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FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILM OF RIZATRIPTAN BENZOATE

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ABSTRACT

Rizatriptan a 5-HT 1B and 5-HT 1D antagonist which is an antimigraine water soluble drug belongs to class III of BCS classification of drugs. The present study was aimed to formulate and evaluate mouth dissolving films of drug using hydroxyl propyl methyl cellulose. Hydroxyl propyl methyl cellulose is the polymer used as film forming agent and propylene glycol used as plasticizer. Mouth dissolving films are meant to be dissolved in saliva and remain in oral cavity until swallowed. The films are prepared by solvent-casting method and characterized by UV studies. The suitable plasticizer concentrations were selected on the basis of flexibility, folding endurance and stickiness of the film. The other excipients like Citric acid and aspartame are used in the preparation as mouth dissolving agent and sweetner. Films were evaluated for various tests like thickness, folding endurance, drug content, disintegrating time, weight variation, *in vitro* dissolution time. The optimized formulation F4 showed satisfactory mechanical properties, disintegration time less than 1 mint and percentage drug release was found to be 98.62% per $2cm^2$. From the above data, it can be concluded that HPMC E15 and Propylene Glycol 400 polymers was successfully used to formulate rizatriptan mouth fast dissolving films by Solvent-casting method.

KEYWORDS: Rizatriptan, HPMC E15, Propylene Glycol 400, Solvent-casting method, Mouth dissolving films.

INTRODUCTION

Oral films are the newer technologies in the manufacturing of orally disintegrating dosage

forms. They are thin elegant films of edible water-soluble polymers of various sizes and shapes like square, rectangle or disc. They are designed to provide rapid disintegration. The strips flexible and portable so they provide ease in transportation during consumer handling and storage, suitability for geriatric and pediatric patients, who experience difficulties in swallowing, mentally ill, the developmentally disable and the patients who are un-cooperative, or are on reduced liquid intake plans or are nauseated.

Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches often in association with a number of autonomic nervous system symptoms. Approximately 15% of the population is affected by migraines at some point in life. Typically the headache affects one half of the head, is pulsating in nature, and lasting from 2 to 72 hours. Associated symptoms may include nausea, vomiting, and sensitivity to light, sound, or smell. The pain is generally made worse by physical activity. Up to one-third of people with migraine headaches perceive an aura: a transient visual, sensory, language, or motor disturbance which signals that the headache will soon occur. Symptoms can be visual, sensory or motor in nature and many people experience more than one.

The new generation anti-migraine drug, rizatriptan benzoate is an orally active binds with high affinity to human 5-HT1B and 5-HT1D receptors which leads to cranial blood vessel constriction. Chemically it is dimethyl({2-[5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethyl})amine. The drug undergoes first-pass metabolism, and the bioavailability is upto 45%.

The objective of the present research was to formulate Mouth dissolving films which can be administered without water, anywhere, anytime. Due to the presence of larger surface area, films provide rapid disintegrating and dissolution in the oral cavity. So mouth dissolving films of rizatriptan prevent its first-pass metabolism and eliminate 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 was obtained from Yarrow Chem. Products, Dombivali (East) Mumbai, HPMC E15 & Propylene Glycol 400, Citric acid, Aspartame was Purchased from SD Fine-Chem Lmtd, Mumbai, Maharastra.

EXPERIMENTAL METHODS

Preformulation studies

Melting point determination

The melting point of rizatriptan was determined by using by capillary tube method.

UV spectroscopy

Calibration curve of Rizatriptan

Drug solution of 100µg/ml solution was prepared using Phosphate buffer as solvent. Then it was subjected to scanning from a wavelength range of 200-400nm.The λmax was determined by UV spectrophotometer and compared with the literature value.

Preparation of drug solution in ph6.8 phosphate buffer

a. Standard stock solution: Accurately weighed 100mg of rizatriptan was dissolved in pH6.8 phosphate buffer in a 100ml volumetric flask and volume is made up with pH6.8 phosphate buffer to get a concentration of 1000µg/ml.

b. Working stock solution

From the stock solution drug solution of 1ml was diluted in100ml (10µg/ml). Similarly concentrations were prepared in Phosphate buffer for 20, 30, 40, 50µg/ml. The working standard was scanned using uv spectrophotometer at 226nm i.e. 400-200nm and λmax was taken.

Drug Excipient Compatibility studies

Drug solution of 10µg/ml concentration was prepared and scanned for λmax. Then solution containing drug and excipients mixture of 10µg/ml concentration in pH-6.8 buffer was prepared and an overlay of UV spectrum was performed.

Formulation of placebo films

Polymers of single or in combination were accurately weighed and dissolved in respective solvent and then casted in a Petri-dish. The films were allowed to dry overnight at room temperature or dried in a hot air oven.

PREPARATION OF DRUG FILMS

The formulation of films by using solvent casting method. The following steps are used in the manufacturing of films by this method.

Step1

The polymers were dissolved in water .The drug and other ingredients were dissolved in solvent. This drug solution was added to the polymer solution and formed a viscous solution.

Step2

Then the solution was mixed by using mixing device for 45minutes with rotating speed 80-100rpm.The entrapped air is removed by vacuum.

Step3

The resulting solution was casted slowly and with continuous flow on a glass plates. The plates were kept in a hot air oven at 60°c for 24 hours. The dried film was gently separated from glass plate and cut into desired sizes.

Fig.1

Fig.2

Experimental Design

Formulation of films

Table 1: Formulation design of Rizatriptan mouth dissolving films.

Sl. NO	INGREDIENTS	F1 (mg)	F2 (mg)	F3(mg)	F4(mg)
1	Rizatriptan	5	5	5	5
2	Hpmc E15	40	45	40	45
3	Propylene Glycol 400	10	10	15	15
4	Citric Acid	3	3	3	3
5	Aspartame	42	37	37	32

CHARACTERIZATION OF FILMS

1. Physical appearance

The physical appearance of the prepared film was observed visually.

2. Thickness

The thickness of films was measured by digital Vernier callipers with least count 0.001mm. The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation.

3. Folding endurance

Folding endurance of the film was determined by repeatedly folding a small strip of film (2*2) at the same place until it broke. The number of times that the film could be folded at the same place without breaking gives the value of folding endurance.

4. Percent elongation

The percent elongation at break was measured by formula given below.

$$\text{Strain (E)} = \frac{\text{Total elongation}}{\text{Original lenth}} \times 100 = = \frac{L-Lo}{Lo} \times 100$$

Where, L = length after force was applied

L0 = original length

5. *Invitro* Disintegration

2ml of water was placed in a petriplates with a film on the surface of water the time taken for the disintegration of the film was measured.

6. Drug content

The Film of area 2x2 cm^2 was cut and dissolved in distilled water. Then solvent ethanol and water, to make polymer soluble, were added to the mixture and the remaining volume was made up with distilled water to 100ml in 100ml volumetric flask. Then 1 ml was withdrawn from the solution and diluted to 10ml.The absorbance of the solution was taken at 226nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.

7. Weight variation

The three films of 2*2 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

8. *Invitro* Dissolution

900ml of phosphate buffer (pH6.8) was used as a media, and was maintained at 37±0.5^{0}c while the basket was set at 100 rpm a film sample of 2cm^2(2*2cm)was cut and taken in to the basket. 5ml of the sample were taken every 2 minutes and the same amount was replaced with fresh buffer. The withdrawn samples were filtered and analysed using a U.V Spectrophotometer at a wavelength of 231nm.

RESULTS AND DISCUSSIONS

Preformulation studies

Melting point determination

The melting points were found to be in the range of 178° to 179°C.

Calibration curve of Rizatriptan

U.V Spectrophoptometric methods were employed for the development of standard calibration curve of Rizatriptan in which dilutions were made with pH 6.8 Phosphate buffer. Concentrations of 10-50µg/ml were analyzed at 226nm. The correlation coefficient was found to be 0.996.

Drug Excipient Compatibility studies

The absorbance of the drug and additive solution were almost closer to the absorbance of the pure drug solution. Thus the analysis revealed that drug has no interference with the excipients used in the formulation.

Table 2: Data obtained in the spectral interference analysis.

S.No	Solution	Absorbance
1	Pure drug	0.178
2	Drug + Excipients	0.179

CHARACTERIZATION OF FILMS

Formulation studies

After the preparation of films by solvent evaporation method they were evaluated for the following.

1. Physical appearance

The physical appearance of the prepared film was observed to be transparent for all the formulations.

2. Thickness

The thickness of the films varied from 0.355 to 0.540 mm. The values obtained for all the formulations are given in the table 3.

3. Folding Endurance

The folding endurance was found to be in the range of 32±057 to 39±0.81. The values for all four formulations are given in the table 3. This data revealed that the films had good mechanical strength along with flexibility.

4. Percentage Elongation

The percentage elongation was found to be in the range of 15 to 37.5%. The formulation F4 showed minimum percentage elongation among all the other films. The results obtained for all the formulations are tabulated in the table 3.

5. *Invitro* disintegration

2ml of pH6.8 phosphate buffer was placed in a petriplates with a film on the surface of buffer the time taken for the disintegration of the film was measured. The results obtained for all the formulations are tabulated in the table 3.

6. Drug Content

This test was performed by dissolving a 4cm^2 area of film in 10ml of pH6.8 phosphate buffer with stirring. This solution was filtered using a Wattmann filter paper, and the filtrate was diluted to 100ml with the same buffer in a volumetric flask. This solution was analyzed by using U.V spectrophotometer. F-4 shows good mechanical properties, disintegration time within 1 mint and percentage drug release was high in less time. The results obtained for all the formulations are tabulated in the table 3.

7. Weight variation

The three films of 2*2 cm^2 was cut and weighed on electronic balance for weight variation test. The results obtained for all formulations were tabulated in the table 3.

8. *Invitro* dissolution

900ml of phosphate buffer (pH6.8) was used as a media, and was maintained at 37±0.5°c while the basket was set at 100 rpm a film sample of 4cm^2 (2*2cm) was cut and taken in to the basket.5ml of the sample were taken every 2 minutes and the same amount was replaced with fresh buffer. The withdrawn samples were filtered and analyzed by using a U.V

Spectrophotometer at a wavelength of 226nm. The results obtained for all the formulations are tabulated in the table 4.

Table 3: Physicochemical evaluation data of Rizatriptan films.

Formulations	Physical appearane	Thickness (mm)	Folding endurance	Percentage Elongation (%)	Weight variation (mg)	*Invitro* disintegration (sec)	Assay (%)
F-1	Transparent	0.355±0.004	32±057	15	0.974±0.002	23	87.7
F-2	Transparent	0.385±0.006	35±0.75	20	0.983±0.04	24	92.8
F-3	Transparent	0.376±0.01	37±0.54	34.5	0.981±0.03	20	93.3
F-4	Transparent	0.540±0.007	39±0.81	37.5	0.986±0.001	18	98.62

Mean ± Standard deviation (n=3)

Table 4: *In vitro* drug release profile of all formulations.

Time (min)	% Drug release			
	F1	F2	F3	F4
2min	27.7	27.2	20.4	26.2
4min	39.2	35.8	38.9	41.2
6min	50	52.2	55.5	57.2
8min	62.6	64.2	69.4	76.3
10min	80	73	79.02	84.4
12min	88.8	86.4	88.93	97.34
14min	93.6	91.8	95.08	

Mean ± Standard deviation (n=3)

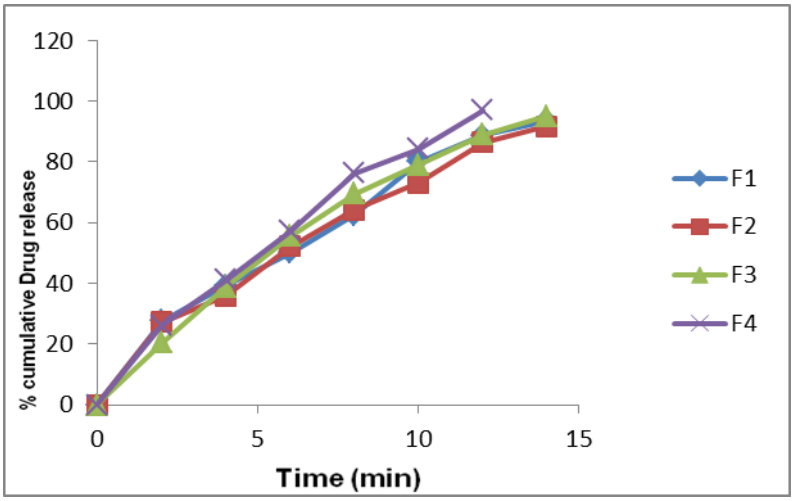

Fig. 3: *In vitro* drug release profile of all formulations.

SUMMARY AND CONCLUSION

The rizatriptan is a serotonin (5-HT1) agonist used for the treatment of migraine with or without aura. The half-life of rizatriptan is 2 to 3 hrs and it undergoes hepatic metabolism, the absolute oral bioavailability is about 40 to 45%. In order to improve the bioavailability and

efficacy, we have prepared mouth dissolving films of rizatriptan. In the present research work, films were prepared using HPMC E15 polymer by Solvent Casting Technique. Rizatriptan is water soluble drug belongs to class III of BCS classification of drugs. Estimation of the drug by U.V method at 226nm was performed. Preformulation studies involving spectral interference analysis, showed no interaction between drug and polymer. Formulation F-4 shows good mechanical properties, disintegration time within 1 mint and percentage drug release was high in less time. So, in order to decrease the migraine effect in patients in less time mouth dissolving films could be a better alternative.

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