wjpmr, 2022, 8(1), 150 – 160.

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

SJIF Impact Factor: 5.922

Research Article

ISSN 2455-3301

WJPMR

FORMULATION, DEVELOPMENT AND EVALUATION OF FAST DISSOLVING ORAL FILM OF ANTI-MIGRAINE DRUG

[1]*Ramji Kurmi, [2]Dr. Kuldeep Ganju, [3]Devendra S. Lodhi and [4]Khushi Chouksey

[1]Sagar Institute of Pharmacy and Technology (SIPTec) Opposite International Airport Jaipur Road Gandhi Nagar Bhopal Madhya Pradesh India-462036.

[2]Professor and Principal, Sagar Institute of Pharmacy and Technology (SIPTec) Opposite International Airport Jaipur Road Gandhi Nagar Bhopal Madhya Pradesh India-462036.

[3,4]Asso. Professor Sagar Institute of Pharmacy and Technology (SIPTec) Opposite International Airport Jaipur Road Gandhi Nagar Bhopal Madhya Pradesh India-462036.

***Corresponding Author: Ramji Kurmi**

M. Pharm IV Sem, Sagar Institute of Pharmacy and Technology (SIPTec) Opposite International Airport Jaipur Road Gandhi Nagar Bhopal Madhya Pradesh India-462036.

Article Received on 25/10/2021 **Article Revised on 15/11/2021** **Article Accepted on 05/12/2021**

ABSTRACT

The fast-dissolving oral films of Rizatriptan benzoate prepared using different film- forming materials by the solvent-casting method which is simple and cost effective. Films showed satisfactory drug dissolution and acceptable physico-mechanical characteristics. Amongst all formulae, the formulation F7 showed the highest dissolution rate. F7 was concluded as optimized formulation because of it showed suitable and satisfactory physico-mechanical properties when compared with marketed formulation. Films were found to be stable at stability conditions. In the present work, it can be concluded that the fast-dissolving films formulation can be an innovative and promising approach for the delivery of Rizatriptan for the treatment of migraine.

KEYWORDS: Rizatriptan, Migraine, Solvent CastingMethod, Fast Dissolving oral film, Innovative approach, Dissolution.

1. INTRODUCTION

Migraine is a neurological syndrome characterized by altered body perceptions, severe headaches, and nausea. Physiologically, the migraine is a neurological condition, which is about three times more common to women than men.[1] Rizatriptan benzoate is known chemically as N, N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine monobenzoate binds to human 5-hydroxytryptamine 1B/1D receptor with high affinity and selectivity. Several clinical trials reveal the effectiveness of oral rizatriptan for the treatment of a migraine headache

The oral route is one of the most preferred routes of drug administration as it is more convenient, cost effective, and ease of administration lead to high level of patient compliance. The oral route is problematic because of the swallowing difficulty for pediatric and geriatric patients who have fear of choking. Patient convenience and compliance-oriented research has resulted in bringing out safer and newer drug delivery systems. Recently, fast dissolving drug delivery systems have started gaining popularity and acceptance as one such example with increased consumer choice, for the reason of rapid disintegration or dissolution, self-administration even without water or chewing. Fast dissolving drug delivery systems were first invented [Figures [Figures 11 and and 2] 2] in the late 1970s as to overcome swallowing difficulties associated with tablets and capsules for pediatric and geriatric patients. Buccal drug delivery has lately become an important route of drug administration. Various bioadhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches, and more recently the use of polymeric films for buccal delivery, also known as mouth dissolving films. The surface of buccal cavity comprises of stratified squamous epithelium which is essentially separated from the underlying tissue of lamina propria and submucosa by an undulating basement membrane.[1] It is interesting to note that the permeability of buccal mucosa is approximately 4-4,000 times greater than that of the skin, but less than that of the intestine.[2] Hence, the buccal delivery serves as an excellent platform for absorption of molecules that have poor dermal penetration.[3] The primary barrier to permeability in otiral mucosa is the result of intercellular material derived from the so-called 'membrane coating granules' present at the uppermost 200 μm layer.[4] These dosage forms have a shelf life of 2-3 years, depending on the active pharmaceutical ingredient but are extremely sensitive to environmental moisture.[5] An ideal fast

dissolving delivery system should have the following properties: High stability, transportability, ease of handling and administration, no special packaging material or processing requirements, no water necessary for application, and a pleasant taste. Therefore, they are very suitable for pediatric and geriatric patients; bedridden patients; or patients suffering from dysphagia, Parkinson's disease, mucositis, or vomiting. This novel drug delivery system can also be beneficial for meeting current needs of the industry. Rapidly dissolving films (RDF) were initially introduced in the market as breath fresheners and personal care products such as dental care strips and soap strips. However, these dosage forms are introduced in the United States and European pharmaceutical markets for therapeutic benefits. The first of the kind of oral strips (OS) were developed by the major pharmaceutical company Pfizer who named it as Listerine® pocket packs™ and were used for mouth freshening. Chloraseptic® relief strips were the first therapeutic oral thin films (OTF) which contained 7 benzocaine and were used for the treatment of sore throat. Formulation of fast dissolving buccal film involves material such as strip-forming polymers, plasticizers, active pharmaceutical ingredient, sweetening agents, saliva stimulating agent, flavoring agents, coloring agents, stabilizing and thickening agents, permeation enhancers, and superdisintegrants. All the excipients used in the formulation of fast dissolving film should be approved for use in oral pharmaceutical dosage forms as per regulatory perspectives.

CLASSIFICATION OF FAST DISSOLVING TECHNOLOGY

For ease of description, fast dissolve technologies can be divided in to three broad groups.
Lyophilized systems.
Compressed tablet-based systems.
OTF.

Lyophilized systems

This system has been by far the most successful among them in terms of sales value, sales volume, and number of worldwide product approvals. The technology around these systems involves taking a suspension or solution of drug with other structural excipients and, through the use of a mould or blister pack, forming tablet-shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units have a very high porosity, which allows rapid water or saliva penetration and very rapid disintegration. Dose handling capability for these systems differs depending on whether the active ingredients are soluble or insoluble drugs, with the dose capability being slightly lower for the former than for some tablet-based systems. The units are capable of incorporating a range of taste masked materials and have more rapid disintegration than tablet-based systems.

Compressed tablet-based systems

This system is produced using standard tablet technology by direct compression of excipients. Depending on the method of manufacture, the tablet technologies have different levels of hardness and friability. These results in varying disintegration performance and packaging needs, which can range from standard high-density polyethylene (HDPE) bottles or blisters through to more specialist's pack designs for product protection, for example, CIMA Labs, PackSolv. The speed of disintegration for fast dissolving tablets compared with a standard tablet is achieved by formulating using water soluble excipients, or superdisintegrate or effervescent components, to allow rapid penetration of water into the core of the tablet. The one exception to this approach for tablets is Biovail Fuisz Technology.[7] It uses the proprietary Shearform system to produce drug loaded candy floss, which is then used for tableting with other excipients. These systems can theoretically accommodate relatively high doses of drug material, including taste masked coated particles. The potential disadvantage is that they take longer to disintegrate than the thin film or lyophilized dosage forms. The loose compression tablet approach has increasingly been used by some technology houses, branded companies, and generic pharmaceutical companies, for inhouse development of line extension and generic fast dissolving dosage forms.

OTF

Oral films, also called oral wafers in the related literature, are a group of flat films which are administered into the oral cavity. Although oral film systems, the third class, have been in existence for a number of years, they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery. Dissolvable OTF or OS have evolved over the past few years from confection and oral care markets in the form of breath strips and become a novel and widely accepted form by consumers for delivering vitamins and personal care products. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug delivery capitalized on the opportunity to transition this technology to OTF formats. Today, OTF are a proven and accepted technology for systemic delivery of APIs for over-the-counter (OTC) medications and are in the early- to mid-development stages for prescription drugs.

Feautres

- Ilm should be thin and elegant.
- Available in various size and shapes.
- Unobstructive.
- It should adhere to the oral cavity easily.
- Should processes fast disintegration without water.
- Rapid release.

Advantages

- Convenient dosing.
- No water needed.

- No risk of chocking.
- Taste masking.
- Enhanced stability.
- Improved patient compliance.
- The drug enters the systemic circulation with reduced hepatic first pass effect.
- Site specific and local action.
- Availability of large surface area that leads to rapid disintegration and dissolution within oral cavity.
- Dose accuracy in comparison to syrup.

Ideal Characteristics

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose up to 40 mg.
- The drug should have smaller and moderate molecular weight.
- The drug should have good stability and solubility in water as well as saliva.
- It should be partially unionized at the pH of oral cavity.
- It should have ability to permeate the oral mucosal tissue.

2. AIM AND OBJECTIVES

- In general, a migraine is a very bad headache that tends to come back. It may occur as often as several times a week or only once every few years. It can last anywhere from a few hours to 3 days.
- The pain usually begins in the morning, on one side of the head. Headache is a painful and common symptom.
- A number of primary headache disorders have been characterized, including tension-type headache, migraine and cluster headache, and overall these disorders account for approximately 95% of all headache complaints.
- Rizatriptan is a triptan drug used for the treatment of migraine headaches. It is a selective 5-hydroxytryptamine1 receptor subtype agonist.
- Mouth dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application.
- It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed. In contrast to other existing, rapid dissolving dosage forms, which consist of liophylisates, the rapid films can be produced with a manufacturing process that is competitive with the manufacturing costs of conventional tablets.
- The objective of present study is to develop oral films of Rizatriptan using different types of super disintegrants to enhance the disintegration and dissolution of Rizatriptan to improve bioavailability of the drug.

3. MATERIAL AND METHODS

Rizatriptan

Rizatriptan is a triptan drug used for the treatment of migraine headaches. It is a selective 5-hydroxytryptamine1 receptor subtype agonist.

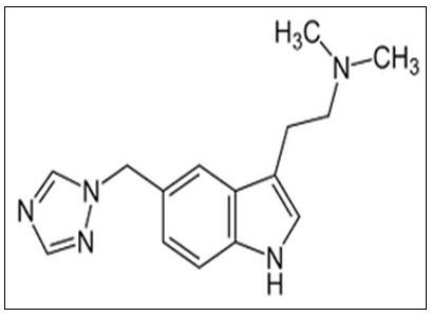

Figure 1: Structure of Rizatriptan.

Mol. Weight: 269.3449
Chemical Formula: $C_{15}H_{19}N_5$
IUPAC Name: Dimethyl ({2-[5-(1H-1, 2, 4-triazol-1-ylmethyl)-1H-indol-3-yl] ethyl}) amine.

PHARMACOLOGY

Indication: For treatment of acute migraine attacks with or without aura.

Pharmacodynamics: Rizatriptan is a selective agonist of serotonin (5-hydroxytryptamine; 5-HT) type 1B and 1D receptors. It is structurally and pharmacologically related to other selective 5-HT1B/1D receptor agonists and has only a weak affinity for 5-HT_{1A}, 5-HT_{5A}, and 5-HT_7 receptors and no significant affinity or pharmacological activity at 5-HT_2, 5-HT_3 or 5-HT_4 receptor subtypes or at alpha1-, alpha2-, or beta-adrenergic, dopamine1,; dopamine2; muscarinic, or benzodiazepine receptors. This action in humans correlates with the relief of migraine headache. In addition to causing vasoconstriction, experimental data from animal studies show that Rizatriptan also activates 5-HT_1 receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels, which may also contribute to the antimigrainous effect of Rizatriptan in humans.

Mechanism of action: Three distinct pharmacological actions have been implicated in the antimigraine effect of the triptans: (1) stimulation of presynaptic 5-HT1D receptors, which serves to inhibit both dural vasodilation and inflammation; (2) direct inhibition of trigeminal nuclei cell excitability via 5-HT1B/1D receptor agonism in the brainstem and (3) vasoconstriction of meningeal, dural, cerebral or pial vessels as a result of vascular 5-HT1B receptor agonism.

Absorption: Rapid following oral administration. Bioavailability is 45%. Food has no effect on the bioavailability of rizatriptan. However, administering rizatriptan with food will delay by 1 hour the time to reach peak plasma concentration. The rate of absorption is not affected by the presence of a migraine attack.

Protein binding: 14%
Metabolism: Rizatriptan is metabolized by monoamine oxidase A isoenzyme (MAO-A) to an inactive indole acetic acid metabolite. In addition, several other inactive metabolites are formed. An active metabolite, N-monodesmethyl-rizatriptan, with pharmacological activity similar to that of the parent compound has been identified in small concentrations (14%) in the plasma.

Route of elimination: Approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism.

Half life: 2-3 hours.

Toxicity: Symptoms of overdose include dizziness, fainting, heart and blood vessel problems, high blood pressure, loss of bowel and bladder control, slow heartbeat, and vomiting.

Uses: Rizatriptan is used to treat migraines. It helps to relieve headache, pain, and other migraine symptoms (including nausea, vomiting, and sensitivity to light/sound). Prompt treatment helps you return to your normal routine and may decrease your need for other pain medications.

Side effect

- Sudden and severe stomach pain and bloody diarrhea;
- Cold feeling or numbness in your feet and hands;
- Heart attack symptoms--chest pain or pressure, pain spreading to your jaw or shoulder, nausea, sweating;
- High levels of serotonin in the body--agitation, hallucinations, fever, fast heart rate, overactive reflexes, nausea, vomiting, diarrhea, loss of coordination, fainting;
- Signs of a stroke--sudden numbness or weakness (especially on one side of the body), sudden severe headache, slurred speech, problems with vision or balance; or
- Dangerously high blood pressure--severe headache, blurred vision, buzzing in your ears, anxiety, confusion, chest pain, shortness of breath, uneven heartbeats, seizure.
- Dizziness, drowsiness, tired feeling; or
- Pain or a feeling of pressure in your throat or chest.

Preformulation characteristics
The following properties of active pharmaceutical ingredients (API) were investigated;

- Organoleptic properties
- Solubility Analysis
- Loss on drying
- Melting point
- UV Spectrophotometric analysis
- FTIR spectroscopy

Organoleptic properties
Organoleptic properties of the drug substance are very important for designing the dosage form. The colour, odour and tests of the drug are characterized**.**

Table 1: Organoleptic characteristics of Rizatriptan.

S. No.	Properties studied	Results
1.	Colour	White to Off-White
2.	Odour	Odorless
3.	Taste	Very Bitter
4.	Appearance/Morphology	Crystalline

Solubility Analysis
An important Physical-chemical property of a drug substance is solubility, especially aqueous solubility.[35] A drug must possess some aqueous solubility for therapeutic efficacy in the physiological pH range of 1 to 8.

For the determination of solubility of Rizatriptan in various solvents that were methanol, ethanol, chloroform and distilled water etc. 5mg of Rizatriptan was added to 10 ml of each solvent in a test tube and shaken for few minutes at room temperature (21.0 ± 1.5°C).

Table 2: Solubility determination of Rizatriptan in various solvent.

Solvents	Results of Solubility
Methanol	Soluble
Ethanol	Soluble
Chloroform	Soluble
Distilled water	Sparingly soluble
6.8 pH phosphate buffer	Soluble
0.1 N HCl	Soluble
0.1 N NaOH	Sparingly soluble

It has been observed that Rizatriptan was soluble in methanol, ethanol, chloroform, 6.8 pH phosphate buffer and 0.1 N HCl, sparingly soluble in distilled water, 0.1 N and NaOH.

Loss on drying (%)
Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified conditions.[36] Loss on drying is directly measured by IR moisture balance. Firstly calibrated the instrument by knob, then taken 5 gram of sample (powder) and fixed the temperature at 100°C to 105°C for 15 minutes and constant reading, and fixed the knob and check percent moisture.

$$\text{Loss on drying (\%)} = \frac{\text{initial weight of sample - weight of sample after drying x 100}}{\text{Initial weight of sample}}$$

Results: Results of Loss on drying of Rizatriptan was found 0.247±0.002%.

Melting point

Melting point of Rizatriptan was determined using open capillary method by melting point apparatus. Fine powder of the drug was filled in glass capillary tube which was sealed at one end. The capillary tube was tied to the thermometer and thermometer was kept in theils tube apparatus and then slowly increased the temperature of the apparatus and recorded the temperature at which drug was completely melted. The observed melting point of the drug was compared with melting point given in literature.

Results: The Rizatriptan was melted at 177-178°C, which is identical to the melting point of pure Rizatriptan as stated in USP.

Determination of UV-visible absorption maxima of Rizatriptan

Preparation of standard solutions

A standard stock solution of Rizatriptan was prepared by dissolving 10 mg (accurately weighed) of the standard Rizatriptan in 10 ml of 6.8 pH phosphate buffer. This stock solution was further diluted to get working standard solutions of 10µg/ml. Aliquots (0.1, 02, 0.3.....1.0 ml) of working standard solution were transferred into a series of 10 ml volumetric flasks to get the desired concentration range for calibration curve. The volumes were made up with 6.8 pH phosphate buffer solution.

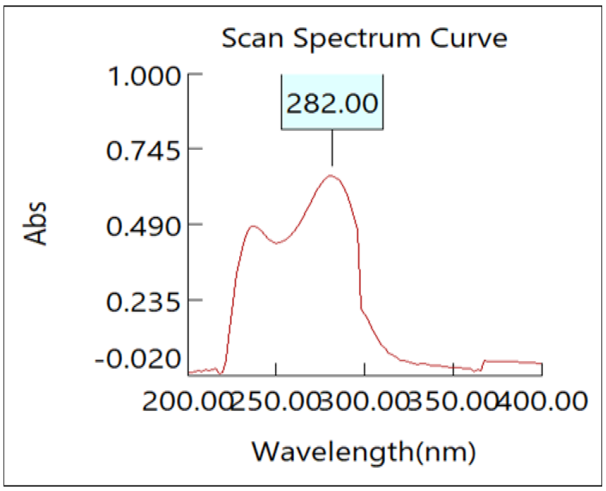

Figure 1: Determination of λ_{max} of Rizatriptan.

Table 3: Calibration curve of Rizatriptan.

S. No.	Concentration (µg/ml)	Absorbance
1.	10	0.228
2.	20	0.454
3.	30	0.685
4.	40	0.904
5.	50	1.098

All values are expressed in S.D (n=3)

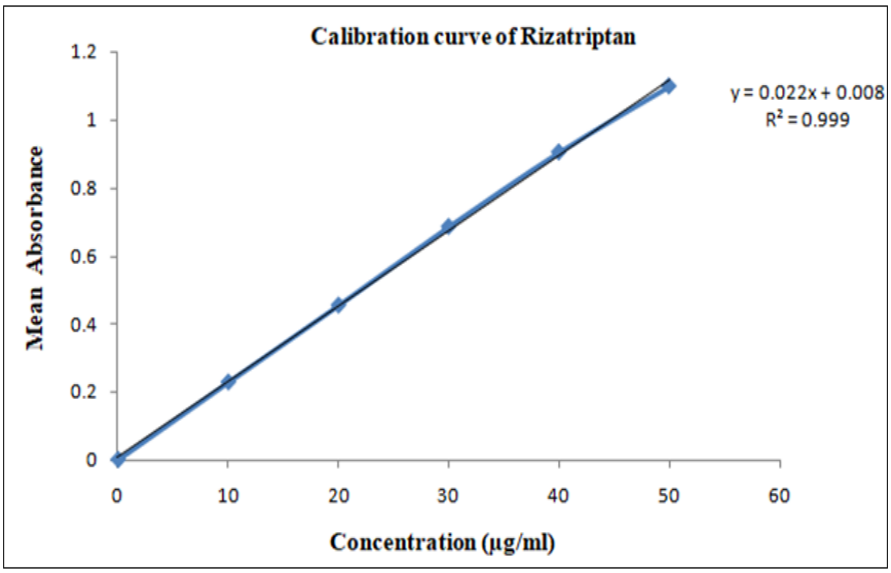

Figure 2: Calibration curve of Rizatriptan.

FTIR spectroscopy of Rizatriptan

The purity of pure drug was determined by I.R. approximately 10 mg of Rizatriptan was triturated with 100 mg of dried potassium bromide (KBr) in agatte mortar. Pellet was prepared by using KBr press pellet method. Pellet was scanned between the ranges of 400 to 2000 cm^{-1} with background correction. The spectrum was recorded and major peaks were determined.

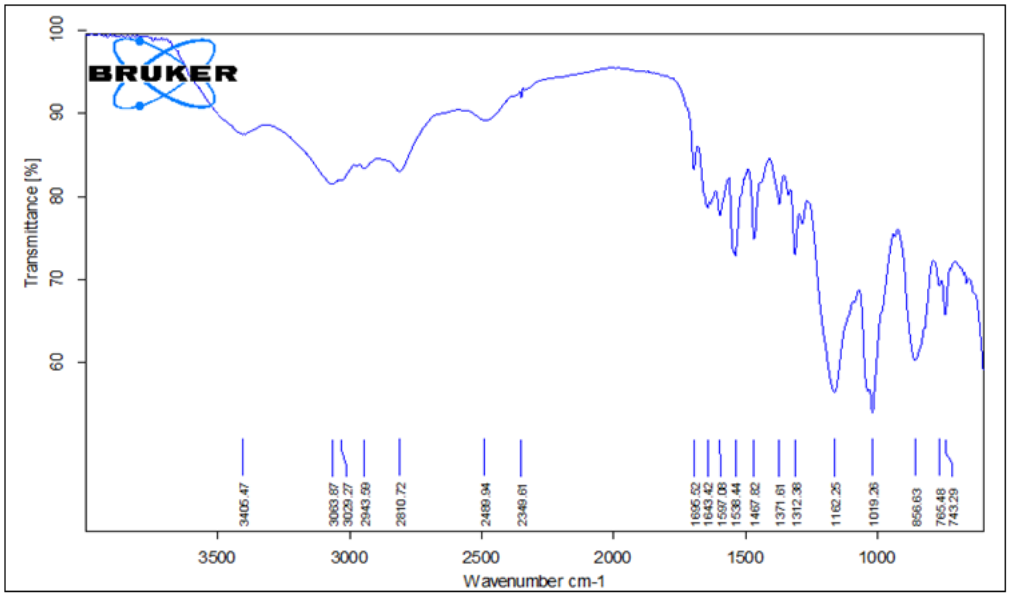

Figure 3: FTIR spectra of Rizatriptan.

PREPARATION AND CHARACTERIZATION

Formulation development of oral film of Rizatriptan

Casting process of fast disintegrating oral film Various methods are available for casting of oral films. This is fast disintegrating oral film hence on the laboratory scale solvent casting technique was adopted for formulation of films.

Solvent casting technique

Drug (Rizatriptan) containing fast dissolving films were fabricated by the solvent casting method. HPMC is known for its good film forming properties and has excellent acceptability.[37] Hence, various grades of HPMC namely HPMC K4, and HPMC K15 were evaluated as film formers. For the fabrication of films, glycerin was used as a humectant. PEG 400 is also reported as lubricant and solubilizer. Therefore PEG 400 along with glycerol was also used for fabrication of films. Apart from these film formers, SSG (Sodium starch glycolate), CP (Crospovidone) and CCS (croscarmellose sodium) alone or in combination with each other along with other excipients were tried. Citric acid for saliva stimulating agent and mannitol as sweeteners used to fabricate the films. The composition of various formulations is given in Table **1.** The polymer was soaked in water for 30 min or heated in water bath to 80°C to get a clear solution. Then a plasticizer was added to it and mixed so as to get homogeneous solution. This solution was then casted onto glass moulds (15*5cm) and was dried in hot air oven at 45° for 24 h.

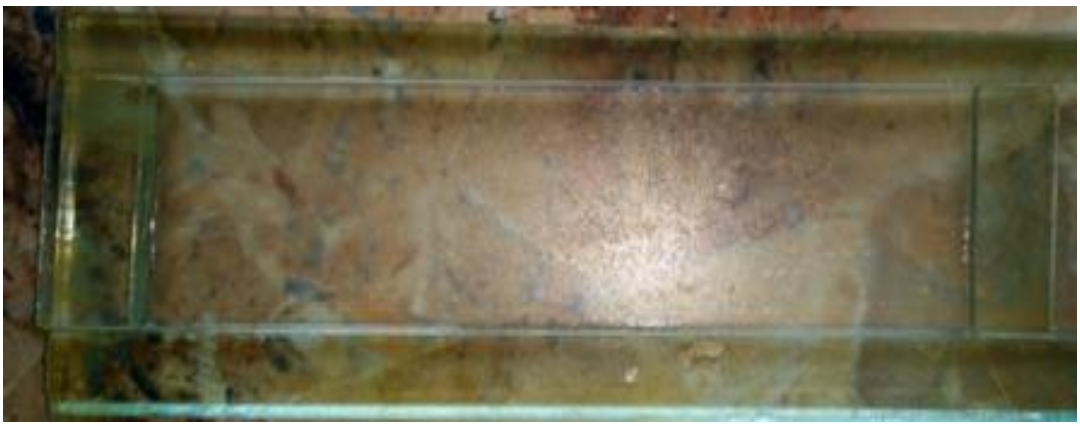

Figure 4: Prepared fast disintegrating oral film.

Parameter Selection for formulation of oral film

1. Size of Film

Size of Film is about 2.5 x 2.5 cm, to provide sufficient space for dissolving in oral cavity by putting film on tongue for swishing or hydrating with saliva, size 2.5 x 2.5 cm were concluded as unit dose of Film.

2. Fabrication of film casting glass reservoir

Film casting glass reservoir is most important glassware which was fabricated keeping view the following aspect:

1. No. of films in one batch
2. Holding capacity of formulation solution for drying
3. Scrapping-off films from film casting glass reservoir

4. Easy to positioned horizontally with gravity for uniform formation of film A 15.0 x 5.0 cm sized film casting glass reservoir was fabricated having depth of 0.5cm. This sized Film casting glass reservoir will produce twelve 2.5 x 2.5 cm.

3. Amount of solution for formulation

An about 30 ml solution was calculated for further study, because this will produce 200 micrometer depth for solvent evaporation and sufficient numbers of films for further evaluations.

4. Temperature and time of drying

Preliminary study suggests that 45±1ºC degree centigrade for 12 hrs adequately dry the film.

5. Speed of mixing at magnet stirrer.200±10 rpm speed for first 30 minutes were optimized for entire study and minutes for all ingredients with same speed were finalized.

Selection and optimization of film forming agents

Different film forming agents and one co-film forming (Table 4) were selected for this research work. The concentration of film forming was important to form a proper thickness for appropriate packaging and handling of oral films. Concentration of film forming agent is optimized on the basis of thickness and appearance of film.

A) Optimization of formulations

Table 4: Selection and optimization of film forming agents.

Name of ingredients (mg) (mg for 12 strips)	F1	F2	F3	F4	F5	F6	F7	F8	F8
Rizatriptan	120	120	120	120	120	120	120	120	120
HPMC K4	100	200	300				50	100	150
HPMC K15				100	200	300	50	100	150
PEG-400	25	25	25	25	25	25	25	25	25
SSG	50	100		-	-	-	25		25
CCS	-	-	50	100	-	-	25	25	
CP	-	-	-	-	-	-	-	25	25
Mannitol	20	20	20	20	20	20	20	20	20
Citric acid	20	20	20	20	20	20	20	20	20
DM water qs to (ml)	30	30	30	30	30	30	30	30	30

Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm^2 films present whole plate = 12
- Each film contains 10 mg of drug.
- 12 no. of films contains mg of drug = 10×12 = 120mg
- The amount of Rizatriptan added in each plate was approximately equal to 600mg.
- **Evaluation of prepared Film**

Thickness

The thickness of patches was measured at three different places using a vernier caliper.[38]

Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated.[39]

Folding Endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance.[40]

Table 5: Evaluation of prepared film for General Appearance, Thickness and weight.

Formulation code	General Appearance	Thickness* (µm)	Weight* (mg)
F1	Transparent	45±2	55±2
F2	Transparent	48±1	62±5
F3	Transparent	49±3	73±3
F4	Transparent	47±5	59±7
F5	Transparent	49±3	65±2
F6	Transparent	52±3	75±4
F7	Transparent	50±4	65±3
F8	Transparent	52±2	72±2
F9	Transparent	55±4	80±3

*Average of three determination (n=3±SD)

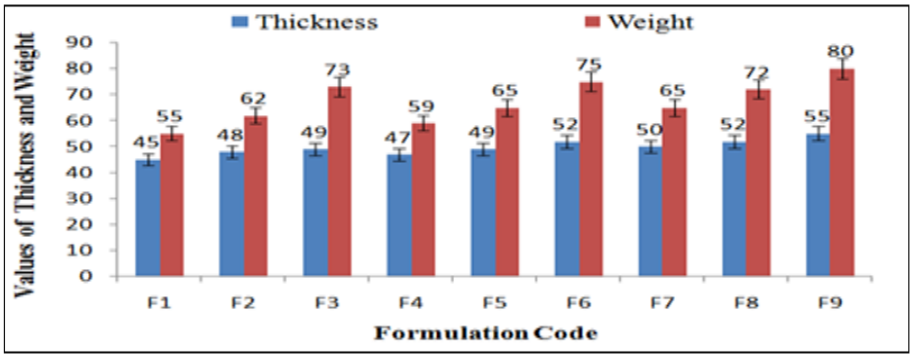

Figure 5: Characterization of prepared fast dissolving oral film (Thickness & Weight).

Percentage of Moisture Content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.[41]

Drug Content Analysis

The film taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and reacted by UV spectrophotometer at 282nm.[42]

Disintegrating time

The most important criteria of present work is that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent was done to minimize the disintegrating time. Three super disintegrating agent (Sodium starch Glycolate, Crospovidone and Croscarmellose Sodium) were selected for this work.[43]

Table 6: Result of Folding Endurance, Disintegrating time, Tensile strength, Percentage Moisture Content and % Assay.

Formulation code	Folding endurance (Times)	Disintegrating time (Sec.)	Tensile strength in kg/cm^2	Percentage of Moisture Content	% Assay
F1	133±4	22±5	0.856±0.001	8.56±0.45	96.65±0.65
F2	126±5	18±6	0.812±0.002	8.32±0.32	97.85±0.48
F3	145±4	15±4	0.785±0.005	8.74±0.48	98.12±0.52
F4	149±6	17±2	0.812±0.001	9.23±0.65	98.65±0.32
F5	142±7	15±5	0.785±0.004	9.45±0.47	97.75±0.41
F6	148±5	10±4	0.658±0.006	9.65±0.35	96.85±0.78
F7	147±4	12±7	0.782±0.004	6.65±0.45	98.74±0.95
F8	185±3	9±8	0.812±0.005	5.41±0.36	99.45±0.41
F9	149±5	11±3	0.855±0.006	7.52±0.41	99.12±0.32

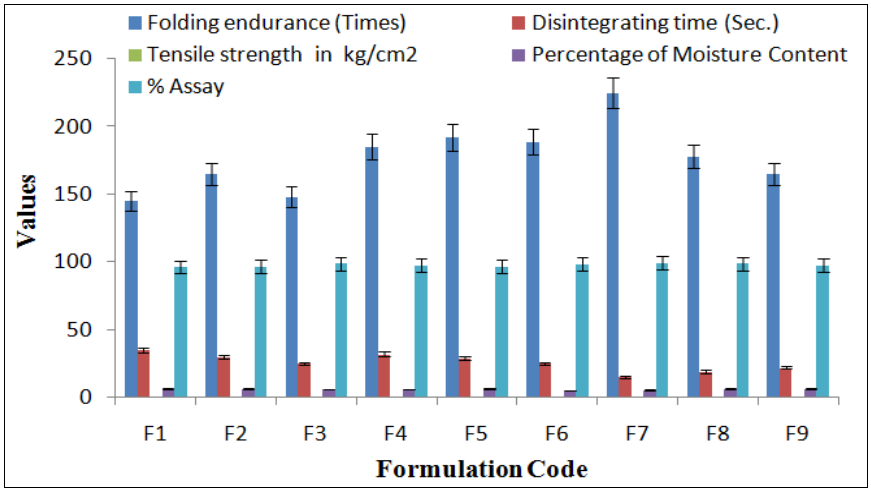

Figure 6: Graph folding endurance, disintegrating time, tensile strength, percentage moisture content and % assay.

RESULTS OF OPTIMIZED FORMULATION

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent to minimizes the disintegrating time**.**

Table 7: Results of Optimized formulation F7.

Name of Ingredients	Composition (mg) Per Strip
Rizatriptan	120
HPMC K4	50
HPMC K15	50
PEG-400	25
SSG	25
CCS	25
CP	-
Mannitol	20
Citric acid	20
DM water qs to (ml)	30

In vitro dissolution study

The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at 37±0.5°C with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Film size required for dose delivery (2.5×2.5 cm^2) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 4, 6, 8, and 10 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved drug was determined using UV-Visible spectrophotometer at 282nm. The results were presented as an average of three such concentrations.

Table 8: *In-vitro* drug release study of Formulation F1-F9.

Time (min.)	Cumulative % Drug release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	Marketed Formulation (Eizact 10mg)
1	25.65	23.32	28.89	24.45	29.98	33.32	42.45	39.98	33.25	12.23
2	43.32	40.56	53.32	45.56	52.23	55.45	65.56	55.56	46.65	23.32
4	52.32	53.32	62.23	53.32	65.56	69.98	88.89	78.89	69.98	45.56
6	65.56	67.78	75.56	69.98	75.65	79.98	95.56	88.45	85.56	52.32
8	78.89	75.65	83.32	79.98	82.23	85.56	99.89	93.36	92.23	65.58
10	83.32	79.89	89.98	93.32	94.45	95.65	99.85	97.78	96.65	73.12

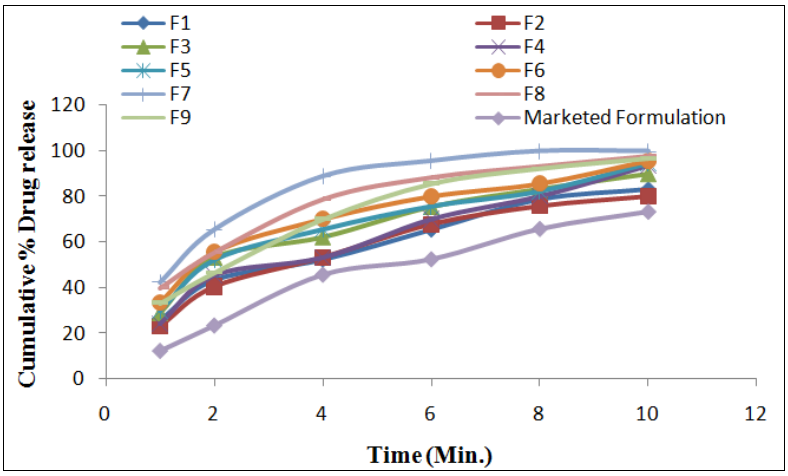

Figure 7: *In-vitro* drug release study of Formulation F1-F9.

Table 8: Results of *in-vitro* release kinetics of optimized formulation F7.

Time (min.)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1.000	0.000	42.45	1.552	64.35	1.809
2	1.414	0.301	65.56	1.770	41.11	1.614
4	2.000	0.602	88.89	1.865	26.68	1.426
6	2.449	0.778	95.56	1.954	10.02	1.001
8	2.828	0.903	99.89	1.976	5.35	0.728
10	**3.162**	**1.000**	**99.85**	**1.996**	**0.88**	**-0.056**

SUMMARY AND CONCLUSION

Drug (Rizatriptan) containing fast dissolving films were fabricated by the solvent casting method. HPMC is known for its good film forming properties and has excellent acceptability. Hence, various grades of HPMC namely HPMC K4, and HPMC K15 were evaluated as film formers. For the fabrication of films, glycerin was used as a humectant. PEG 400 is also reported as lubricant and solubilizer. 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 formulations F1, F2, F3, F4, F5, & F6 show drug release up to 83.32-95.65% at the end of 10min. Rapid drug dissolutions were observed in F7, which release 99.85% respectively. The optimized formulation (F7) shows highest percent of drug release at the end of 10 min. The initial release of the optimized formulation was more (42.45%) when compared with innovator product, therefore the onset of action was very quick compare with the innovator product. *In vitro* release rate study of optimized formulation Vs conventional marketed tablet has shown that F7 release was found to be faster and complete within 8 min. In vitro release of Marketed Product was found to be 73.12 in 10 min. The *In vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equsation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r^2' values of Peppas model was maximum i.e 0.924 hence indicating drug release from formulations was found to follow Peppas model release kinetics. Stability studies were carried out with optimized formulation F7 which was stored for a period of one, two and three months at 40±2^{o}C temperature and 75±5% relative humidity for a period 3 months. The% Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of film was found to slightly decrease at higher temperature. Minor difference was found between evaluated parameters before and after ageing/storage and all was in acceptable limits. Therefore formulation remains stable for sufficient time. The fast-dissolving oral films of Rizatriptan benzoate prepared using different film-forming materials by the solvent-casting method which is simple and cost effective. Films showed satisfactory drug dissolution and acceptable physico-mechanical characteristics. Amongst all formulae, the formulation F7 showed the highest dissolution rate. F7 was concluded as optimized formulation because of it showed suitable and satisfactory physico-mechanical properties when compared with marketed formulation. Films were found to be stable at stability conditions. In the present work, it can be concluded that the fast dissolving films formulation can be an innovative and promising approach for the delivery of Rizatriptan for the treatment of migraine.

REFERENCES

1. Honey Goel, Parshuram Rai, Vikas Rana, and Ashok K. Tiwary. Orally Disintegrating Systems: Innovations In Formulation And Technology. Recent Patents On Drug Delivery & Formulation, 2008; 2: 258-274.
2. Arun Arya, Amrish Chandra, Vijay Sharma And Kamla Pathak.Fast Dissolving Oral Films: An Innovative Drug Delivery System And Dosage Form, International Journal of Chem tech Research, Jan-Mar, 2010; 2: 576-583.
3. Thakur Smriti, Mouth Dissolving Films: A Review, International Journal Of Pharma And Bio Sciences, Januwary, 2013; 4(1): 899-908.
4. Bhyan B, Jangra S, Kaur M, Singh H. Orally Fast Dissolving Films: Innovations In Formulation And Technology. Int J Pharm Sci Rev Res., 2011; 9: 506.
5. Bhura N, Sanghivi K, Patel U, Parmar B. A Review On Fast Dissolving Film. Int J Res Bio Sci., 2012; 3: 66-9.
6. Aggarwal J., Singh G., Saini S., Rana A. C.Fast Dissolving Films: A Novel Approach To Oral Drug Delivery. Int. Res. J. Of Pharm, 2011; 2(12): 69-74.
7. Mahajan A., Chhabra N., Aggarwal G. A Formulation and Characterization Of Fast Dissolving Buccal Films: A Review. Scholars Res. Library Der Pharmacia Lettre., 2011; 3(1): 152-165l.
8. Arya A., Chandra A., Sharma V., Pathak K. Fast Dissolving Oral Films: An Innovative Drug Delivery System And Dosage Form. Int. J. Of Chemtech. Res., 2010; 2(1): 576-583.
9. Soni MM, Patel KR. Formulation and evaluation of fast dissolving film of lurasidone Hcl. Int. J. Pharm. Res. Bio.Sci., 2016; 5(2): 101-123.
10. Pathan A, Gupta MK, Jain NK, Dubey A, Agarwal A. Formulation and evaluation of fast dissolving oral film of promethazine hydrochloride using different surfactant. J. Innov. Pharm. Bio.Sci., 2016; 3(1): 74-84.
11. Nair SS, Padamanabhan R, Sreena K.Development and Evaluation of fast dissolving oral thin film containing prochlorperazine maleate. Eur. J. Pharm. Medical Res., 2016; 3(1): 379-384.
12. Newton AMJ, Rani SM, Sukhjinder K. Fabrication and evaluation of fast disintegrating oral hybrid films of propranolol hydrochloride by using pectin and synthetic polymers. J. Dev.Drugs., 2016; 5(2): 157.
13. Reddy S, Devi S, Naik V, Mounica NVN, Rao AA. Formulation and evaluation of fast dissolving buccal films conaining zolmitriptan. Int.J.Pharm. chem. Res., 2016; 1(1): 129-140.
14. Patil JS, Deokar AB, Vilegave KV, Morani DO, Dhadde SB. Design, evaluation and characterization of rapidly dissolving oral strips of metoprolol succinate. J. Pharm. Analy. Insights, 2016; 1(2): 1-6.
15. Haque SE, Sheela A. Development of polymer-bound fast-dissolving metformin buccal film with disintegrants. Int. J. Nanomedicine, 2015; 10(1): 199-205.

16. Thakur S, Raju L, Soni A, Agnihotri B. Formulation and evaluation of fast dissolving film of losartan potassium. World J. Pharmcol. Res. Tech., 2015; 3(6): 179-189.
17. Sri rekha M, Sultana SKS, Mahathi K, Parveen P, Prathima B, Devi AS. Formulation and evaluation of fast dissolving buccal film containing isradipine solid dispersion. Amer. J. Pharmtech. Res., 2015; 5(2): 221-247.
18. Pawar SV, Junagade MS. Formulation and evaluation of mouth dissolving film of risperidone. Int.J.PharmTech. Res., 2015; 8(6): 218-230.
19. Jelvehgaril M, Montazam SH, Soltani S, Mohammadi R, Azar K, Montazam SA. Fast dissolving oral thin film drug delivery systems consist of ergotamine tartrate and caffeine anhydrous. Pharm.Sci., 2015; 21: 102-110.
20. Goutam K, Garg R, Sharma A, Singh A, Sharma P, Kaushal S. Formulation and evaluation of oral fast dissolving films of promethazine theoclate. Indo. Ameri. J.Pharm. Res., 2015; 5(8): 2536-2544.
21. Mundada AS, Jain RA. Formulation, development and optimization of fast dissolving oral film of montelukast sodium. Int. J. Drug Dev. Res., 2015; 7(4): 40-46.
22. Dwivedy BN, Dabral P, Kumar R. Preparation and evaluation of mouth dissolving film of pantoprazole sodium. World J. Pharm. Pharmceut. Sci., 2014; 3(8): 1564-1576.
23. Kumar R, Pandey GS, Sharma R, Singh Y, Teotia UVS. Effects of maltodextrin and glycerin on mechanical properties of oral fast dissolving film of salbutamol sulphate. Int. J. Adv. Pharm. Bio. Chem., 2014; 3(1): 199-209.
24. Saleem MA, Jahangir MA, Patel HR, Kazmi I, Muheem A, Ahmad K. Formulation and evaluation of fast dissolving films of levocetirizine. World J. Pharm. Pharmceut. Sci., 2014; 3(9): 1310-1323.
25. Prabhu P, Dubey A, kamath K. formulation and Evaluation of fast-dissolving films of lisinopril. Egyp. Pharm. J., 2015; 14: 56-64.
26. Swamy NGN, Kumar SS. Formulation and evaluation of fast dissolving oral films of palonosetron hydrochloride using Hpmc-E5.Int.J. Pharm. Chem. Sci., 2014; 3(1): 145-150.
27. Pandey P, Chauhan S. Fast dissolving sublingual films of zolmitriptan: A novel approach for migraine attacks. Ind. J. Pharm. Edu. Res., 2014; 48(1): 67-72.
28. Deepthi A, Reddy V, Navaneetha K. Formulation and evaluation of fast dissolving oral films of zolmitriptan. Ameri. J. Adv. Drug Deliv., 2014; 2(2): 153-163.
29. Kumar SK, Nagabhushanam MV, Sambasiva Rao KRS, Bhikshapathi DVRN. Formulation development and in vivo evaluation of zolmitriptan oral dissolving films.Int.J.Pharm.Bio.Sci., 2013; 4(3): 638-654.
30. Patel HJ, Patel PB, Kamdar KM, Patel KB, Shah AA, Patel ZP. Development and optimization of fast dissolving film of losartan potassium. Amer. J. Pharm. Health Res., 2013; 1(2): 35-44.
31. Kathpalia H, Sule B, Gupte A. Development and Evaluation of Orally Disintegrating Film of Tramadol Hydrochloride. Asian Journal of biomedical and pharmaceutical sciences, 2013; 3(24): 27-32.
32. Bansal G, Garg V, Siddiqui MD. Investigation of polymers alone and in combination for the development of oral thin film. Int. J. Inv. Pharm. Sci., 2013; 1(3): 31-235.
33. Albert, A.A. and Serjeant, E.P. (1984). Ionization constants of Acids and Bases. Wiley, Newyork.
34. Yalkowiski, S. H. and Roseman, T.J (1981). Techniques of solubilisation of Drugs, Chapter 3, ed. S.H. Yalkowski Marcel Dekker, Newy.
35. Indian pharmacopeia, 2007; 4.
36. European Pharmacopoeia. Directorate for the Quality of Medicines of the Council of Europe (EDQM), 2004; 1: 628.
37. PK Lakshmi, J sreekanth, Aishwarya Sridharan, "Formulation development of fast releasing oral thin films of Cetriizine dihydrochloride with Eudagrit EPO nad optimization through Taguchi orthogonal Experimental design", Asian journal of pharmaceutical Sciences, 2005.
38. Patel AR, Dharmendra S, Jignyasha P, Raval A. Fast dissolving films (FDFS) as a newer venture in fast dissolving dosage forms. Int J Drug Deliv Res., 2010; 2: 232-46
39. Barnhart. S, Rathborne M, Hadgraft J, Roberts M, Lane M, Thin film oral dosage forms, in: Modified release drug delivery technology 2nd edition, Drugs and the Pharmaceutical Sci., 209-216.
40. Nishimura, M., K. Matsuura, T. Tsukioka, H. Yamashita, N. Inagaki, T. Sugiyama and Y. Itoh,. In vitro and in vivo characteristics of prochlorperazine oral disintegrating film, International J. Pharmaceutics, 2009; 368(1-2): 98-102.
41. E. Jayjock, Robert Schmitt, Chilling Chein, Gloria Tirol, "Determination Of fast dissolve Oral Film Dissolution Rate via Conductivity" The Dow Chemical Company, 2005.
42. S. K. Yellanki, S. Jagtap, and R. Masareddy, "Dissofilm: a novel approach for delivery of phenobarbital; design and characterization," *Journal of Young Pharmacists*, 2011; 3(3): 181–188.
43. P. Joshi, H. Patel, V. Patel, and R. Panchal, "Formulation development and evaluation of mouth dissolving film of domperidone," *Journal of Pharmacy and Bioallied Sciences*, 2012; 4(5): S108–S109.