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Research Article

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Formulation and Evaluation of Zolmitriptan Oro Flash Films

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ABSTRACT

The present study was aimed to formulate and evaluate fast dissolving oral films of Zolmitriptan using propylene glycol, HPMC-E50 LV and sodium starch glycolate. The suitable plasticizer and its concentration were selected based on flexibility, tensile strength and stickiness of the film. The films are prepared by solvent casting method and characterized by UV, FTIR studies. The films were evaluated for SEM, disintegration time, Folding endurance, Tensile Strength, Mouth dissolving time, Thickness, content uniformity and in vitro dissolution studies.

Keywords: Thickness; Tensile strength; Folding endurance

INTRODUCTION

Many pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. Generally, a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking. Hence, orally dissolving tablets have come into existence. Even with these differences, most of the existing oral dissolving drug delivery systems are in the form of solid tablets and designed to dissolve/disintegrate in the patient's mouth without the need to drink or chew. However, the fear of taking solid tablets and the risk of choking for certain patient populations still exist despite their short disintegration/ dissolution times. Hence oral film drug delivery is a better alternative in such cases. The oral availability of many drugs is poor because of the pH of the stomach, the presence of enzymes, and extensive first-pass metabolism. Traditionally, these drugs were being administered as parenteral drug delivery systems, which invariably lead to poor patient compliance. This has made the pharmaceutical industry look for alternative routes of drug delivery like film drug delivery. Intraoral fast dissolving drug delivery system is placed on the top or the floor of the tongue. The formulation is retained at the site of application and rapidly releases the active agent for local or systemic absorption [1,2].

MATERIALS AND METHODS

Preformulation Studies

FTIR studies:

FTIR studies were conducted using FTIR instrument on pure Zolmitriptan drug along with the mixture of polymers in different ratios in order to find the compatibility and is found to be compatible with all ingredients [3,4].

DSC studies:

DSC is performed to find out the interaction between drug and excipients and also to find the effect of temperature and compression force on the sample. Samples are placed in aluminum pan in thematically sealed the temperature was raised to 100ºC per minute using nitrogen gas and the difference in temperature was noted [5,6] (Table 1).

Table 1: Materials required for zolmitriptan oro flash films.

Materials	Category	Procured From
Zolmitripatan	Anti-migraine	Apotex laboratories, Bengaluru.
HPMC-E50 LV	Film Forming Polymer	LOBA Chemie Pvt. Ltd. Mumbai.
Propylene Glycol	Plasticizer	LOBA Che mie Pvt. Ltd. Mumbai
Citric Acid	Saliva Stimulating Agent	Thermos Fisher Scientific India Pvt. Ltd. Mumbai
Sodium Starch Glycolate	Super Disintegrants	LOBA Chemie Pvt. Ltd. Mumbai
Sucrose	Sweetener	Thermo Fisher Scientific India Pvt. Ltd. Mumbai
Cross carmalose sodium	Super disintegrants	LOBA Chemie Pvt. Ltd. Mumbai
Synthetic food color	Coloring agent	Commercial sources.

Formulation Methodology of Zolmitriptan Oro Flash Film

Zolmitriptan oral films were prepared with four different compositions. In which the effect of super disintegrants and polymer concentration on the rate of dissolution was studied. The formulations were prepared as per the Table 2. In this method, polymer solution is prepared and kept overnight to dissipate dissolved or entrapped bubbles. Prior to this polymer solution, the drug was dissolved in in 1/4th quantity of 25ml water with an aliquot of alcohol-water mixture. Then, the other excipients were also added viz., citric acid and menthol. This solution is added to the above polymer solution under magnetic stirring. After few minutes, plasticizer was added to this drug-polymer dispersion. After swelling of the polymer solution, it was casted on the film former apparatus with spreader. The temperature of the apparatus was maintained at 50°C. The casted solution was retained for 6hrs and then it was slowly peeled off from the apparatus. It was kept in desiccators for further studies [7,8].

Table 2: Formulation table for zolmitriptan oro flash films

Ingredients	F1	F2	F3	F4
Zolmitriptan (mg)	100	100	100	100
Hydroxy propyl methylcellulose (HPMC)-E50 LV (%)	5	5	10	10
Propylene glycol (% W/W)	20	20	20	20
Sodium starch glycolate-Primojel (%)	3	8	-	-
Citric acid (mg)	50	50	50	50
Menthol(ml)	2	2	2	2
Cross carmalose sodium(%)	-	-	3	8
Purified water (ml) q.s	25	25	25	25

Evolution Tests for Oro Flash Films

Weight variation test:

The study was carried out on ten films obtained from each formulation batch. The mean weight of film as well as the deviation from the mean was calculated and recorded [9,10].

Transparency:

It can be determined using a simple UV – Visible spectrophotometer. The film samples are made into small pieces and placed in spectrophotometer cell. This determines the transmittance of films at 600 nm. The transparency of film is calculated by using formula [11,12].

Transparency = (log T600) / b = -εc

Where, T600= transmittance at 600 nm
b= film thickness (mm)
c= is concentration

Thickness of film:

Thickness of film is measured using dial gauge or Vernier calipers or screw gauge or microscope. Thickness at different points were measured from which the average thickness of film is determined [13,14].

Folding endurance:

The folding endurance is 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 or cracking gives the value of folding endurance. Folded up to 300 times which is considered satisfactory to reveal good film properties [15,16].

Surface pH of film:

The surface pH of film 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 oral mucosa. It was determined to keep the surface pH as close to neutral as possible. The films were allowed to swell in closed Petri dish at room temperature for 30 minutes. In that, 1ml of solution was placed under digital pH meter to determine the surface pH of film [3,17].

Water uptake test or swelling study:

The film sample was taken weighed and placed on a pre-weighed stainless steel wire mesh. The wire mesh is submerged in a Petri dish containing 40 ml of 6.8 phosphate buffer. Increase in weight of film was determined at regular time intervals until constant weight is obtained. The hydration ratio of the film was calculated using following formula [10,17].

Swelling index (SI) = (Wt – W0) /W0

Where, Wt = weight of film at‘t’ time
W0 = weight of film at ‘0’time

Drug content or drug uniformity:

The drug content and uniformity test was performed to ensure uniform and accurate distribution of drug. Each film was dissolved in 50 ml volumetric flask containing methanol. Then solution was filtered through what Mann filter paper No. 41. Aliquot of a 1 ml of filter solution taken into 25 ml of volumetric flask made up to 25 ml with 6.8 phosphate buffer. Then solution analyzed by U.V spectrophotometer at 223 nm against in phosphate buffer pH 6.8 solution as blank [6,18].

***In vitro* disintegration test:**

The disintegration time is the time when a film starts to break or disintegrate. The disintegration test of fast dissolving film was carried out using single unit disintegration apparatus containing 900 ml of 6.8 phosphate buffer. Switch on the disintegration apparatus and set temperature to 37.5 ± 0.5°C. After reaching, the temperature film is placed on disintegration apparatus time required to start break film is noted as disintegration time of particular film [8,18].

***In vitro* dissolution studies:**

In vitro dissolution study can be performed using the 8-stage USP type –II apparatus paddle as per the pharmacopeia. Mainly paddle type dissolution was used to study the rate of drug dissolution test from the developed oral films. It is customary to assess the tendency of the strip to float on to the dissolution medium or not. *In vitro* dissolution can be performed by using USP- Type II apparatus (Disso 2000 with auto sampler) containing 6.8 phosphate buffer at the speed of 50 rpm with 37.5 ± 0.5°C [9,10].

RESULTS AND DISCUSSION

FTIR Studies

The FT-IR spectra of zolmitriptan and its respective films were recorded. The FTIR spectra of pure zolmitriptan (Figure 1) displayed bands at 3450 cm^{-1} due to N-H stretch, at 1736 cm^{-1} due to C=O stretching, at 1651 cm^{-1} due to heterocyclic C=C stretching. The spectra also showed bands at 1370 cm^{-1} due to C-H bending. The FTIR spectrum of film containing zolmitriptan 5.2 exhibited characteristic bands consistent with the molecular structure of zolmitriptan such as bands at 3456 cm^{-1} due to N-H stretch, at 1736 cm^{-1} due to C=O stretching, at 1650 cm^{-1} due to heterocyclic C=C stretching, at 1370 cm^{-1} due to C-H bending. Thus, the presence of characteristic absorption bands of zolmitriptan and the film containing zolmitriptan suggest that there was not any drug to excipient incompatibility in the designed formulation.

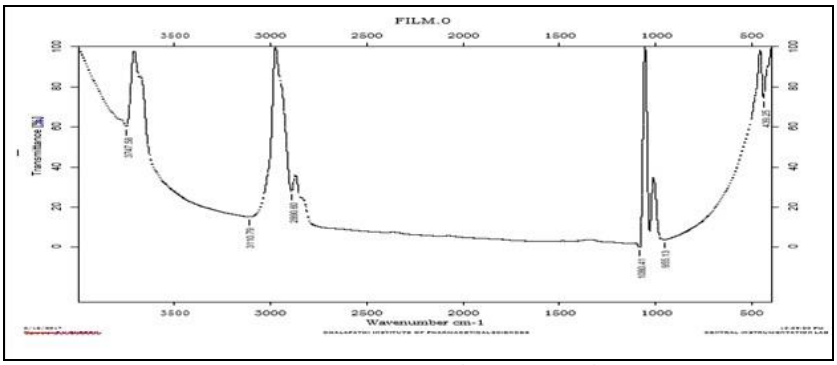

Figure 1: FTIR spectrum of zolmitriptan film

Differential Scanning Calorimetry

The DSC thermogram of zolmitriptan exhibited an endothermic peak at 132°C corresponding to its melting point of the drug. The DSC thermograms of zolmitriptan with other excipients does not show profound shift in peaks, which indicates compatibility. The DSC thermogram of the individual drug and drug with HPMC were shown in Figures 2 and 3.

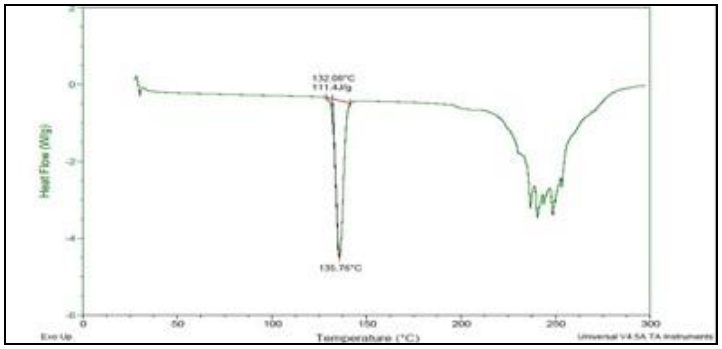

Figure 2: DSC thermogram of zolmitriptan pure drug

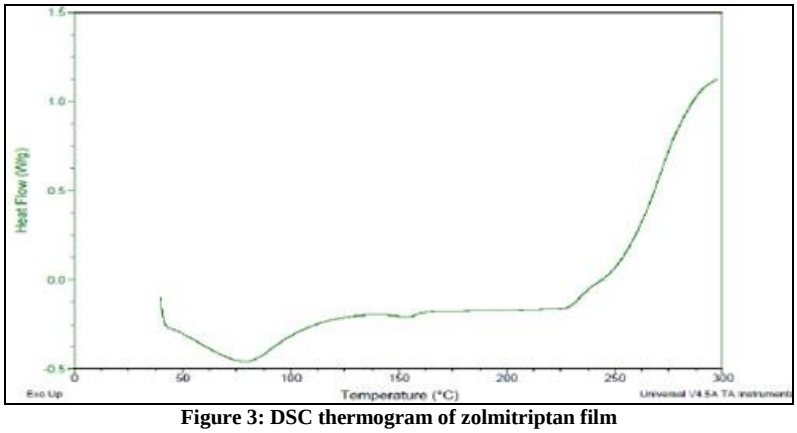

Figure 3: DSC thermogram of zolmitriptan film

Scanning Electron Microscopy

The prepared film containing zolmitriptan was clear and colorless. The scanning electron photomicrograph of the film at 1000 X magnification showed smooth surface with some little pores and without any scratches or transverse striations were shown in Figure 4.

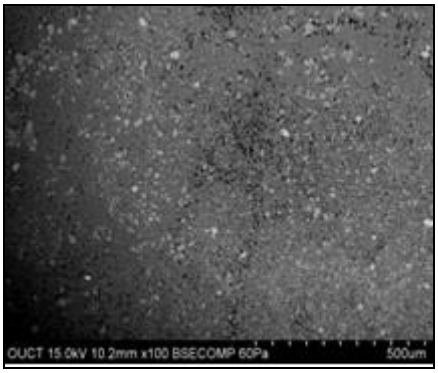

Figure 4: Scanning electron photomicrograph of the film

Physical Appearance and Surface Texture of Films

The appearance of all the films were uniform having transparent in appearance. The observation suggests that the films were having smooth surface and they were elegant enough to see. The results are shown in Table 3 and it is shown in Figure 5.

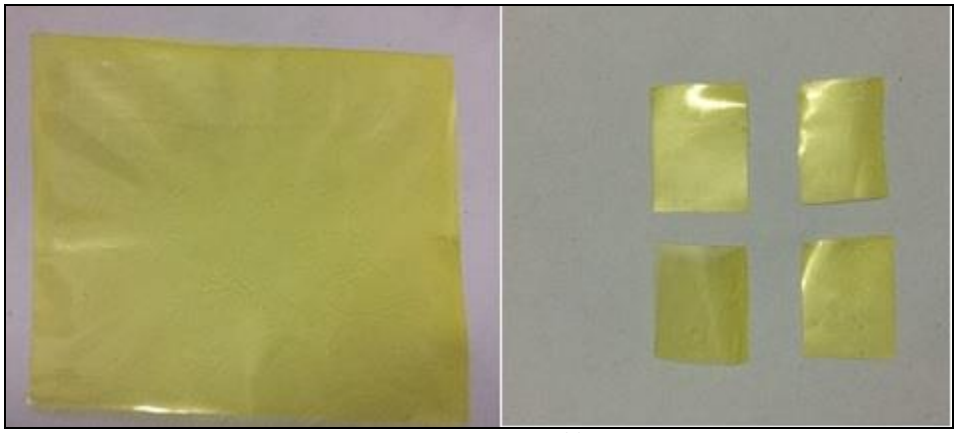

Figure 5: Photographs of films

Weight Uniformity

As all batches do not have uniform amount of ingredient in it, hence their weight and thickness were varied. Weight uniformity of the films was found to be between 34.1 ± 0.072 mg to 77.0 ± 0.144 mg. The results are shown in Table 3.

Thickness

Thickness of the films was found to be between 0.0208 ± 0.002 mm to 0.299 ± 0.005 mm. A very low standard deviation values indicated that the method used for the formulation of film is reproducible and gave film of uniform thickness and hence dosage accuracy in each film can be ensured. The results are shown in Table 3.

Surface pH

Surface pH of all films was found to be in the range of 6.53 to 6.80. All films were found to be in the range of salivary pH. The results are shown in Table 3.

Table 3: Physical properties of film

Formulation code	Physical appearance	Surface texture	Weight uniformity (mg±SD)	Surface pH	Thickness (mm±SD)
F1	Transparent	Very smooth	34.1 ± 0.072	6.67	0.0208 ± 0.002
F2	Transparent	Very smooth	46.2 ± 0.057	6.8	0.145 ± 0.004
F3	Transparent	Very smooth	57.1 ± 0.173	6.65	0.199 ± 0.004
F4	Transparent	Very smooth	63.4 ± 0.11	6.76	0.283 ± 0.003

Percentage Moisture Loss and Percentage Moisture Absorption

The study of percentage moisture loss and percentage moisture absorption gives the idea about the stability of the film in different environmental conditions. More the moisture absorption property of the film less stable it will be. However it was found that the % moisture absorption and percentage moisture loss was found to be appreciable with the use of hydrophilic polymer HPMC. Percentage moisture loss was found to be between 1.23 to 3.91 and percentage moisture absorption was found to be between 2.21 to 5.87. The results are shown in Table 4.

Disintegration Time

The disintegrating time limit of 30seconds or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral films. Although, no official guidance is available for oral fast disintegrating film, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeia disintegrating time for films is 5-30 sec. The *in vitro* disintegration time of the films were found to be between 10 ± 0.31 to 58 ± 0.45 sec. Study showed that disintegration time was increased with increase in the polymer concentration. The results are represented in Table 4.

Drug Content

Drug content of the films was found to be between 97.62 ± 0.011% to 100.01 ± 0.063%. The observed result indicate that the drug was uniformly dispersed throughout the film. The results are shown in Table 4.

Table 4: Physical properties of film

Formulation code	%Moisture loss (X±SD)	Disintegration time (sec) (X±SD)	%Drug content (X±SD)	Folding endurance (X±SD)
F1	12.3	2.61	97.62 ± 0.011	262 ± 2
F2	1.85	3.48	98.04 ± 0.022	273 ± 5
F3	2.63	4.98	98.86 ± 0.034	272 ± 6
F4	2.95	5.01	99.63 ± 0.005	281 ± 3

***In vitro* Release Studies**

Dissolution study indicates the rate and extent of absorption. The *in vitro* dissolution of Zolmitriptan films were carried out using 900 ml phosphate buffer of pH 6.8 using USP II paddle type apparatus. *In vitro* dissolution study for all the batches were performed for 5minutes. The results are shown in Table 5.

Cumulative % Drug Dissolution of Zolmitriptan Films

Table 5: *In vitro* release studies of fast dissolving oral films of Zolmitriptan

Time (mins)	F1	F2	F3	F4
0	0	0	0	0
0.5	36	47	56	58
1	45	78	89	87
1.5	52	80	91	89
2	65	82	96	92
2.5	73	85	98	95
3	76	86	100	97
3.5	78	90	99	98
4	82	92	99	99
4.5	85	95	99	99
5	87	97	99	99
T50%	1.3	1.4	0.6	0.5
T90%	5	2.5	3.7	1.4

***In vitro* Drug Release Study of Zolmitriptan Oral Films**

Dissolution rate studies data of all the films F1 to F4 was depicted in Table 5 respectively the release rate of drug took 5 mins. The low release rate was due to less level of super disintegrants and the molecular weight of the polymer. The results are shown in Figure 6.

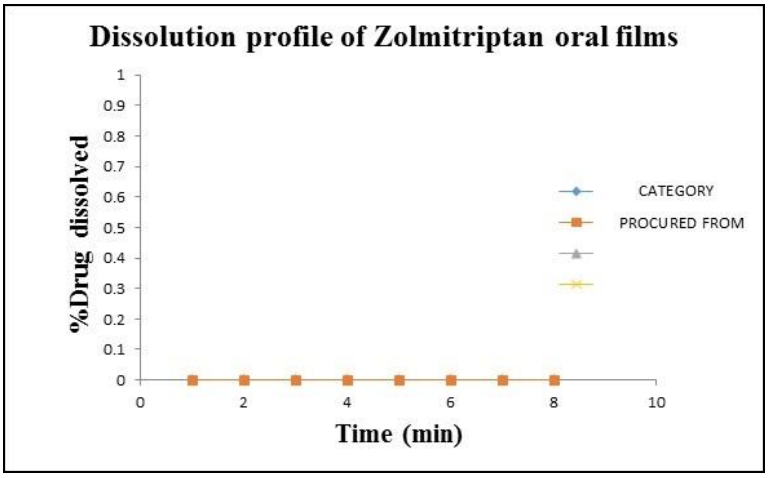

Figure 6: *In vitro* release studies of zolmitriptan oral films

Dissolution studies of F3 to F4 revealed that the film containing HPMC E-50 LV has release 90.98%, 99.74% respectively of drug in 5 minutes. It was found that increase in the polymer concentration significantly increased the dissolution time of drug. The slow drug release mechanism for higher polymer concentration can be explained by reduction in permeability due to change in the morphology of the polymer. Increased polymer concentration may have provided the matrix with higher tortuosity and poor water porosity for diffusion of drug. Moreover, higher polymer concentration would have resulted in viscous environment of the system inhibiting movement of water into the matrix for easy diffusion of the drug into the surroundings.

CONCLUSION

The following conclusions can be drawn from the obtained results. The drug zolmitriptan was found to feasible to develop into oral flash films. The method solvent casting adopted for the formulation of zolmitriptan oral films is convenient and economical. The super disintegrants employed in this work was found to appreciable and prospective. The drug-excipient compatibility by FT-IR and DSC revealed no

physicochemical interaction. Oral film formulation F3 having cross carmalose sodium, as super disintegrants has shown appreciable dissolution profile than the other formulations. The oral films obtained found clear, enough physical strength and showed reasonable degree of disintegration time. The *in vitro* dissolution studies of all the formulations in contrast of pure drug showed better release profile.

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