Available online on 25.04.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

Formulation and Evaluation of Fast Dissolving Oral Films of an Anti-Migrain Drug (Zolmitriptan)

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ABSTRACT

Zolmitriptan known for its anti-migrain activity. The fast dissolving oral film of drug Zolmitriptan was designed in order to relief and ease the pain caused to patient suffering from Migraine followed by nausea, vomiting and sensitivity towards light/sound. The oral film was prepared using HPMC (Hydroxy Propyl Methyl Cellulose) as polymer and PEG as plasticizer by solvent casting method. The aim of preparing fast dissolving oral film of drug zolmitriptan was to have better Bioavability, quick onset of action (quick relief) and to prevent first pass metabolism. Films were subjected to physicochemical characterization such as thickness, weight variation, folding endurance drug content and were found to be satisfactory. The surface pH of all the films was found to be neutral. The results of the studies indicated that HPMC E50 could be used as a film forming polymer for the formulation. All the films prepared using HPMC E50 showed acceptable mechanical properties. On the basis of tensile strength, drug content and *in vitro* dissolution, formulation F3 was found to be the promising formulation showing better strength and good drug release profile. Also this formulation was stable for a period of 45 days with no significant change in drug content and drug release profile. Thus it could be said that the fast dissolving sublingual film of Zolmitriptan could be a better option for acute treatment of migraine attacks compared to the available conventional dosage forms.

Keywords: Zolmitriptan, Fast dissolving, HPMC

Article Info: Received 21 Feb 2019; Review Completed 27 March 2019; Accepted 17 April 2019; Available online 25 April 2019

Cite this article as:

Rathore N, Nizami T, Mangal A, Malviya N, Chauhan V, Salvi N, Formulation and Evaluation of Fast Dissolving Oral Films of an Anti-Migrain Drug (Zolmitriptan), Journal of Drug Delivery and Therapeutics. 2019; 9(2-A):59-61

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INTRODUCTION

Fast dissolving films are most advanced form of solid oral dosage form due to its flexibility. It improve efficacy of active pharmaceutical ingredient (API) by dissolving in the short time in oral cavity after the contact with less amount of saliva as compared to mouth dissolving tablet. The oral cavity covers the cheek, lips, tongue, hard palate and soft palate. The lining of the oral cavity is referred to as the oral mucosa. [1]The delivery system is simply placed on the patient tongue or any oromucosal tissue. Instantly wet by saliva due to the presence of hydrophilic polymer, the film rapidly hydrates and dissolves to release the medication for oromucosal absorption.[2] Migraine attacks typically unfold through a sequence of events that occur over the time course of several hours to days, and typically progresses through four phases.[3] Treatment for migraine headaches can be divided into two broad categories, acute treatments that are taken once a migraine begins, in order to reduce the intensity or abort the attack. The objective of the study is to develop oral fast dissolving films (OFDF's) for Zolmitriptan in order to improve the bioavailability.[4] Zolmitriptan Oral Fast Dissolving Films (ZOFDF's) is systemically optimized using full factorial design.

Objective

The aim of preparing fast dissolving oral film of drug zolmitriptan was to have better Bioavability, quick onset of action (quick relief) and to prevent first pass metabolism.

MATERIALS

Zolmitriptan was obtained as a gift sample from Angel Biopharma, Ahmedabad, India. PVA, maltodextrin, HPMC and polymers were purchased from S.D. Fine Chem Ltd, India. All other chemicals used were analytical grade and were used without purification. Double distilled water was used in the study.

METHOD

Fast dissolving oral films were prepared by using a combination of polymers by solvent casting technique. The formulations were prepared. The hydrophilic polymers namely Maltodextrin (MD) and Polyvinylalchol (PVA), HPMC were accurately weighed and dissolved in distilled water and propylene glycol (PG) was added as a plasticizer. Drug and other ingredients were added to the polymeric dispersion under constant stirring with a magnetic stirrer and the resultant homogeneous solution was poured into a petridish.

Then the films were dried in an oven at 50ºC for 24 h. The dried films were wrapped in a butter paper, covered with an aluminum foil and kept in desiccators.

Evaluation of fast dissolving films

1. Appearance, Size and Shape

The formulated films were checked for their appearance, shape and thickness. The thickness of the films was determined at two different places using a digimatic micrometer for each formulation and mean value was calculated.

2. Thickness

The thickness of the film was measured using digital verneir calipers. The thickness of each film was determined at six different locations and standard deviation was calculated.

3. Weight variation

The patches were subjected to mass variation study by individually weighing randomly selected patches. The average of five observations of each batch was calculated. Such determinations were carried out for each batch.

4. Drug Content

The film of specified area (2×2cm) was cut and put in a volumetric flask containing 100 ml of phosphate buffer pH 6.8. The medium was stirred on a magnetic stirrer for proper dissolution for 6 hours. The contents were filtered using Whatman filter paper and the filtrate was analyzed by UV spectrophotometer (Shimadzu-1800) at 206 nm. The experiments were performed in triplicate.

5. Folding Endurance

It was determined by repeatedly folding a small strip of the patch (2×2cm) at the same place till it broke. The number of times a film can be folded at the same place without breaking gave the value of folding endurance. Further, less folding endurance value indicates more brittleness.

6. Disintegration time

In-vitro disintegration time was determined visually in a petridish 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 disintegrate.

7. *In-vitro* drug release

For *in-vitro* dissolution studies, each film was placed with the help of forceps in a 50 ml glass beaker containing 25 ml of phosphate buffer pH 6.8. The temperature of the dissolution media was maintained at 37±0.5ºC; 50 rpm. During the study, 3ml of aliquots were withdrawn at 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 minutes and were replaced by fresh buffer. The amount of drug release in the media was determined by a UV-Visible Spectrophotometer (Shimadzu-1800) at 206 nm.

8. Surface pH

The surface pH of the films was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The 2 cm X 2 cm film was dissolved in 2 ml of distilled water. The pH was measured by bringing the electrode in contact with the surface of the film and allowing it to equilibrate for 1 minute.

RESULT AND DISSCUSION

The prepared films were smooth, transparent, flexible and uniform. The films were casted in a 10 cm diameter petridish. For evaluation purposes 2 cm^2 area was cut from it. The thickness of the film , standard deviation values were low indicating uniformity in thickness as shown in table 2. It was observed that all the batches were uniform in weight with no significant difference in the weight of the individual formulation from the average value. Drug content of all the formulations was determined using UV-Visible spectrophoto- meter. Drug content was found to vary 86.62±0.50 to 98.14±0.64 % in films. The surface pH of the films ranged from 6.52±0.27 to 6.72±0.18. 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. It was observed that *in vitro* disintegration time varies from 9.33±1.52 to 22.33±0.57 sec for all the formulations. *In vitro* disintegration time of FDFs containing PVA and Maltodextin as polymers was affected by the thickness of the film.

Table 1: Composition of Zolmitriptan Oral Film

S.No.	Ingredients	Formulation		
		F1	F2	F3
1	Zolmitriptan (Mg)	20	20	20
2	HPMC (%)	2	1	2
3	Propylene Glycol (ml)	1	1	2
4	Sodium Starch Glycolate (%)	4	5	3
5	Aspartame (mg)	13	13	13
6	Water (ml)	10	10	10

Table 2: Evaluation of Physico-Mechanical Parameters of Fast Dissolving oral Film of Zolmitriptan.

S.No.	Evaluation Parameter	Stability Study For Formulation		
		F1	F2	F3
1.	Appearance	Transparent	Transparent	Transparent
2.	Thickness	0.18±0.006	0.21±0.01	0.22±0.01
3.	Weight Variation	0.080±0.002	0.085±0.003	0.110±0.001
4.	%Drug Content (Sec+/-Sd))	98.14±0.64	97.57±0.91	86.62±0.50
5.	Floding Endurance (Folds)	344.66±2.5	349.66±1.52	378.33±1.52
6.	Disintegration Time (Sec+/-)	9.33±1.52	19.66±1.15	22.33±0.57
7.	*In-Vitro* Drug Release	97.72% DR in 10 min	97.47%DR in 10 min	97.31%DR in 10 min
8.	Surface pH	6.59±0.18	6.52±0.27	6.72±0.18

CONCLUSION

So from this study it can be concluded that oral fast dissolving film of zolmitriptan was successfully designed. Also this formulation was stable for a period of 45 days with no significant change in drug content and drug release profile. Thus it could be said that the fast dissolving film of Zolmitriptan could be a better option for acute treatment of migraine attacks compared to the available conventional dosage forms.

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