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Formulation and evaluation of rapidly dissolving films of zolmitriptan

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ABSTRACT

Oral films are the newer technologies in the manufacturing of orally disintegrating dosage forms. They are thin and elegant usually made of edible water-soluble polymers of various sizes and shapes like square, rectangle or disc. The strips may be flexible or brittle, opaque or transparent. They are designed to provide rapid disintegration on the tongue without the need for water. This work investigated the possibility of developing Zolmitriptan fast dissolving strips allowing fast, reproducible drug dissolution in the oral cavity, and thus decreasing the migraine effect in patients in less time and enhancing the patient compliance. All the formulations were prepared with HPMC 5cps, Propylene glycol, Acesulfame potassium, peppermint flavor. The dissolution of the film samples evaluated gave maximum release within 12 minutes indicating the rapid drug release profile which entails in faster onset of action for the medicament.

Keywords: Zolmitriptan, migraine, HPMC, fast dissolving films

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INTRODUCTION

For decades, oral drug delivery has been known as the most widely used route of drug administration when compared to all the other routes that have been explored for delivery of different dosage forms to systemic circulation. The reason for such popularity of oral route may be attributed to its ease of administration [1]. To overcome the difficulties experienced by geriatric and pediatric patients in swallowing conventional oral dosage forms, oral fast dissolving films were developed [2]. They are ultra thin postage stamp size films prepared using hydrophilic polymers with an active agent and other pharmaceutical excipients [3]. They undergo rapid disintegration in the salivary fluids of the oral cavity in less than a minute, where they release the drug which is swallowed orally with the saliva and the absorption of drug takes place in the gastro-intestinal tract [4].

Polymers play an important role in the formation of film as they make up to 40% w/w of the film content. Hydrophilic polymers are most widely used in the preparation of film that dissolves rapidly in the oral cavity and drug is delivered to the systemic circulation [5]. The polymers are responsible for the strength of the film. The film should be tough to prevent damage during handling and transportation. The polymers can be use as single or in combination as per requirement [6].

Zolmitriptan is a seratonin (5-HT 1) agonist used for the treatment of migraine [7]. This work investigated the possibility of developing Zolmitriptan fast dissolving strips allowing fast, reproducible drug dissolution in the oral cavity and thus decreasing the migraine effect in patients in less time.

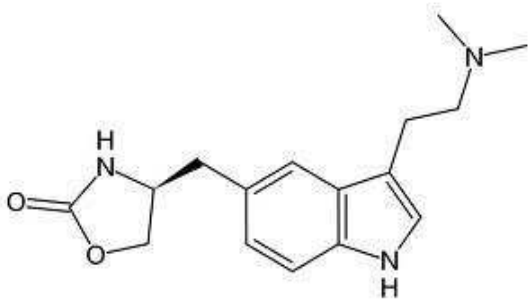

Fig. 1: Structure of Zolmitriptan

MATERIALS AND METHODS

Materials

Zolmitriptan (Pharmatrain, Hyd), Hydroxy propyl methylcellulose 5cps (Pharmatrain, Hyd), Propylene glycol (Pharmatrain, Hyd), Acesulfame potassium (Pharmatrain, Hyd), Peppermint flavor (Pharmatrain, Hyd), Xylitol (Pharmatrain, Hyd).

Methods

Characterization of Zolmitriptan

Melting point determination

Melting point of Zolmitriptan was determined by capillary tube method. Fine powder of the drug was filled into a glass capillary tube which was previously sealed at one end. The capillary tube tied to a thermometer was subjected to increasing temperatures and the temperature at which Zolmitriptan melts was recorded.

Ultraviolet spectroscopy

The samples were subjected to UV spectrophotometric analysis and were scanned for absorption maxima (λ_{max}) in the range of 200-400nm using UV-Vis spectrophotometer in an appropriate medium. The obtained data was compared with that of reference values in literature [8].

Compatibility studies

FTIR study was carried out check compatibility of drug with polymers. Infrared spectrum of Zolmitriptan was determined on Fourier transform Infrared spectrophotometer using KBr dispersion method. The baseline correlation was done using dried potassium bromide. The spectrum of dried mixture of drug and potassium bromide was run followed by drug with various polymers by using FTIR spectrophotometer. The range of scanning was between 400-4000 cm^{-1} [9].

Formulation of placebo films

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

Formulation of drug films

The polymer was dissolved in hot water. The drug and other ingredients were dissolved in solution. This drug solution was added to the polymer solution and formed a viscous solution. Then the solution was mixed by using mixing device for 45minutes with rotating speed 60-80rpm.The entrapped air was removed by vacuum. The resulting solution was casted slowly and with continuous flow on a glass plates. The plates were kept in a hot air oven at 60^0c for 24 hours. The dried film was gently separated from glass plate and cut into desired sizes.

Table 1: The purpose of key ingredients

Ingredients	Category
Zolmitriptan	Drug
H.P.M.C 5cps	Polymer
Propylene glycol	Plasticizer
Xylitol	Filler
Acesulfame potassium	Sweetening agent
Peppermint flavor	Flavoring agent
Water	Solvent
Ethanol	Solvent

Table 2: Formulation Code

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Drugs	125	125	125	125	125	125	125	125
H.P.M.C 5cps	25%	10%	35%	40%	45%	50%	35%	40%
Xylitol	1375	1250	1125	1000	875	750	875	750
Propylene glycol	10%	10%	10%	10%	10%	10%	20%	20%
Acesulfame potassium	100	100	100	100	100	100	100	100
Peppermint Flavor	25	25	25	25	25	25	25	25
Water*	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Ethanol*	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Total	2500	2500	2500	2500	2500	2500	2500	2500

EVALUATION OF ORAL SOLUBLE FILMS

Physical Evaluation

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

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.

Tensile Strength

The tensile strength was determined by the instrument which was designed such that it had horizontal wooden platform with fixed scale and attachments for two clips that holds strip under test. Out of the two clips one was fixed and other was movable. Weights were hanged to one end of pulley and the other end of pulley was attached with movable clip. The wooden platform was such fitted that it would not dislocate while the test is running. Three strips of patch were cut having 2cm length and 2cm breadth. The thickness and breadth of strips were noted at three sites and average value was taken for calculation.

The rate of change of stress was kept constant with the increment of 0.5g per 2 minutes. The elongation was observed and the total weights taken were used for calculation. The tensile strength was calculated by using following formula [8]

$$\text{Tensile stress(S)} = \frac{\text{Applied force}}{\text{Cross sectional area}} = \frac{m*g}{b*t}$$

Where, S = tensile stress in 980 dynes/ cm^2
m = mass in grams
g = acceleration due to gravity (980 dynes/ cm^2)
b = breadth of strip in centimeters
t = thickness of strip in centimeters

The strain is change resulting in size of strip after the force was applied to its original size. Therefore, the strain can be given as,

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

Where, L = length after force was applied

L_o = original length

Percent elongation

The percent elongation at break was measured by formula given below [9]

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

Where, L = length after force was applied

L_o = original length

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 and concentration was calculated. By correcting dilution factor, the drug content was calculated.

Weight variation

The three films of 2*2 cm^2 were 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.

***In vitro* Disintegration**

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

***In vitro* Dissolution**

USP apparatus 1 (basket type apparatus) was used to test dissolution rate. 900ml of phosphate buffer (pH6.8) was used as a media, and was maintained at 37 ± 0.5^0c 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 was taken every 2 minutes and the same amount was replaced with fresh buffer. The withdrawn samples were filtered and analyzed using a U.V Spectrophotometer.

Stability studies

The stability studies were carried out according to ICH to assess the drug formulation stability. Optimized FV formulation was sealed in aluminum packaging laminated with polyethylene. Sample were kept at 40 ^{0}C and 75% RH for 3 months. At the end of the study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics

RESULTS

Melting point determination

The melting points were found to be in the range of 178° to 179°C according to literature. The reported melting point was 178.5°C to 179°C.

Compatibility studies

The Zolmitriptan indicates presence of absorption peak due to the presence of N-H of the lactam, as well as secondary amine, suggesting that the functionalities are present in the drug molecule. The aromatic and aliphatic C-H absorption are noticed from 2850 cm-1 to 3100 cm^{-1}.The characteristics C=O-O of the drug exhibited a absorption peak at 1750 cm-1 which is in cyclic form. These are the characteristics of the Zolmitriptan.

In IR spectrum of the H.P.M.C indicating that the strong hydroxyl peak is observed at 3400 cm-1, suggesting that primary hydroxyl group is present. C-H aliphatic nature are found to present in molecule giving absorption peak from2833 cm-1 to 2974 cm-1 so, in this molecule these characteristics are observed in spectra.

When this is along with drug presenting formulation taken for IR spectra. In this IR all the characteristics absorption peak of the drug and HPMC are observed and found that no chemical reaction taken place. Hence drug present in free state not in the form of reaction product.

FTIR studies conducted on pure drug and physical mixtures of all ratios showed that there is no marked interaction between drug and selected polymers.

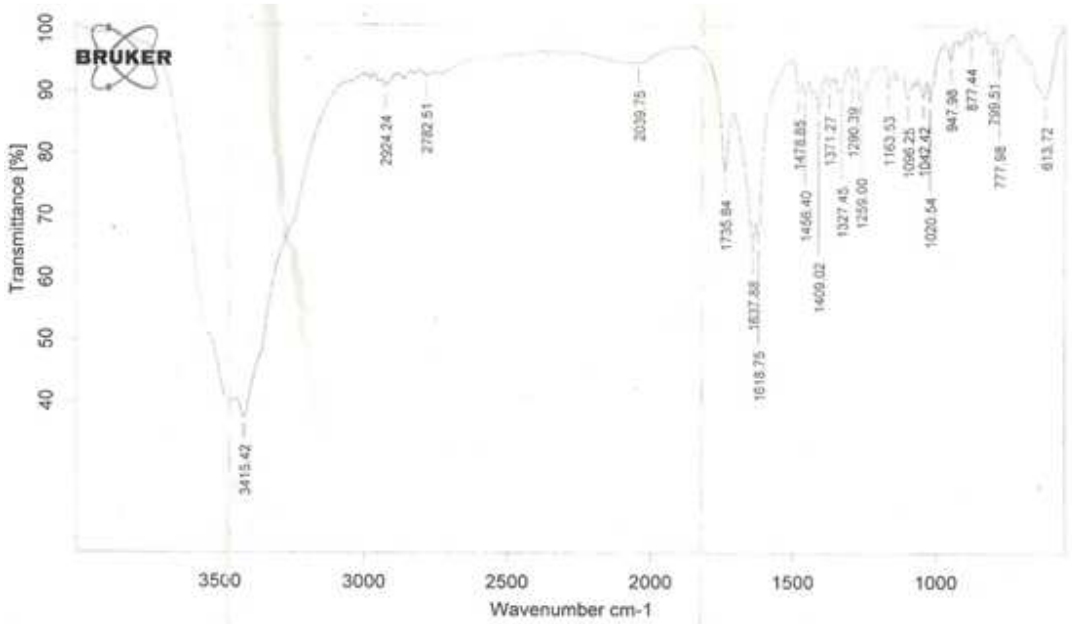

Fig. 2: FTIR of pure drug

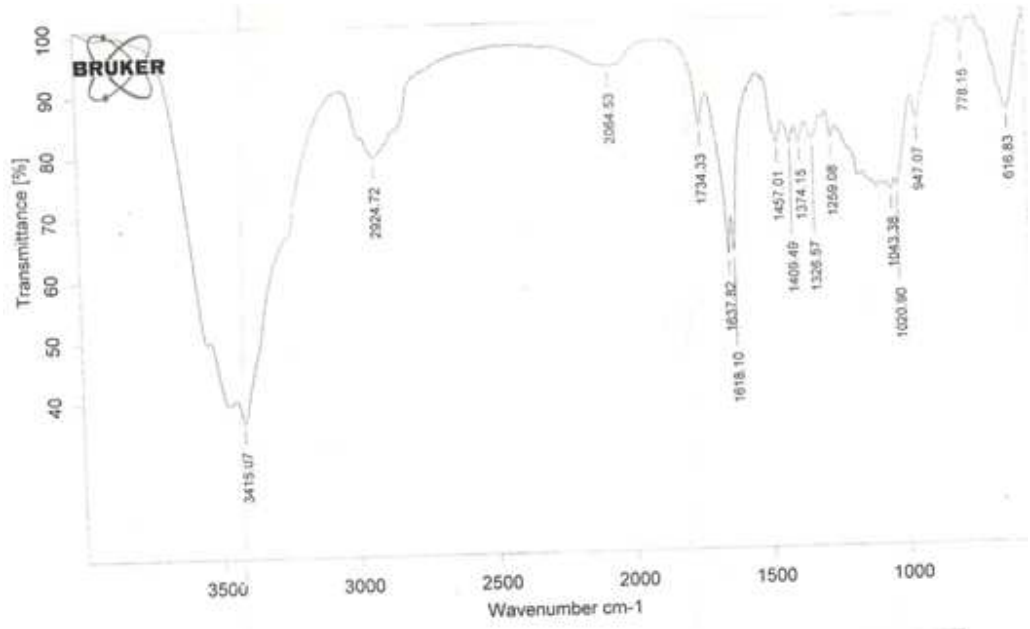

Fig. 3: FTIR of H.P.M.C 5cps

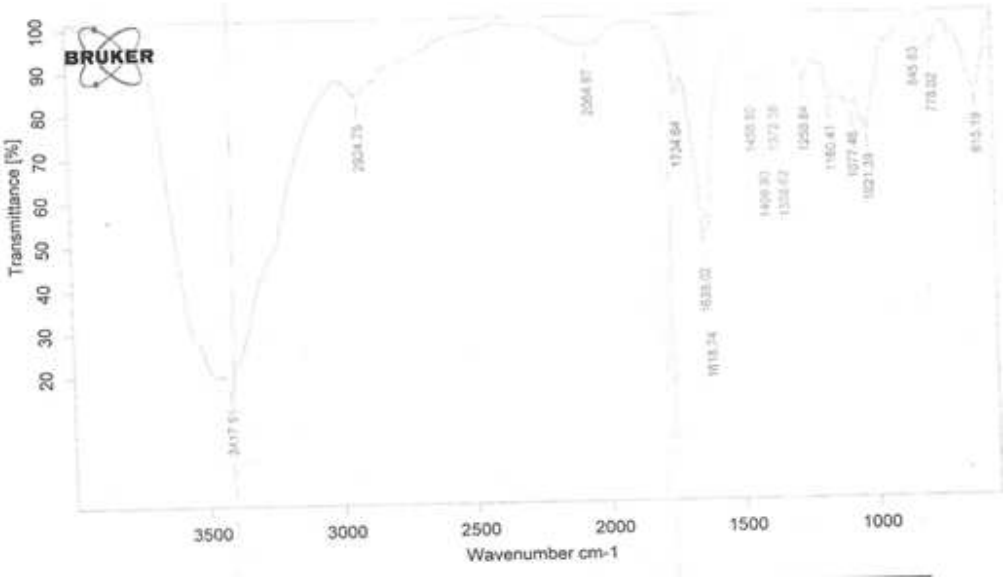

Fig. 4: FTIR OF DRUG AND H.P.M.C 5cps mixture

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

1. Thickness:
The thickness of the films varied from 0.25 to 0.6 mm.

2. Folding Endurance:
The folding endurance was found to be in the range of 21 to 25. These values revealed that the films had good mechanical strength along with flexibility

3. Tensile strength:
The tensile strength was found to be in the range of 43.6 to 63. The formulation F4 and F8 showed the best tensile strength.

4. % Elongation:
The % elongation was found to be in the range of 5 to 17.5%. The formulation F4 and F8 showed minimum % elongation among all the other films.

Table 3: Physicochemical evaluation data of Zolmitriptan films

Formulation	Thickness (mm)	Folding endurance	Tensile strength (gm/cm^2)	% Elongation
F-1	0.342	20	43.4	13
F-2	0.380	25	51.6	19
F-3	0.374	25	46.3	17.3
F-4	0.521	21	59.1	7.2
F-5	0.510	23	53	10
F-6	0.54	25	62	4
F-7	0.425	25	52.3	12.3
F-8	0.543	25	59.1	7.2

Weight variation
The three films of 2*2 cm^2 was cut and weighed on electronic balance for weight variation test.

***In vitro* disintegration:**
All the formulations disintegrated in less than 22 seconds.

Drug content:
F8 formulation showed highest drug content when compared to the other formulations.

Table 4: Evaluation parameters of Zolmitriptan

Formulation trials	Weight variation(mg)	*In vitro* disintegration (sec)	Assay (%)
F-1	0.975	18	87.7
F-2	0.985	20	90.8
F-3	0.986	20	93.3
F-4	0.986	23	98.62
F-5	0.983	22	97.6
F-6	0.979	23	95.6
F-7	0.981	21	95.5
F-8	0.989	22	98.2

***In vitro* dissolution**
All the formulations showed drug release in less than 14minutes.

Table 5: *In vitro* dissolution studies of all formulations

Time in min	F1	F2	F3	F4	F5	F6	F7	F8
2	27.6	27.1	20.2	26.1	30.14	16.01	23.0	29.8
4	39.1	35.6	38.5	41.2	46.5	34.0	37.3	46.4
6	48	52.0	55.3	57.2	58.3	47.06	53.66	62.7
8	62.3	64.1	69.2	76.3	71.2	61.22	70.72	81.63
10	77	70	79.00	84.3	85.3	74.34	86.2	93.33
12	88.5	86.2	88.91	99.33	91.1	87.46	93.5	97.5
14	93.4	91.5	96.06	-	95.0	96.0	-	-

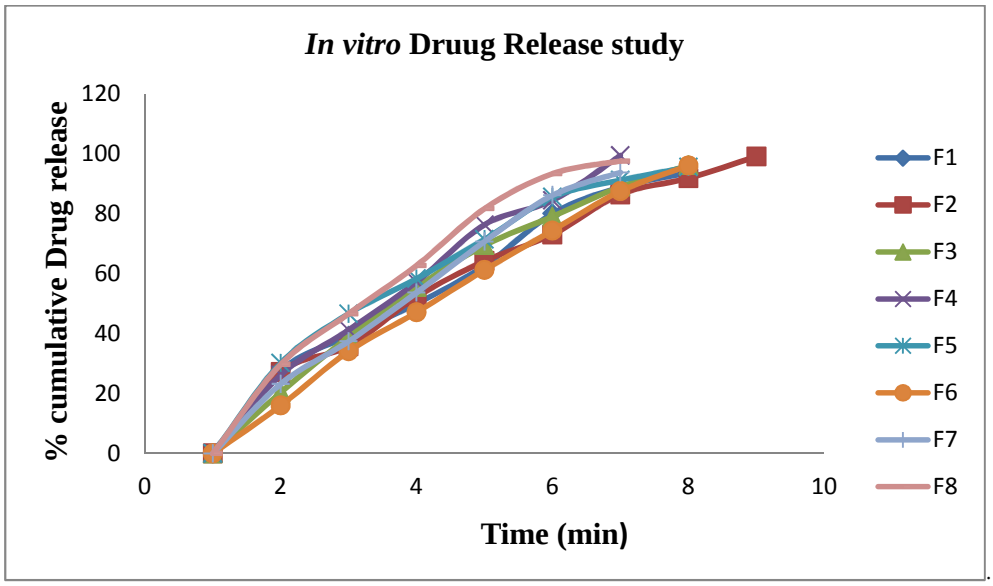

Fig. 5: Comparative *In vitro* Drug release from all formulations

Table 6: Regression coefficient (R^2) values for different kinetic models for all formulations

Formulation Code	Regression coefficient (R^2)			
	Zero order	First order	Higuchi	Peppas
F1	0.983	0.943	0.970	0.985
F2	0.982	0.826	0.978	0.985
F3	0.974	0.936	0.972	0.991
F4	0.994	0.758	0.961	0.992
F5	0.966	0.920	0.99	0.991
F6	0.993	0.904	0.943	0.994
F7	0.991	0.942	0.950	0.994
F8	0.972	0.944	0.975	0.992

Stability studies

The stability studies were carried out according to ICH to assess the drug formulation stability. Optimized FV formulation was sealed in aluminum packaging laminated with polyethylene. Sample were kept at 40 ^{0}C and 75% RH for 3 months. At the end of the study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics. The optimized formula was subjected for the stability studies.

Table 7: Stability studies for F-4

Parameters	Stability data	
	Initial	3 months (40^{0}C±75%RH)
Thickness(mm)	0.54±0.07	0.52±0.008
Folding endurance	21±0.01	20±0.01
Tensile strength(gm/cm^2)	59.3	57
Invitro disintegration(sec)	18	20
***In vitro* dissolution (%)**	99.4	99.1

Table 8: Stability studies for F-8

Parameters	Stability data	
	Initial	3 months(40^{0}C±75%RH)
Thickness(mm)	0.545±0.07	0.52±0.008
Folding endurance	25±0.057	20±0.01
Tensile strength(gm/cm^2)	59.3	58.2
***In vitro* disintegration(sec)**	18	21
***In vitro* dissolution (%)**	97.5	96.1

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