International Journal of Drug Development & Research
| January-March 2012 | Vol. 4 | Issue 1 | ISSN 0975-9344 |
Available online http://www.ijddr.in
Covered in Official Product of Elsevier, The Netherlands
SJR Impact Value 0.03,& H index 2

FULL Length Research Paper
Covered in Index Copernicus with IC Value 4.68 for 2010

Formulation and evaluation of fast dissolving sublingual films of Rizatriptan Benzoate

Bhyan Bhupinder*[1], Jangra Sarita[2]
[1]Department of Pharmaceutical Sciences, Lovely Professional University, Jalandhar-Delhi G.T. Road (NH-1), Phagwara. Punjab, India.
[2]Seedling College of Pharmacy, Jaipur National University, Jaipur-302025, Rajasthan, India.

Abstract

Rizatriptan Benzoate, a serotonin 5-HT_1 receptor agonist is a new generation antimigraine drug which has oral bioavailability of 47% due to hepatic first pass metabolism. The present study investigated the possibility of developing Rizatriptan benzoate fast dissolving sublingual films allowing fast, reproducible drug dissolution in the oral cavity, thus bypassing first pass metabolism to provide rapid onset of action of the drug. The fast dissolving films were prepared by solvent casting method. Low viscosity grade of hydroxylpropyl methylcellulose (HPMC E 15) and maltodextrin were used in combination as film forming polymer, due to their hydrophilic nature and palatable taste. To decrease the disintegration time of formulations sodium starch glycolate was used as disintegrating agent. Glycerol, mannitol, aspartame and sodium lauryl sulphate were used as a cooling agent, sweetening agent and oral penetration enhancer respectively. All the films formulations (F1-F8) was evaluated for their thickness, weight variations, tensile strength, percentage elongation, folding endurance, surface pH, *in-vitro* disintegration, drug content, *in-vitro* drug release and ex-vivo permeation. Disintegration time showed by the formulations was found to be in range of 25-50 sec. Formulations F1 and F2 showed 90% in-vitro drug release within 7 min and 61% ex-vivo drug permeation within16 min. The film showed an excellent stability at least for 4 weeks when stored at 40° C and 75% in humidity.

*Corresponding author, Mailing address:
Bhyan Bhupinder
E.mail: bhyan2021@gmail.com

Key words:
Fast dissolving films, Fast disintegration, Oral strips, Sublingual films.

***How to Cite this Paper*:**
Bhyan Bhupinder*, Jangra Sarita "Formulation and evaluation of fast dissolving sublingual films of Rizatriptan Benzoate", Int. J. Drug Dev. & Res., Jan-March 2012, 4(1): 133-143

Article History:----------
Date of Submission: 24-11-2011
Date of Acceptance: 19-12-2011
Conflict of Interest: NIL
Source of Support: NONE

INTRODUCTION

There has been increased demand for the novel dosage form to gain more patient compliance. Fast dissolving films recently have acquired great importance in the pharmaceutical industry due to their unique properties and specific advantages like no need of water for disintegration, accurate dosing,

rapid onset of action, ease of transportability, ease of handling, pleasant taste and improved patient compliance [1]. Fast dissolving film is a type of drug delivery system, which when placed in the oral cavity it rapidly disintegrates and dissolves to release the medication for oromucosal and intragastric absorption, without chewing and intake of water [2]. This technology evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers. These films have a potential to deliver the drug systemically through intragastric, sublingual or buccal route of administration and also has been used for local action [3, 4]. This type of technology offer a convenient way of dosing medication, not to special population groups like pediatric, geriatric, bedridden patients, mentally ill patients, but also to the general population. The sublingual mucosa is relatively permeable due to thin membrane and large veins. It gives rapid absorption and instant bioavailability of drugs due to high blood flow [5, 6]. As the fast-dissolving film is taken through the sublingual route, rapid absorption of drug is possible, which finally leads to quick onset of drug action and prevent the first pass-metabolism of the drug.

Migraine is one of the ten most disabling disorders worldwide, and despite recent developments in the management of migraine, it remains underdiagnosed and undertreated [7]. Disability due to migraine headache and associated symptoms has been estimated to cost American employers $US 13 billion per year, due to missed work days and impaired work performance. Epidemiological studies in migraine reveal that the vast majority of patients (>90%) have experienced nausea during a migraine attack. Similarly, most (almost 70%) have vomited at some time during an attack so they avoid intake of excess of liquid [8]. Also the migriane sufferers have marked reduction in their functional abilities so they would be benefited from the acute treatment that help them to resume their functional abilities as quick as possible. The new generation anti-migraine drug, Rizatriptan benzoate is an orally active serotonin 5-HT1receptor agonist that potently and selectively binds to 5-HT1B/1D subtypes. Chemically it is *N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate. The initial gut absorption of Rizatriptan is high (90%); however, the compound undergoes moderate first-pass metabolism, which limits the bioavailability to 47% [9]. So orally fast dissolving sublingual films of Rizatriptan prevents its first-pass metabolism and eliminates the need of intake of water by the patient during the migraine attack and provide fast onset of action which would be beneficial to migraine sufferers in resuming their functional abilities as soon as possible.

MATERIALS AND METHODS

Rizatriptan benzoate was received as gift samples from SMS pharmaceuticals Ltd., Hyderabad, India. Hydroxypropyl methyl cellulose (E-15) was procured from The Dow chemicals, China. Maltodextrin, sodium starch glycolate and sodiumlaurylsulphate was obtained from Loba Chemie, Mumbai, India. Glycerine was obtained from Qualikems Fine Chem, Vadodara, India. Mannitol and aspartame was purchased from Central Drug House, New Delhi.

Drug polymer compatibility studies

Drug polymer compatibility studies were carried out using FTIR. The sample was dispersed in KBr powder and analyzed. Spectra were obtained by powder diffuse reflectance on a FT-IR spectrophotometer type FT-IR Shimadzu 8400S, Shimadzu Ltd, USA.

UV Spectrum Analysis of Rizatriptan Benzoate

The solution was scanned in the range of 200 to 400 nm to fix the maximum wave length and UV spectrum was obtained.

Standard plot of Rizatriptan Benzoate in pH 6.8 Phosphate buffer

The standard plot of Rizatriptan Benzoate was prepared in pH 6.8 phosphate buffer. 50 mg of drug was weighed accurately and dissolved in 50 ml of phosphate buffer. Appropriate dilutions were made with buffer to obtain test solutions ranging from 2 µg/ml to 8 µg/ml. The absorbance of the drug in the buffer was then measured on a double beam UV-visible spectrophotometer at λ_{max} of 226 nm against the respective blank.

Standard plot of Rizatriptan Benzoate in pH 7.4 Phosphate buffer

The standard plot of Rizatriptan Benzoate was prepared in pH 7.4 phosphate buffer. 50 mg of drug was weighed accurately and dissolved in 50 ml of phosphate buffer. Appropriate dilutions were made with buffer to obtain test solutions ranging from 1 µg/ml to 6 µg/ml. The absorbance of the drug in the buffer was measured on a double beam UV-visible spectrophotometer at λ_{max} of 226 nm against the respective blank.

Method of preparation of fast dissolving sublingual film of Rizatriptan Benzoate.

Fast-dissolving film of rizatriptan benzoate was prepared by the solvent-casting method [11]. Aqueous solution I was prepared by dissolving the polymer and glycerine in specific proportion-in distilled water and was allowed to stir for 4 hours and kept for 1 hour to remove all the air bubbles entrapped. Aqueous solution II was prepared by dissolving the rizatriptan benzoate, mannitol, and strawberry flavor in specific proportion, in distilled water. Both aqueous solutions I and II were mixed and stirred for 1 hour. Then the mixture solution was casted onto a plastic petri dish and it was dried in the oven at 50°C for 24 hour. The film was carefully removed from the petri dish, checked for any imperfections, and cut according to the size required for testing (square film: 2 cm length, 2 cm width). The samples were stored in a glass container maintained at a temperature of 30°±1°C and relative humidity 60±5% until further analysis.

EVALUATION

Thickness

The thickness of the patch was measured using digital Vernier Calliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the patch and average was taken and SD was calculated.

Weight variation

Four centimeter square of the film was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.

Folding endurance

Folding endurance was determined by repeated folding of the film at the same place till the strip breaks [10]. The number of times the film is folded without breaking was computed as the folding endurance value.

Tensile strength

Tensile testing was conducted using a texture analyzer AG/MC1 (Acquati, Italy), equipped with a 5 N load cell. The film was cut into 30 × 20 mm strips. Tensile tests were performed according to ASTM International Test Method for Thin Plastic Sheeting (D 882-02). Each test strip was placed in tensile grips on the texture analyzer. Initial grip separation was 20 mm and crosshead speed was 1 inch/min. The test was considered concluded when the film breaks. Tensile strength, was computed with help of load require to break the film and cross sectional area to evaluate tensile properties of the films. *Tensile strength* (TS) Tensile strength is the maximum stress applied to a point at which the film specimen breaks

and can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it was expressed in force per unit area (MPa) [12].

Tensile Strength = Force at break (N)/ Cross sectional area (mm^2)

Percentage elongation

For the determination of percentage elongation of the film formulations, the distance between the tensile grips of the tensile strength testing machine was measured before and after the fracture of the film. Then the percentage elongation of the films was computed with the help of the formula given below:-

$\%E = D_f - D_o/D_o \times 100$

Where:-

%E = Percentage elongation

D_o = Distance between the tensile grips before the fracture of the film.

D_f = Distance between the tensile grips after the fracture of the film

Surface pH

The surface pH of fast dissolving film was determined in order to investigate the possibility of any side effect in vivo. As an acidic or alkaline pH may cause irritation of the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral film was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film [13]. The procedure was performed in triplicate and average with standard deviation was reported.

Disintegration

In vitro disintegration time was determined visually in a petri dish containing 25 ml of pH 6.8 phosphate buffer with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

Drug Content

Drug content determination of the film was carried out by dissolving the film of 4 cm^2 in 100 ml of pH 6.8 phosphate buffer using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically at λ_{max} of 226 nm. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded.

***In-vitro* dissolution**

The dissolution study was carried out using USP Type I (Basket type) dissolution apparatus. The dissolution was carried out in 900 ml of pH 6.8 phosphate buffer maintained at 37 ± 0.5°C at 50 rpm. 10 ml aliquots of samples were taken at various time intervals which were replaced with same volume of fresh pH 6.8 phosphate buffer maintained at 37 ± 0.5°C. Rizatriptan Benzoate in the samples was then determined spectrophotometrically at λ_{max} of 226 nm. The results were expressed as mean of three determinations.

***Ex-vivo* permeation studies**

Ex vivo permeation studies through porcine oral mucosa (ventral surface of tongue) was carried out using the Franz diffusion cell of internal diameter of 2.5 cm. The buccal mucosa was excised and trimmed evenly from the sides, washed in isotonic phosphate buffer of pH 6.8 and used immediately. The membrane was stabilized before mounting to remove the soluble components. The mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with 15 ml of isotonic phosphate buffer of pH 7.4 which was maintained at 37± 0.2°C and hydrodynamics were maintained using magnetic stirrer. One film of dimension 2 cm × 2 cm was previously moistened

with a few drops of pH 6.8 phosphate buffer and placed in donor compartment. The donor compartment was filled with 1 ml of pH 6.8 phosphate buffer. 1 ml samples from receptor compartment were withdrawn at suitable time interval which was then replaced with 1 ml of pH 7.4 phosphate buffer [14]. The percentage of Rizatriptan Benzoate permeated was determined by measuring the absorbance in UV-Visible spectrophotometer at λ_{max} of 226 nm.

Stability study

Stability study was carried out at two different storage conditions, one was normal room conditions and other was 40°C/75% RH for 4 weeks. Each piece of the films of formulation F1 and F2 was packed in butter paper followed by aluminum foil and plastic tape. After 4 weeks, the films were evaluated for the physical appearance, surface pH, drug content and in vitro drug release.

RESULTS AND DISCUSSION

UV Spectrum Analysis of Rizatriptan Benzoate

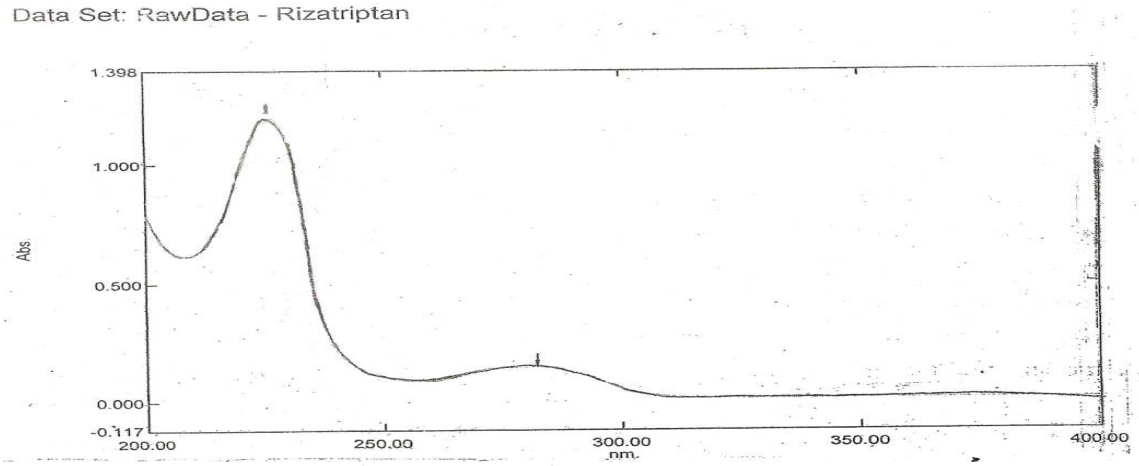

Figure 1: Scan of Rizatriptan Benzoate

Table 1: Standard curve of Rizatriptan Benzoate in pH 6.8 phosphate buffer at λ_{max} 226 nm

S. No	Concentration (µg/ml)	Absorbance
1	0	0.000
2	2	0.261±0.002
3	4	0.534±0.016
4	6	0.793±0.018
5	8	0.977±0.005

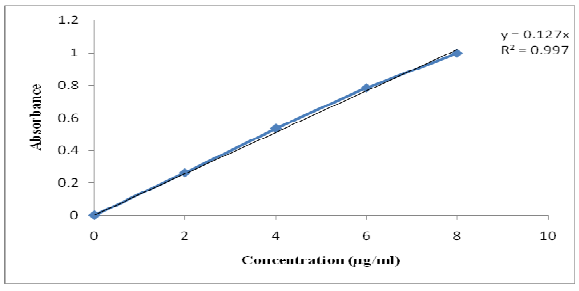

Figure 2: Standard curve of Rizatriptan Benzoate in pH 6.8 Phosphate Buffer

Table 2: Standard curve of Rizatriptan Benzoate in pH 7.4 phosphate buffer at λ_{max} 226 nm

S. No	Concentration µg/ml	Absorbance
1	0	0.000
2	1	0.168±0.041
3	2	0.314±0.063
4	3	0.448±0.018
5	4	0.570±0.005
6	5	0.718±0.007
7	6	0.850±0.011

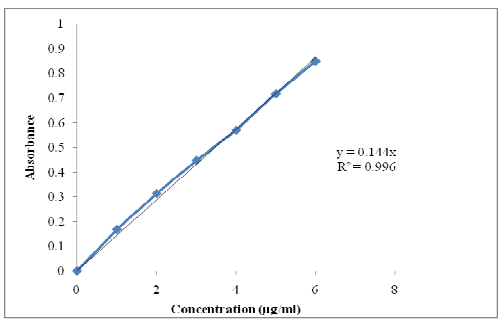

Figure 2: Standard curve of Rizatriptan Benzoate in pH 7.4 Phosphate Buffer

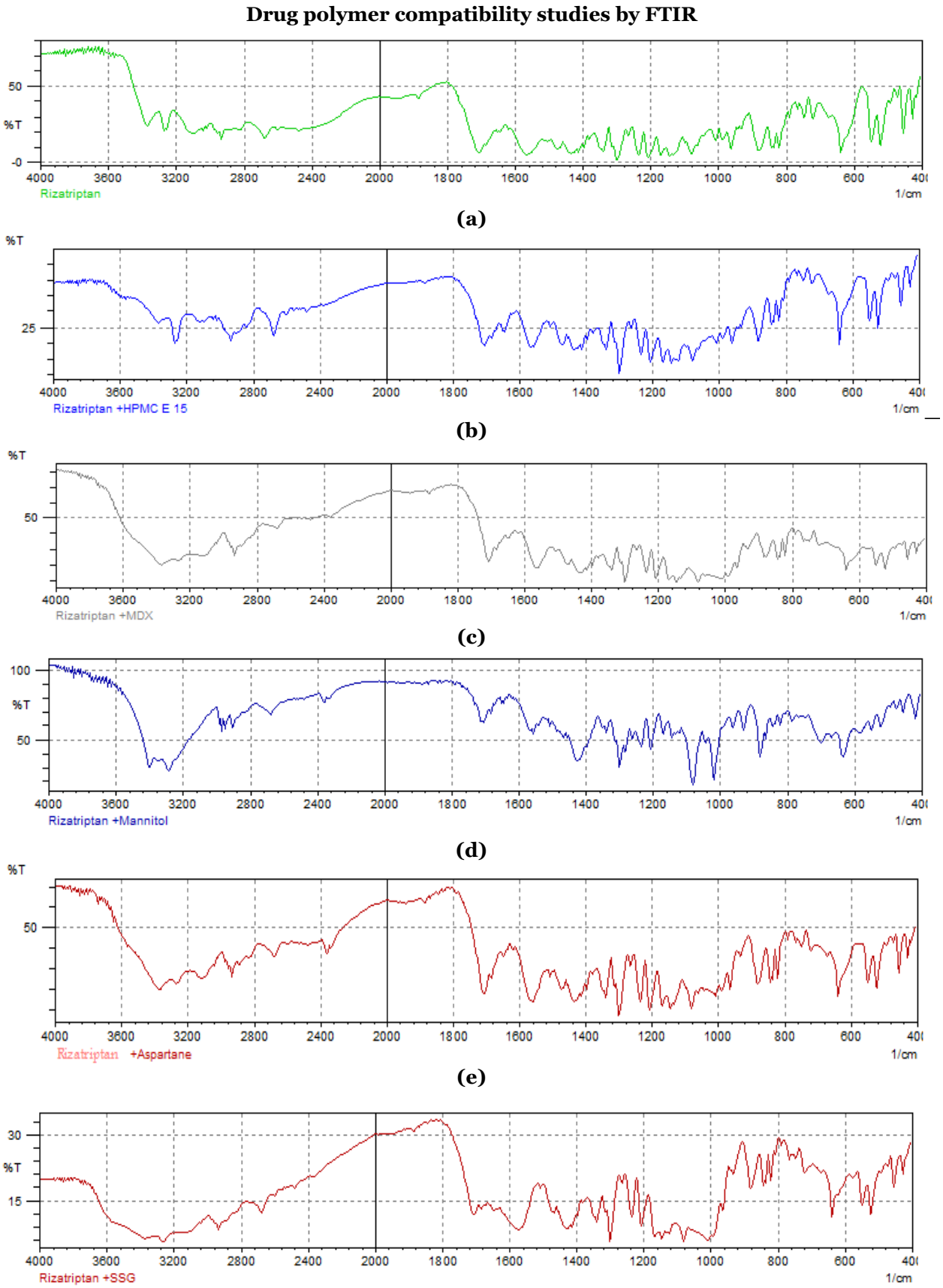

Figure 11: FTIR spectra of (a) Pure Rizatriptan Benzoate (b) Physical mixture of Rizatriptan Benzoate and HPMC E-15 (c) Physical mixture of Rizatriptan Benzoate and Maltodextrin (d) Physical mixture of Rizatriptan Benzoate and Mannitol (e) Physical mixture of Rizatriptan Benzoate and Aspartame (f) Physical mixture of Rizatriptan Benzoate and Sodium starch glycolate.

Table 3: Composition of Rizatriptan Benzoate fast dissolving films

Formulations	RTB (mg)	HPMC E-15 (mg)	MDX (mg)	GLY (mg)	SSG (mg)	SLS (mg)	MNT (mg)	ASP (mg)	Col. (ml)	Flv. (ml)	Water Upto (ml)
F1	7.265	15	20	5	1	0.5	5	2	0.05	0.05	q.s
F2	7.265	15	20	10	1	0.5	5	2	0.05	0.05	q.s
F3	7.265	20	20	5	1	0.5	5	2	0.05	0.05	q.s
F4	7.265	20	20	10	1	0.5	5	2	0.05	0.05	q.s
F5	7.265	25	20	5	1	0.5	5	2	0.05	0.05	q.s
F6	7.265	25	20	10	1	0.5	5	2	0.05	0.05	q.s
F7	7.265	30	20	5	1	0.5	5	2	0.05	0.05	q.s
F8	7.265	30	20	10	1	0.5	5	2	0.05	0.05	q.s

Table 4: Evaluation of physicomechanical parameters of fast dissolving film of rizatriptan benzoate

Formulation Code	Thickness (mm)	Weight (mg) per 4 cm^2	Tensile strength (MPa)	Percentage elongation	Folding endurance (no. of folds)
F1	0.05 ± 0.004	49.00 ± 1.000	1.82	5	145.3 ± 9.451
F2	0.06 ± 0.004	52.66 ± 0.577	1.53	5	195.0 ± 13.453
F3	0.08 ± 0.008	51.66 ± 0.577	2.95	5	171.3 ± 6.110
F4	0.08 ± 0.004	58.00 ± 1.000	2.71	10	185.3 ± 12.013
F5	0.10 ± 0.008	58.33 ± 0.577	3.55	10	142.6 ± 11.372
F6	0.10 ± 0.014	62.00 ± 1.000	3.10	15	183.6 ± 9.073
F7	0.13 ± 0.008	63.33 ± 0.577	4.01	10	155.3 ± 8.504
F8	0.15 ± 0.008	68.66 ± 0.577	3.85	20	184.6 ± 10.692

Table 5: Surface pH, disintegration time and drug content of fast dissolving films loaded with rizatriptan benzoate

Formulation Code	Surface pH of films	Disintegration time in Sec (Starts)	Drug content (%)
F1	6.67 ± 0.050	25.6 ± 1.154	93.6±1.040
F2	6.76 ± 0.078	29.3 ± 1.527	92.5±1.044
F3	6.81 ± 0.045	31.3 ± 2.309	93.6±0.700
F4	6.82 ± 0.036	28.6 ± 3.785	93.4±0.871
F5	6.74 ± 0.025	34.6 ± 3.511	93.9±0.360
F6	6.90 ± 0.030	33.3 ± 4.509	93.7±1.001
F7	6.82 ± 0.030	45.0 ± 3.000	94.6±0.700
F8	6.93 ± 0.015	49.3 ± 2.081	94.4±0.300

All values are mean of 3 readings ± standard deviation

Table 6: Comparative *in vitro* dissolution of formulations in pH 6.8 phosphate buffer

Time (min)	% Cumulative drug release ± S.D (n=3)							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	44.4±0.893	42.1±0.489	35.2±1.204	36.4±0.384	32.8±0.941	33.2±1.054	28.6±0.705	27.2±0.847
4	67.1±1.294	68.9±0.571	62.4±0.030	60.6±0.592	53.5±0.553	53.8±0.223	47.7±0.552	49.3±1.390
6	88.7±0.992	89.0±0.623	79.5±0.468	79.7±0.837	66.7±0.438	71.0±0.725	61.5±0.692	62.9±0.547
8	91.8±0.537	92.5±0.839	89.9±0.936	88.1±1.088	78.9±0.691	79.1±0.269	74.3±0.832	75.0±0.684
10	92.8±0.348	92.7±0.759	91.2±0.773	91.6±0.457	85.4±0.285	86.2±0.395	80.5±0.480	81.3±2.034
15	93.3±0.429	92.8±0.845	92.1±0.403	93.0±0.248	90.7±0.772	91.4±0.772	87.5±0.296	86.2±0.166
30	93.9±0.532	93.2±0.134	93.8±0.631	93.6±0.740	93.4±0.499	94.3±0.579	93.2±0.188	94.5±0.257

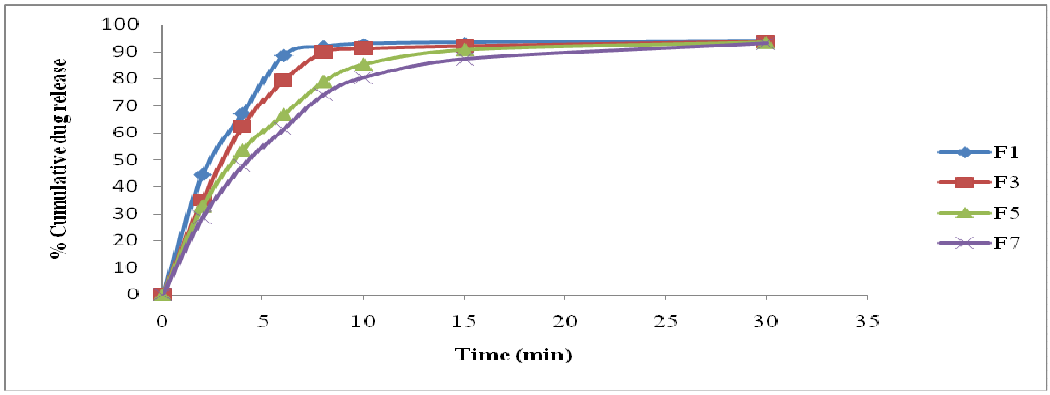

Figure 17: Plot of in vitro release of Rizatriptan Benzoate from the films containing 5 mg of glycerine

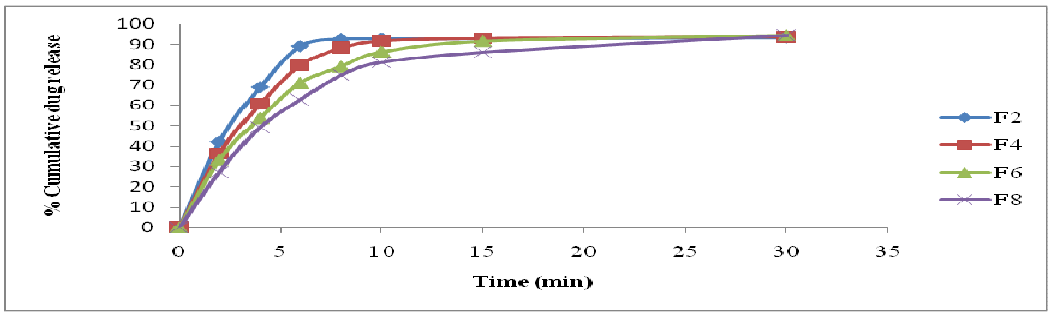

Figure 18: Plot of in vitro release of Rizatriptan Benzoate from the films containing 10 mg of glycerine

Table 7: Comparative *ex vivo* permeation of different formulations of fast dissolving films

Time (min)	% Drug permeated ± S.D (n=3)							
	F1A4	F1B4	F2A4	F2B4	F3A4	F3B4	F4A4	F4B4
0	0	0	0	0	0	0	0	0
2	3.3±0.204	3.0±0.276	1.8±0.533	2.7±0.760	2.9±0.441	3.0±0.745	1.9±0.612	1.8±0.195
4	7.5±0.489	7.0±0.765	5.4±1.381	4.9±0.921	5.2±0.755	4.4±0.299	2.7±0.504	2.0±0.865
6	16.9±1.250	15.9±0.990	10.2±1.095	8.5±0.974	7.8±1.023	9.1±0.536	5.1±0.941	4.3±1.107
8	28.7±2.096	25.9±0.625	17.1±2.507	16.6±1.93	12.8±0.997	11.9±0.847	7.6±1.079	8.5±1.479
10	39.1±0.853	36.7±1.430	26.7±1.466	27.1±2.224	19.3±1.702	20.7±1.548	12.9±2.110	11.7±1.546
12	47.6±0.554	48.3±2.142	34.9±0.596	35.3±2.180	25.7±3.221	28.3±0.825	19.2±1.047	19.5±0.877
14	55.2±0.863	58.4±1.538	43.6±0.914	43.9±0.839	33.5±1.692	34.6±0.491	25.4±2.721	25.9±1.231
16	61.2±0.371	64.5±0.801	51.7±0.758	50.7±1.631	40.3±0.759	40.4±2.056	31.7±1.866	33.0±0.822
18	66.8±0.509	69.0±1.573	55.5±2.356	57.5±1.097	45.6±2.733	47.0±2.638	36.7±1.324	37.5±2.476
20	71.0±1.029	72.9±0.836	59.4±1.431	60.9±1.543	49.7±1.317	48.5±1.504	42.5±0.945	40.6±1.349

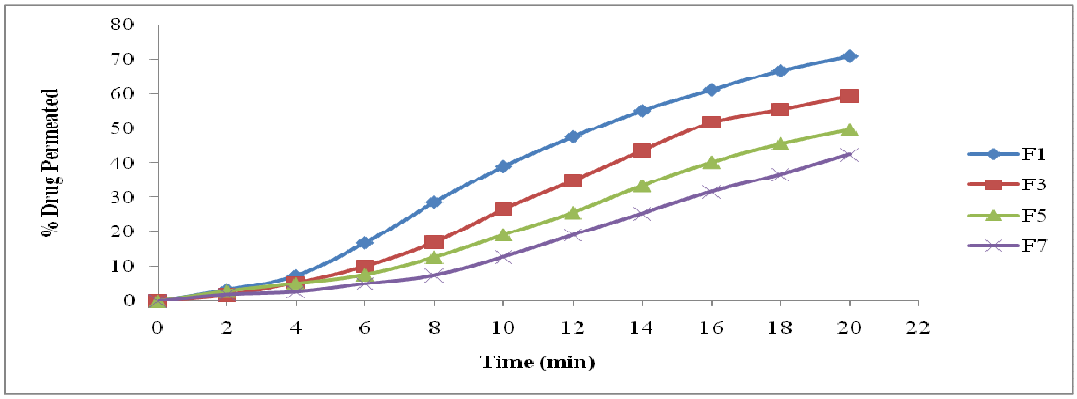

Figure 19: Plot of ex vivo permeation of Rizatriptan Benzoate from the films containing 5 mg of glycerine

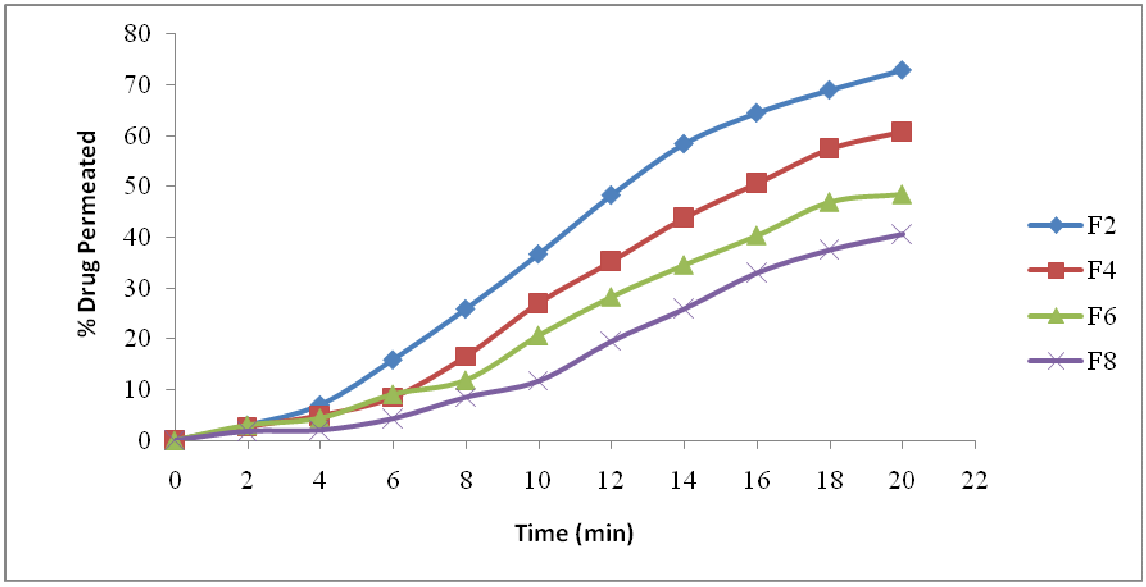

Figure 20: Plot of ex vivo permeation of Rizatriptan Benzoate from the films containing 10 mg of glycerine

DISCUSSION

Physical evaluation

1) Film thickness

As all the formulations contain different amount of polymers, hence the thickness was gradually increases with the amount of polymers. All the film formulations were found to have thickness in the range of 0.05 mm to 0.15 mm. The results are given in the table 4 shows gradual increase in the thickness.

2) Weight variations

Three films each of 4 cm^2 were cut at three different places from the casted film and weight variation was determined. Weight variation varies from 49.00 ± 1.000 to 68.66 ± 0.577 mg. The result of weight variation is shown in table 4.

Evaluation of mechanical properties

A suitable FDF requires moderate tensile strength, acceptable percentage elongation and folding endurance. Study of mechanical properties was undertaken for all the selected formulations. Table 4 shows the comparative mechanical properties of various formulations prepared during the study. The tensile strength was found to increase with increase with concentration of HPMC E-15 whereas the increase in the concentration of glycerine leads in the decrease in the tensile strength. The tensile strength of formulation F7 was found maximum 4.01. The percentage elongation of all the batches ranges from 5-20. It increased upon increasing the amount of plasticizer and polymer as shown by the formulations. Formulation F8 had highest percentage elongation. Folding endurance increases with increase in the concentration of glycerine. The number of time the film fold until it broke is reported in the table 4.

Surface pH

The surface pH of the films was ranging from 6.67 ± 0.050 to 6.93 ± 0.015 as shown in table 5. Since the surface pH of the films was found to be around the neutral pH, there will not be any kind of irritation to the mucosal lining of the oral cavity.

In vitro disintegration

It was observed that *in vitro* disintegration time varies from 25 to 50 sec for all the formulations. In *vitro* disintegration time of OFDFs containing HPMC E-15 and maltodextin as polymer was affected

by the thickness of the film. I*n vitro* disintegration time of the films was found to increased with increase in the amount of the polymer.

Determination of drug content of the films

The prepared film formulations were assayed for drug content. It was observed that all the formulations were satisfactory in uniformity of drug as given in table 5.

***In-Vitro* drug release tests**

The *in vitro* drug release profiles of the formulations in pH 6.8 phosphate buffer show differences depending on their composition as given in table 6. A rapid dissolution of all the film preparations was observed by the dissolution test, in which approximately 90% of Rizatriptan Benzoate dissolved within 15 min. The formulations F1 and F2 showed approximately 90% drug release within 6 minutes. It was also observed that HPMC E-15 was able to modulate the Rizatriptan release as higher amount of HPMC E-15 resulted in release of drug at slower rate.

***Ex-vivo* drug permeation**

Drug ex-vivo drug permeation it was found that the formulation F1 and F2 showed better drug permeation of 71.0% and 72.9% in 20 min respectively, when compared to other formulation as shown in table 7. The percentage amount of drug permeated was plotted against time to obtain permeation profile as shown in figure 19-20. It was observed that other film formulation took longer time probably due to higher content of HPMC E-15.

Stability study

The stability study of the formulation F1 and F2 was carried out at normal room conditions and 40°C/75% RH for a period of one month. The films does not show any change in appearance and flexibility. The drug content and surface pH was found almost constant for upto one month. The *in vitro* dissolution time of the films after the stability study was also not found to be affected.

CONCLUSION

The results of the present study indicated that HPMC E15 could be used as a film forming polymer for formulation of fast dissolving film containing rizatriptan benzoate. Acceptable mechanical properties were obtained for all the batches with *in-vitro* disintegration time of 30 s. On the basis of data obtained from *in-vitro* dissolution and *ex-vivo* permeation studies that F1 and F2 are promising formulation suitable for the immediate release of rizatriptan benzoate for the systemic use since they exhibited maximum drug release and permeation respectively. The formulation batch F1 and F2 was found to be stable for a period of one month at 40°C/75%RH.

REFERENCES

1) Arya A, Chandra A, Sharma V, Pathak K, Fast dissolving oral films: an innovative drug delivery system and dosage form. Int. J. ChemTech Res. 2010; 2: 576-583.
2) Dixit RP, Puthli SP, Oral strip technology: Overview and future potential. J. Controlled Release. 2000 139, 94-97.
3) Patel RA, Prajapati SD. Fast dissolving films (fdfs) as a newer venture in fast dissolving dosage forms. Int. J. Drug Dev. Res. 2010; 2: 232-246.
4) Dinge A, Nagarsenker M, Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity. AAPS PharmSciTech. 2008; 9: 51-58.
5) Hoogstraate AJ, Verhoef JC, Tuk B, Pijpers A. In-vivo buccal delivery of flourescein isothiocyanate-dextran 4400 with glycodeoxycholate as an absorption enhancer in pig. J Pharm Sci, 1996; 8: 457–460.
6) Keiko T, Yasuko O, Tsuneji N, Thorseinn L, Kozo T. Buccal absorption of ergotamine tartrate using the

bioadhesive tablet system in guinea-pigs. Int J Pharm. 2002; 238: 161– 170.

7) Antonaci F, Dumitrache C. A review of current European treatment guidelines for migraine. J Headache Pain. 2010 11, 13-19
8) Bartleson JD, Treatment of migraine headaches. Mayo Clin. Proc. 1999; 74: 702-708.
9) Vya P K, Halpin A R, Disposition and pharmacokinetics of the antimigraine drug rizatriptan in humans. Durg Metabol. Dispo. 1999; 28: 89-95.
10) Singh S, Gangwar S, Garg G, Garg V, Sharma P. Formulation and evaluation of rapidly disintegrating film of levocetrizine hydrochloride. Der. Pharmacia Lettre. 2010; 2: 434-439.
11) Bhyan BH, Jangra SA, Kaur MA, Singh HA. Orally fast dissolving films: innovations in formulation and technology. Int J Pharm Sci Rev & Res. 2011; 2: 50-57.
12) Han HJ, Floros DJ, Casting antimicrobial packaging films and measuring their physical properties and antimicrobial activity. J. Plastic Film and Sheeting. 18, 287-298.
13) Kunte S, Tandale P, Fast dissolving strips: a novel approach for the delivery of verapamil. J. Pharm. Bioallied Sci. 2011; 2: 325-328.
14) Koland M, Charyulu NR, Fast dissolving films of ondenstron hydrochloride: effect of additives on in vitro drug release and mucosal permeation. J. Young Pharma. 2010; 2: 216-222.