for a total of 6 months. Aluminum foils were used for film packaging. Viewing MDFs at 10x magnification using a binocular microscope (Olympus-CH20i) helped further establish their morphological characteristics (Upreti *et al*., 2014).

Thickness:
A screw gauge with a range of 0-10mm and a rotation of 0.001mm was used to measure the thickness of RIZ MDFs. With the thickness gauge's anvil cranked and the pointer set to zero, we were able to insert the film. The dial was read while holding the film against the anvil. Six separate estimates were made, and the mean and standard deviation were computed for each set of data.

Drug Content
Each 1cm2 film was cut from the top, middle, and bottom thirds and dissolved in 5mL of distilled water in a 10 mL volumetric flask. Distilled water was used to get the correct volume.
After properly diluting the samples with synthetic saliva, the RPHPLC technique was used to determine the levels of RIZ in the MDFs.

Variation of Mass
By weighing pieces of film that were 1cm2 in size and taken from various locations, the authors of a 2013 study (Nair AB et al) were able to determine the mass difference across batches of formulations generated for each medicine. There were three separate sets of calculations done (Pawar *et al*., 2019).

Tensile Strength:
The tensile strength of a film is defined as the stress at which it breaks under tension. Using a MINI Tech Tensiometer-UTM9051 (Dak Systems Inc., Mumbai, India) with a load cell of 500N (50kg) capacity and Test Bench II software, the tensile strength of RIZ MDFs was determined. Pneumatic grips were used to hold 10cm by 2cm by whatever thickness of MDF was necessary. The program was fed all the measurements in order to get the cross-sectional area. The MDF was folded tightly and inserted between the pneumatic grips. In order to shatter the film, the instrument was run at a speed of 5 mm/min. Everything was done in duplicate to ensure accuracy.

Percent Elongation (%E)
Test Bench-II was used to determine the % elongation of RIZ MDFs under tensile load in this investigation. The calculations were done in triplicate for accuracy.

Folding Endurance
Folding endurance was measured by repeatedly folding the film at the same spot until it broke for RIZ MDFs. This demonstrates how fragile the film is. The folding endurance value of a film is determined by counting the number of times it can be folded without tearing (Kokare *et al*., 2015). The calculations were done in triplicate for accuracy.

In-vitro Disintegration Studies:
Here, we compare the results of two in-vitro disintegration experiments (drop and Petri dish techniques) of RIZ MDFs (Garsuch *et al*., 2010). Both approaches required little media to provide realistic simulations of natural environments

Drop Method
One drop of distilled water was pipetted onto a 1 cm 2 MDF that was spread out flat on a glass slide in a Petri dish. The duration of the drop's dissolution of the film and subsequent whole formation was timed. The calculations were done in triplicate for accuracy.

Petri dish Method:
A 2x2 cm film was put on top of 2mL of distilled water in a Petri dish and the time it took for the film to fully dissolve was recorded. The calculations were done in triplicate for accuracy.

In-Vitro drug release studies:
500 mL of artificial saliva was used as the dissolving medium in in-vitro drug release experiments of RIZ MDFs using a USP Type V dissolution rate testing system (Okamoto *et al* 2001). The set parameters included 370°C and 50 rpm. Each film cut to the correct size for a 5 mg dosage (3 2.4 cm2 for RIZ).
At regular intervals, 2 mL of the dissolving media was discarded and replaced with new sample. Using the RP-HPLCPDA technique, we examined the samples. The dissolving tests were repeated three times.

Stability Studies
The RIZ MDFs were tested for stability, including (F11) with 1% w/w RIZ and HPMC E3, (F7) with 1.25% w/w ZOL and HPMC E3, and (F5) with 1.25% w/w ALMO and HPMC E3. Aluminum pouches containing the MDFs were sealed and kept for six months at 40oC/75 5% RH. Selected RIZ MDFs were analysed for their appearance, weight, drug content, and in vitro drug release capabilities.

Statistical Analysis
One-way analysis of variance (with Fisher's LSD post hoc test) was performed on the experimental data for each medication using SYSTAT software (SYSTAT Software Inc., San Jose, USA). Significant findings were defined as those with a probability level of p 0.05.

RESULTS AND DISCUSSION:

In total 16 formulations were prepared. All were observed to be Homogenous, transparent, colorless, both sides smooth. The thickness of formulation ranged from 68.22 ± 4.08 to 108.27 ± 4.08mm. The variation in mg ranged from 3.85 ± 0.204mg to 4.45 ± 0.108mg. The tensile strength extends from 3.12 ± 0.07 to 14.82 ± 0.26. The % elongation varied from 40.19 ± 0.96 to 97.64 ± 1.40. The folding endurance ranged from 31±35 to 115±29.63. The least disintegration time was observed for formulation F11 which is 7.65 ± 0.58 seconds while maximum disintegration time of 65.32 ±1.50 seconds was noted for 65.32 ± 1.50. The more disintegration time may be the result of a higher concentration of polymer, which leads to the creation of a gel layer with a high viscosity due to closer contact between the polymer particles. Intimate contact reduces the drug particles' mobility in swollen matrices, lengthening the disintegration time.

The formulation F11 was proved to be ideal among all. The drug release data of RIZ F11 (n=3) was then noted. The drug percent release in 5 seconds was estimated to be 13.84 ± 1.57. The regression value for first order spot was calculated to be 0.969. The Mean 'k' (sec^{-1}) (0-40 sec).

"F11 (1% w/w RIZ with HPMC E3 and PVP K 30), were all subjected to stability tests." The MDFs were sealed in aluminum pouches and kept for 6 months at 40 degrees Celsius and 75 percent relative humidity. It was determined how MDFs looked, how much medicine they contained, and how well they released the medication. No crystallization was seen in the MDFs, and their appearance did not alter during the course of the research. The weight variation at sixth month was noted to be 98-100%. The RIZ content at sixth month was determined to be 96-103%. To further assess the MDFs, we saw them at 10x magnification using a binocular microscope (Olympus-CH20i).

The current study's findings suggest that mouth-dispersing oral film formulations could represent a novel drug dosage form for use in pediatric and geriatric populations, among others. As a result, it was discovered that rizatriptan MDFs were more effective in treating migraine.

Table 1: Morphological properties of RIZ (1%w/w) MDFs

Formulations	Initial Properties	Time Points (months)						
	0 months	0.5	1	2	3	4	5	6
F1	Homogenous, transparent, colorless, both sides smooth	x*	-	-	-	-	-	-
F1(A)	-do-	x*	-	-	-	-	-	-
F2	-do-	x*	-	-	-	-	-	-
F2(A)	-do-	x*	-	-	-	-	-	-
F3	-do-	x*	-	-	-	-	-	-
F4	-do-	x*	-	-	-	-	-	-
F5	-do-	x*	-	-	-	-	-	-
F6	-do-	x*	-	-	-	-	-	-
F7	-do-	x*	-	-	-	-	-	-
F8	-do-	x*	-	-	-	-	-	-
F9	-do-	x*	-	-	-	-	-	-
F10	-do-	x	x	x	x	x	x	x
F11	-do-	x	x	x	x	x	x	x
F12	-do-	x	x	x	x	x	x	x
F13	-do-	x	x	x	x	x	x	x
F14	-do-	x	x	x	x	x	x	x
F15	-do-	x	x	x	x	x	x	x
F16	-do-	x	x	x	x	x	x	x

x* - Crystallization; x- no change

Table: 2. Thickness of RIZ MDFs (n=6)

F. Code	Thickness Mean ± SD	Content (mg)	Variation of mass (mg)	Tensile strength	Percent Elongation (cm)	Folding endurance	Disintegration Time (sec)
F1	68.22 ± 4.08	1.01 ± 0.02	3.85 ± 0.204	3.38 ± 0.26	93.02 ± 0.80	110±20	11.29 ± 1.15
F1(A)	98.33 ± 4.08	1.43 ± 0.06	4.86 ± 0.287	11.68 ± 0.45	40.19 ± 0.96	51±9.53	65.32 ± 1.50
F2	78.33 ± 4.08	1.08 ± 0.06	4.21 ± 0.085	7.63 ± 0.44	73.00 ± 0.27	79±12.57	18.33 ± 0.57
F2(A)	108.27 ± 4.08	1.39 ± 0.02	5.13 ± 0.170	14.82 ± 0.26	32.50 ± 0.52	31±35	74.98 ± 2.00
F3	71.67 ± 4.08	1.04 ± 0.03	4.13 ± 0.047	3.85 ± 0.16	92.15 ± 0.79	102±22	8.32 ± 0.57
F4	78.33 ± 4.08	1.11 ± 0.05	4.45 ± 0.108	12.93 ± 0.29	71.45 ± 1.37	74±40	9.65 ± 0.58
F5	68.33 ± 4.08	0.70 ±	3.79 ±	3.97 ±	94.86 ± 0.30	108±4.15	9.97 ± 1.00

		0.01	0.152	0.16			
F6	70.00 ± 0.00	0.75 ± 0.02	3.99 ± 0.082	2.99 ± 0.15	85.08 ± 2.79	94±8.11	14.30 ± 1.55
F7	71.67 ± 4.80	0.77 ± 0.04	4.05 ± 0.054	3.83 ± 0.57	80.87 ± 0.22	90±20	11.66 ± 0.58
F8	71.67 ± 4.80	0.79 ± 0.02	4.06 ± 0.079	2.98 ± 0.02	78.18 ± 0.72	88±60	13.33 ± 0.58
F9	84.67 ± 5.16	0.80 ± 0.02	4.18 ± 0.062	4.58 ± 0.34	74.76 ± 0.31	82±14.85	20.66 ± 0.58
F10	60.00 ± 0.00	0.59 ± 0.02	3.40 ± 0.082	3.12 ± 0.07	97.64 ± 1.40	115±29.63	9.65 ± 0.58
F11	68.33 ± 4.08	0.62 ± 0.02	3.95 ± 0.085	3.75 ± 0.13	91.07 ± 0.80	109±5.22	7.65 ± 0.58
F12	68.33 ± 4.08	0.64 ± 0.04	3.93 ± 0.062	4.41 ± 0.43	89.38 ± 0.70	107±14.82	8.65 ± 0.58
F13	71.67 ± 4.08	0.65 ± 0.02	4.07 ± 0.037	2.50 ± 0.34	83.18 ± 0.25	92±10.41	12.63 ± 1.15
F14	78.33 ± 4.08	0.68 ± 0.02	4.11 ± 0.012	2.75 ± 0.30	81.34 ± 0.22	88±13.22	10.29 ± 1.15
F15	78.33 ± 4.08	0.71 ± 0.02	4.19 ± 0.033	2.54 ± 0.48	79.94 ± 0.99	84±41.23	11.63 ± 1.15
F16	84.67 ± 5.16	0.73 ± 0.02	4.31 ± 0.098	4.57 ± 0.33	75.71 ± 0.54	80±8.15	17.64 ± 1.15

Table 3: Drug release data of RIZ F11 (n=3)

Time(sec)	Percent RIZ released			Mean ± SD
	Trial 1	Trial 2	Trial 3	
0	0.00	0.00	0.00	0.00 ± 0.00
5	12.10	15.16	14.27	13.84 ± 1.57
10	24.29	24.91	25.73	25.64 ± 1.31
20	41.32	41.96	45.91	43.07 ± 2.48
30	58.43	52.63	58.05	54.37 ± 3.24
40	75.91	74.63	77.82	74.12 ± 1.61
50	84.86	90.59	89.33	88.26 ± 3.01
60	105.26	102.09	104.00	103.79 ± 1.60

Table 4: DP_5 and First order kinetic data of RIZ formulations

Formulation	DP_5⋆ (Mean ± SD)	R2 (First order plot)	Mean 'k' (sec^{-1}) (0-40 sec)
F11	13.84 ± 1.57	0.969	0.032

DP_5⋆: Drug percent released at 5 sec.

Table: 5. Stability studies data for MDFs (n=3)

MDFs	Parameter	Time period (months)		
		0	3	6
RIZ MDFs	Appearance	Transparent	Transparent	Transparent
	Weight variation	95-101%	97-101%	98-100%
	RIZ content	98-105%	98-103%	96-103%

CONCLUSION:

A brand-new fast-dissolving film dosage form for the oral cavity was created and assessed. Numerous factors, including the impact of plasticizers and PVA concentration on film properties, were investigated. The compatibility of excipients with the medication was verified. The solvent casting method produced a PVA-based fast dissolving strip of rizatriptan with acceptable mechanical properties and a satisfactory drug release percentage in formulation F11. The prepared film lacked interactions between the drug and polymer and had a smooth, transparent surface. The film's high percentage of drug release in 6.8 pH phosphate buffer suggested that it might be useful for treating migraine conditions where rapid drug bioavailability is required.

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