DEVELOPMENT AND CHARACTERIZATION OF MOUTH DISSOLVING FILMS ZOLMITRIPTAN

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Abstract

This study focuses on the formulation and characterization of mouth dissolving films (MDFs) loaded with zolmitriptan (ZOL). Eleven different formulations of ZOL MDFs were prepared, each containing 1.25% w/w of the drug, and subsequently evaluated for various parameters. The morphological properties assessment revealed that all formulations exhibited homogeneity, transparency, and colorlessness, with both sides being smooth. The thickness of the films varied between 70.00±0.00 and 108.33±4.08 mm. The formulation F2(A) demonstrated the highest drug content at 1.39±0.01%, while F6 exhibited the lowest at 0.70±0.01%. The weight variation ranged from 4.00±0.01 in F7 to 5.67±0.03 in F2(A). The tensile strength exhibited variability from 3.38 ± 0.26 µm to 15.32 ± 0.11 µm in F5, and the % elongation ranged from 32.50 ± 0.52 cm to 97.64 ± 1.40 cm. The folding endurance showed a range from 16±60 in F2(A) to 115±50 in F7. The disintegration time, assessed by both drop and Petri plate methods, varied across formulations. The drop method indicated the lowest disintegration time in F7 and F4 at 11.00±0.00, while the Petri plate method showed the lowest time of 22.33±0.58 seconds in F4. Based on the overall evaluation, formulation F7 was deemed the ideal formulation. In vitro drug release from ZOL, F7 was observed to be 101.94±1.61 in 180 seconds. The first-order release kinetics showed an R_2 value of 0.996, while the Higuchi kinetics exhibited an R_2 value of 0.993, indicating that the formulation follows first-order release kinetics. Stability studies conducted over six months demonstrated that, at the end of the period, the formulation remained transparent with a weight variation of 97-99% and drug content of 96-99%. Therefore, it can be concluded that the F7 formulation of Zolmitriptan MDF is a viable option for the efficient administration of the drug.

Keywords: Zolmitriptan, MDF (Mouth dissolving film), Formulation, Disintegration time

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Introduction

The primary choice for drug administration is often oral, as it provides a convenient, comfortable, flexible, and consistent approach for patients, widely recognized and accepted by them. However, modern inventive inventions have introduced various alternatives to the traditional oral route, catering to the diverse needs of individuals, including the young, elderly, ill, and those with difficulties following traditional oral drug delivery methods (Keshavarao et al., 2011).
Oral disintegrating films, a form of oral medication delivery, emerged in the latter half of the 1970s as an alternative for patients who faced challenges swallowing conventional dosage forms. These films, made with hydrophilic polymers, dissolve rapidly upon contact with saliva, providing a user-friendly option. In comparison to oral dissolving tablets that came before them, these films, often similar in size to a postage stamp, addressed issues such as biting and swallowing, making them more patient-friendly (Nagar et al., 2011; Pawar et al., 2019).

Mouth Dissolving Film (MDF) formulations represent a cutting-edge advancement in the pharmaceutical industry, holding the potential to become a highly promising dosage form for treating various illnesses. These formulations offer increased safety, effectiveness, patient acceptance, and compliance compared to traditional forms. While currently limited to certain diseases, the versatility of MDFs suggests they could be employed for the treatment of additional conditions with the right Active Pharmaceutical Ingredient (API) (Dahiya et al., 2009; Senthilkumar and Vijaya, 2015).

Individuals experiencing migraines, with or without an aura, can find relief through the acute treatment with 5-HT(1B/1D/1F) receptor agonists like zolmitriptan. Zolmitriptan, a selective agonist of the 5-hydroxytryptamine 1B/1D receptor, exhibits only modest affinity for the 5-HT 1A receptor subtypes. Its primary effects on the 5-HT 1B/1D receptors involve the constriction of intracranial blood vessels and the prevention of pro-inflammatory neuropeptides release from trigeminal perivascular nerve endings. Radioactive [3H]-zolmitriptan labels in the trigeminal nucleus caudalis and nucleus tractus solitaries cells indicate its ability to cross the blood-brain barrier (Lipton and Stewart, 1993).

While zolmitriptan is available in various forms such as fast-dissolving tablets and nasal sprays, it is not currently offered in the form of a mouth dissolving film (MDF). Therefore, this study focuses on the formulation and characterization of mouth dissolving films loaded with zolmitriptan, presenting a potential novel approach for the acute treatment of migraines.

Materials and Methods

Chemicals and reagents

Sodium chloride, potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate, potassium phosphate dibasic, water, etc., were sourced from S.D. Fine Chemicals.

Preparation of MDF

As an initial step, dummy mouth dissolving films (MDFs) were fabricated using various polymers and plasticizers to determine the optimal blend for producing films with the desired mechanical strength and visual appearance. Zolmitriptan (ZOL) MDFs were then prepared in 5g batches using specific formulations. The ZOL medications were dissolved in a solvent combination of water and methanol in a separate beaker. Subsequently, plasticizers and other components were added with continuous stirring. The final step involved adding the polymer to each beaker and thoroughly stirring the mixture. Using a wet film applicator from Paul N. Gardner Company Inc, USA, the mixture was cast onto a glass plate at thicknesses of 30mil (750μm) and 40mil (1000μm) after a 2-minute sonication to remove air bubbles. The films were dried in a hot air oven at 40 degrees Celsius for 60 minutes. Once dried, the films were carefully removed from the glass plate, wrapped in foil, and stored in a desiccator until further use. The wet film applicator employed in this study was in accordance with the methodology described by Upreti et al. (2014).

Table 1: Formulae of HPMC-ZOL MDFs

Formulae (5g size)												
Ingredients (mg)	**F1***	**F2***	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
ZOL	100	100	100	100	-	-	-	-	-	-	-	-
	-	-	-	-	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
HPMC E3	375	375	375	375	375	375	375	375	-	-	-	-
HPMC E5	-	-	-	-	-	-	-	-	375	375	375	-
HPMC E15	-		-	-	-	-	-	-	-	-	-	375
PEG 400	25	-	25	-	-	25	25	25	25	25	25	25
Glycerol	-	25	-	25	25	-	-	-	-	-	-	-
PVP K30	-	-	2	2	-	-	2	-	-	2		-
SLS	-	-	-	-	-	-	-	2	-	-	2	-
Water	1730	1730	1728	1728	1767	1767	1765	1765	1767	1765	1765	1765
Pineapple flavour	10	10	10	10	10	10	10	10	10	10	10	10
Aspartame	10	10	10	10	10	10	10	10	10	10	10	10
Methanol	2750	2750	2750	2750	2750	2750	2750	2750	2750	2750	2750	2750

Evaluation of MDFs

Detailed analyses of the following attributes were performed on the produced ZOL MDFs.

Morphological properties

Zolmitriptan (ZOL) mouth dissolving films (MDFs) underwent a visual evaluation to assess attributes such as uniformity, color, clarity, and surface quality. All formulations were stored in a controlled environment with maintained temperature (25 ± 2°C) and humidity (65 ± 5%) for duration of 6 months, with aluminum foils utilized for film packaging. To establish a more detailed understanding of their morphological characteristics, the MDFs were examined at 10x magnification using a binocular microscope (Olympus-CH20i).

Thickness

A screw gauge with a range of 0-10mm and a rotation of 0.001mm was used to measure the thickness of, ZOL, and MDFs. With the thickness gauge's anvil cranked and the pointer set to zero, we were able to insert the film. The dial was read while holding the film against the anvil. Six separate estimates were made, and the mean and standard deviation were computed for each set of data.

Drug Content

Each 1cm2 film was cut from the top, middle, and bottom thirds and dissolved in 5mL of distilled water in a 10 mL volumetric flask. Distilled water was used to get the correct volume. After properly diluting the samples with synthetic saliva, the RP-HPLC technique was used to determine the levels of ZOL, the MDFs.

Variation of Mass:

By weighing pieces of film that were 1cm2 in size and taken from various locations, the authors of a 2013 study ere able to determine the mass difference across batches of formulations generated for each medicine. There were three separate sets of calculations done (Dinge *et al.*, 2008).

Tensile Strength

The tensile strength of a film is defined as the stress at which it breaks under tension (El-Setouhy DA et al., 2010). Using a MINI Tech Tensiometer-UTM9051 (Dak Systems Inc., Mumbai, India) with a load cell of 500N (50kg) capacity and Test Bench II software, the tensile strength of RIZ, ZOL, and ALMO MDFs was determined. Pneumatic grips were used to hold 10cm by 2cm by whatever thickness of MDF was necessary. The program was fed all the measurements in order to get the cross-sectional area. The MDF was folded tightly and inserted between the pneumatic grips. In order to shatter the film, the instrument was run at a speed of 5 mm/min. Parameter was done in duplicate to ensure accuracy.

Percent Elongation (%E):

Test Bench-II was used to determine the % elongation of RIZ, ZOL, and ALMO MDFs under tensile load in this investigation. The calculations were done in triplicate for accuracy.

Folding Endurance:

Folding endurance was measured by repeatedly folding the film at the same spot until it broke for ZOL MDFs. This demonstrates how fragile the film is. The folding endurance value of a film is determined by counting the number of times it can be folded without tearing. The calculations were done in triplicate for accuracy (Maheswari *et al.*, 2014).

In-vitro Disintegration Studies:
Here, we compare the results of two in-vitro disintegration experiments (drop and Petri dish techniques) of RIZ, ZOL, and ALMO MDFs (Garsuch V et al., 2010). Both approaches required little media to provide realistic simulations of natural environments

Drop Method:
One drop of distilled water was pipetted onto a 1 cm 2 MDF that was spread out flat on a glass slide in a Petri dish. The duration of the drop's dissolution of the film and subsequent whole formation was timed. The calculations were done in triplicate for accuracy.

Petri dish Method:
A 2x2 cm film was put on top of 2mL of distilled water in a Petri dish and the time it took for the film to fully dissolve was recorded. The calculations were done in triplicate for accuracy.

In-Vitro drug release studies:
500 mL of artificial saliva was used as the dissolving medium in in-vitro drug release experiments of ZOL MDFs using a USP Type V dissolution rate testing system (Okamoto *et al* 2001). The set parameters included 370°C and 50 rpm At regular intervals, 2 mL of the dissolving media was discarded and replaced with new sample. Using the RP-HPLCPDA technique, we examined the samples. The dissolving tests were repeated three times.

Stability Studies:
A variety of ZOL MDFs were tested for stability, (F7) with 1.25% w/w ZOL Aluminum pouches containing the MDFs were sealed and kept for six months at 40oC/75 5% RH. Selected ZOL, MDFs were analysed for their appearance, weight, drug content, and in vitro drug release capabilities.

Statistical Analysis:
One-way analysis of variance (with Fisher's LSD post hoc test) was performed on the experimental data for each medication using SYSTAT software (SYSTAT Software Inc., San Jose, USA). Significant findings were defined as those with a probability level of p 0.05.

Results and Discussion
A total of 11 formulations of Zolmitriptan (ZOL) mouth dissolving films (MDFs) were prepared at a concentration of 1.25% w/w and subjected to comprehensive evaluations. Morphological assessments revealed that all formulations exhibited homogeneity, transparency, and colorlessness, with smooth surfaces on both sides. Film thickness ranged from 70.00±0.00 to 108.33±4.08 mm, and the highest drug content was observed in formulation F2 (A) at 1.39±0.01%, while the lowest was in F6 at 0.70±0.01%. Weight variation spanned from 4.00±0.01 in F7 to 5.67±0.03 in F2 (A). Tensile strength varied between 3.38 ± 0.26 µm and 15.32 ± 0.11 µm in F5, while % elongation ranged from 32.50 ± 0.52 cm to 97.64 ± 1.40 cm. Folding endurance varied from 16±60 in F2 (A) to 115±50 in F7. The drop method indicated the lowest disintegration time in F7 and F4 at 11.00±0.00, while the Petri plate method showed the lowest time of 22.33±0.58 seconds in F4. Considering these results, formulation F7 was deemed the ideal. In-vitro drug release for ZOL F7 was 101.94±1.61 in 180 seconds. The R^2 value for first-order kinetics was 0.996, and for Higuchi kinetics, it was 0.993. Stability studies over six months demonstrated that, at the end of the sixth month, the formulation remained transparent with weight variation of 97-99% and drug content of 96-99%.

Table 2: Morphological properties of ZOL (1.25%w/w) MDFs

Formulations	Initial Properties		Time Points (months)					
	0 months	0.5	1	2	3	4	5	6
F1	Homogenous, transparent, colorless, both sides smooth	x*	-	-	-	-	-	-
F1(A)	-do-	x*	-	-	-	-	-	-
F2	-do-	x*	-	-	-	-	-	-
F2(A)	-do-	x*	-	-	-	-	-	-
F3	-do-	x*	-	-	-	-	-	-
F4	-do-	x*	-	-	-	-	-	-
F5	-do-	x	x	x	x	x	x	x
F6	-do-	x	x	x	x	x	x	x
F7	-do-	x	x	x	x	x	x	x
F8	-do-	x	x	x	x	x	x	x
F9	-do-	x	x	x	x	x	x	x
F10	-do-	x	x	x	x	x	x	x
F11	-do-	x	x	x	x	x	x	x

Table 3: Results of various evaluation parameters

F. Code	Thickness Mean ± SD	Drug content%	Weigh variation	Tensile strength (µm)	% elongation (cm)	Folding endurance	Disintegration time (Sec)	
							Drop method	Petri plate method
F1	70.00±0.00	1.09±0.05	4.06±0.16	3.38 ± 0.26	93.02 ± 0.80	106±30	21.33±0.58	30.00±0.00
F1(A)	100.00±0.00	1.30±0.16	5.48±0.05	11.68 ± 0.45	40.19 ± 0.96	34±50	60.33±0.58	82.33±0.58
F2	78.33±4.08	1.18±0.04	4.35±0.08	7.78 ± 0.28	73.00 ± 0.27	74±4.58	17.33±1.73	27.67±0.58
F2(A)	108.33±4.08	1.39±0.01	5.67±0.03	8.85 ± 0.60	32.50 ± 0.52	16±60	50.67±2.31	75.67±0.58
F3	71.67±4.08	1.06±0.02	4.11±0.02	8.47 ± 0.36	92.15 ± 0.79	109±11	12.00±0.00	24.00±1.00
F4	80.00±4.08	1.08±0.03	4.78±0.01	9.54 ± 0.15	71.45 ± 1.37	78±7.54	11.00±0.00	22.33±0.58
F5	81.67±4.08	0.75±0.02	4.67±0.03	15.32 ± 0.11	94.86 ± 0.30	72±7.54	17.67±0.58	28.67±1.15
F6	68.33±4.08	0.70±0.01	3.52±0.00	10.40 ± 0.32	85.08 ± 2.79	107±4.24	23.00±0.00	32.33±0.58
F7	70.00±0.00	0.75±0.00	4.00±0.01	12.63 ± 0.21	80.87 ± 0.22	115±50	11.00±0.00	24.67±0.58
F8	70.00±0.00	0.76±0.02	4.00±0.02	8.08 ± 0.14	78.18 ± 0.72	114±5.29	12.66±0.58	24.00±0.00
F9	78.33±4.08	0.71±0.03	4.32±0.03	7.40 ± 0.36	74.76 ± 0.31	92±60	28.00±0.00	38.00±0.00
F10	80.00±0.00	0.76±0.02	4.35±0.02	8.67 ± 0.34	97.64 ± 1.40	87±30	18.67±0.58	34.00±0.00
F11	80.00± 0.00	0.75±0.05	4.41±0.08	7.78 ± 0.28	91.07 ± 0.80	82±3.60	20.00±0.00	35.00±0.00
F12	88.33±4.08	0.79±0.06	4.95±0.06	4.41 ± 0.43	89.38 ± 0.70	88±2.64	33.33±0.58	42.67±0.58

Table 4: In-vitro drug release data of ZOL F7 (n=3)

Time(sec)	Percent ZOL released			Mean ± SD
	Trial 1	Trial 2	Trial 3	
0	0	0	0	0±0.00
5	24.15	21.59	23.35	23.03±1.31
10	33.62	30.21	31.48	31.77±1.72
20	41.52	44.87	43.15	43.18±1.68
30	48.26	49.31	50.02	49.20±0.89
40	54.92	54.78	57.14	54.28±1.19
50	60.61	62.22	63.86	62.23±1.09
60	68.47	69.36	70.64	69.49±2.91
80	72.69	74.13	78.47	75.76±2.22
100	81.28	85.49	84.63	83.80±1.69
120	92.37	94.51	91.17	92.68±1.69
180	103.35	102.28	100.19	101.94±1.61

Table 5: DP_5 and First order kinetic data of ZOL formulations

Formulation	DP_5★ (Mean ± SD)	R^2 (First order plot)	Mean 'k' (sec^{-1}) (0-40 sec)
F7	23.03 ± 1.31	0.996	0.025

Table 6: Higuchi plot-R^2 values of ZOL formulations

Formulation	R^2	KH(sec-1/2)
F7	0.993	12.18

Table 7: Stability studies data for MDFs (n=3)

MDFs	Parameter	Time period (months)		
		0	3	6
ZOL MDFs	Appearance	Transparent	Transparent	Transparent
	Weight variation	95-100%	96-100%	97-99%
	ZOL content	95-100%	95-99%	96-99%

Conclusion

The mouth dissolving films of Zolmitriptan were successfully prepared. The drug Zolmitriptan is used to treat acute migraine headaches in adults was chosen to prepare mouth dissolving film. HPMC E3 , HPMC E5 , HPMC E15 , PEG 400, Glycerol, PVP K30 used for production of mouth dissolving films containing Zolmitriptan In light of this physiochemical description Zolmitriptan in vitro drug diffusion and release kinetics revealed 101% of the drug at the 180 seconds mark. According to the evaluation test, Zolmitriptan films show promise for development as quickly dissolving films with the aforementioned

excipients that can improve diffusion, which could affect release and, consequently, bioavailability.

References

1. Keshavarao KP, Mudit D, Gunashekara K, Anis S, Singh Mangla N, Ajay K. Formulation and evaluation of mouth dissolving film containing rofecoxib. IRJP. 2011;2(3):273-8.
2. Nagar P, Chauhan I, Yasir M. Insights into polymers: film formers in mouth dissolving films. Drug Invent Today. 2011 Dec 1;3(12).
3. Pawar R, Sharma R, Sharma P, Darwhekar GN. A review on mouth dissolving film. J Drug Deliv Ther. 2019 Nov 15;9(6):206-10. doi: 10.22270/jddt.v9i6.3676.
4. Dahiya M, Saha S, Shahiwala AF. A review on mouth dissolving films. Curr Drug Deliv. 2009 Oct 1;6(5):469-76. doi: 10.2174/156720109789941713, PMID 19751197.
5. Senthilkumar K, Vijaya C. Formulation development of mouth dissolving film of etoricoxib for pain management. Adv Pharm. 2015 Jan 26;2015:1-11. doi: 10.1155/2015/702963.
6. Lipton RB, Stewart WF. Clinical applications of zolmitriptan (Zomig™, 311C90). Cephalalgia. 1997 Oct;17(18);Suppl 18:53-9. doi: 10.1177/0333102497017S1807, PMID 9399017.
7. Upreti K, Kumar L, Anand SP, Chawla V. Formulation and evaluation of mouth dissolving films of paracetamol. Int J Pharm Pharm Sci. 2014;6(5):200-2.
8. Dinge A, Nagarsenker M. Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity. AAPS PharmSciTech. 2008 Jun;9(2):349-56. doi: 10.1208/s12249-008-9047-7, PMID 18431674.
9. Maheswari KM, Devineni PK, Deekonda S, Shaik S, Uppala NP, Nalluri BN. Development and evaluation of mouth dissolving films of amlodipine besylate for enhanced therapeutic efficacy. J Pharm (Cairo). 2014;2014:520949. doi: 10.1155/2014/520949, PMID 26556197.
10. Garsuch V, Breitkreutz J. Comparative investigations on different polymers for the preparation of fast-dissolving oral films. J Pharm Pharmacol. 2010 Apr;62(4):539-45. doi: 10.1211/jpp.62.04.0018, PMID 20604845.
11. Okamoto H, Taguchi H, Iida K, Danjo K. Development of polymer film dosage forms of lidocaine for buccal administration: I. Penetration rate and release rate. J Control Release. 2001 Dec 13;77(3):253-60. doi: 10.1016/s0168-3659(01)00509-0, PMID 11733093.