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Formulation Development & Evaluation of Mouth Dissolving Film of Zolmitriptan as an Antimigraine Medication

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Abstract

Zolmitriptan is a selective serotonin receptor agonist of the $5HT_{1B}$ and $5HT_{1D}$ subtypes, both centrally and peripherally. It has been used clinically for the acute treatment of migraine attacks with or without aura and cluster headaches. Zolmitriptan has oral bioavailability of 40-48% due to hepatic first pass metabolism and has short half life of 3 h. To overcome the above draw back the present study was carried out to formulate and evaluate mouth dissolving film of Zolmitriptan. The films were prepared from water soluble polymers such as Hydroxypropyl methylcellulose (HPMC K4M), and polyvinylalcohal (PVA) by solvent casting method. Propylene glycol as plasticizer, Sodium saccharin as sweeteners and other excipient such as citric acid, tween 80 were also included. The IR spectral studies showed no interaction between drug and polymer or with other additives. Satisfactory results were obtained when subjected to physicochemical tests such as uniformity of weight, thickness, surface pH, folding endurance and uniformity of drug content. Films were also subjected to *in vitro* drug release studies by using USP dissolution apparatus. The film formulation F5 containing HPMC K4M was found to be suitable in form of MDF based on in vitro evaluation studies.
Keywords: Mouth dissolving film, Antimigraine drug, Solvent casting method, HPMC, PVA.

Contents

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1. Introduction

Among the delivery routes, the oral route is the most acceptable from patient compliance aspects. More than 70% of drugs are available in market in the form of oral drug delivery system due to pain avoidance and versatility [1, 2]. In various intraoral dosage forms fast dissolving drug delivery system is most convenient mode of administering drugs to overcome problem related to swallowing difficulties [3, 4]. More recently, Mouth- dissolving films are gaining interest as an alternative to fast-dissolving tablets to definitely eliminate patients' fear of chocking and overcome patent impediments [5,6]. Mouth dissolving films are solid dosage forms, which disperse or dissolve within one minute, when placed in the mouth without drinking or chewing. 7 Mouth dissolving film is simply placed on the

patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed [8].

Migraine is a common, chronic, multifactorial neurovascular disorder, typically characterized by recurrent disabling attacks of severe headache, autonomic nervous system dysfunction and, in up to a third of patients, neurological aura symptoms.9 Migraine can occur in children as well as adult and it is three times more common in women than in men. Usual symptoms in adult include extreme pain on one or both side of the head, throbbing in nature, pain in eye, jaw, face or neck, photophobia and phonophobia, nausea and vomiting and symptoms worsen with ever minor exertion. Usually migraines episodes typically last 4-72 h. Sometimes tension headache, cluster headache and the headache of subarachnoid hemorrhage are mistaken for headache. Occasionally children have the symptoms that escort a migraine which are light sensitive nausea, and vomiting without headache. This type is called abdominal migraine, usually be hard to diagnose [10].

Ergot derivatives used to be the only specific treatments for migraine attacks, although they had many limitations. Improved understanding of the neurobiology of migraine and 5-HT (5-hydroxytryptamine serotonin) receptors have resulted in a new class of selective 5- $HT_{1B/1D}$ agonists, known as the triptans. Sumatriptan is the first and most widely prescribed triptan: most European countries use 100 mg as the primary oral dose, whereas North America and some other countries use 50 mg. 2.5 mg Zolmitriptan had a slightly higher response rate than 100 mg sumatriptan ($p<0\cdot05$)9. Zolmitriptan is a second-generation triptan prescribed for patients with migraine attacks, with and without an aura, and cluster headaches. It has a selective action on serotonin receptors and is very effective in reducing migraine. It binds with high affinity to human recombinant 5-HT_{1D} and 5-HT_{1B} receptors[11, 12].

2. Materials and Method

Materials:

Zolmitriptan was obtained as a gift sample from Glenmark Generics Limited (Colvale) Goa, India. Polymers, organic solvents used were of analytical grade and other chemical of laboratory gread.

Method of Preparation of Mouth Dissolving Film:

Solvent casting method

The mouth dissolving films of Zolmitriptan were prepared by the solvent casting technique using HPMC K4M and PVA as a film forming polymer. Propylene glycol as a plasticizer. Citric acid as saliva stimulating agent. Sodium saccharin as a sweetening agent. The mouth dissolving films of Zolmitriptan were formulated by solvent casting method, by dissolving weighed quantity of drug in required volume of water.

The selected concentration of polymers added to another beaker and dissolve by adding sufficient amount of water. Then both the solution was mixed together. Initially stirring was carried out at low RPM and later at higher speed. The required quantity of plasticizer was added drop wise. The solution was casted on to Petri dish (area of 64 cm^2) within inverted funnel and allowed to dry overnight at room temperature. The films were removed carefully and an area of 4 cm^2 was punched out so that each film contained 2.5 mg of the drug. The dried films were wrapped in butter paper then cover with aluminum foil and kept in desiccators.

Table 1: Formulation of Zolmitriptan mouth dissolving film (Weight in mg)

S.No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1.	Zolmitriptan	40	40	40	40	40	40	40	40
2.	PVA	400	600	400	600	-	-	-	-
3.	HPMC K4M	-	-	-	-	400	600	400	600
4.	Propylene glycol (%)w/w	25	25	30	30	25	25	30	30
5.	Citric acid	45	45	45	45	45	45	45	45
6.	Sodium saccharin	10	10	10	10	10	10	10	10
7.	Tween 80 (ml)	1	1	1	1	1	1	1	1
8.	Water(ml)	20	20	20	20	20	20	20	20

Drug polymer compatibility studies

Drug polymer compatibility studies were carried out using FTIR spectrometer.

EVALUATIONS OF MOUTH DISSOLVING FILMS:

Appearance

All prepared films were checked for their appearance either they are transparent or opaque or presence of air bubble.13

Thickness uniformity

The thickness of the film was measured using digital Vernier Caliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different Spots of the film and average was taken and Standard Deviation was calculated.14

Weight variation of the film

Two centimeter square of the film was cut at three different places in the caste film. The weight of each filmstrip was taken and the weight variation was calculated.15

Folding endurance

Folding endurance of the film was determined repeatedly by folding a small strip of film (2 cm x 2 cm) at the same place until it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance.16

Surface pH

The surface pH of the films was determined in order to investigate the possible side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the buccal mucosa. The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 1 h. pH was noted with the electrode of the pH meter. The average of three determinations for each formulation was done.17

Drug content:

This parameter was determined by dissolving film of 2 × 2 cm diameter(an area of 4 cm2) containing 2.5 mg of Zolmitriptan in 50 ml simulated salivary fluid with occasional shaking. Filtration was carried out to remove insoluble residue, 1 ml of the filtrate was diluted to 10 ml with simulated salivary fluid (pH 6.8). The absorbance was measured at 282.6 nm using an UV spectrophotometer. The experiments were carried out in triplicate for the films of all formulations.18

Disintegration Time

In vitro disintegration time was determined visually in a petridish containing 25 ml of pH 6.8 simulated salivary fluids with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates. 14,19

In-vitro dissolution studies

Dissolution study was carried out in USP basket type apparatus containing 300 ml of the simulated salivary fluid (pH 6.8) as a dissolution medium at 50 rotations per minute. The film was placed in the basket, maintained at 37± 0.5°C. 5ml aliquots were withdrawn at different time intervals and same amount of fresh dissolution medium was added. The aliquots were assayed for drug content at 282.6 nm wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated.20,21

3. Results and Discussion

FTIR studies

The comparison of the IR spectrum exposed that there is no appreciable change in the positions of characteristic absorption bands of groups and bonds. The spectra of these, even though slightly differ in appearance but no change is observed in the positions of the bands in the spectra. This clearly suggests that the drug remains in the same form even in its formulations representing that there is no interaction between the drug and polymer used for the study. The results are shown in Figure1, 2, 3.

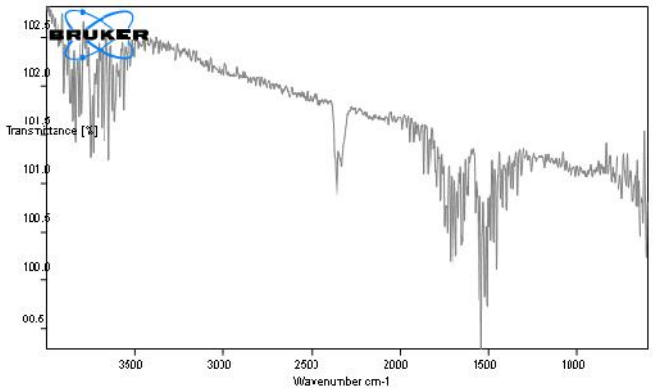

Figure 1: IR spectra of Zolmitriptan

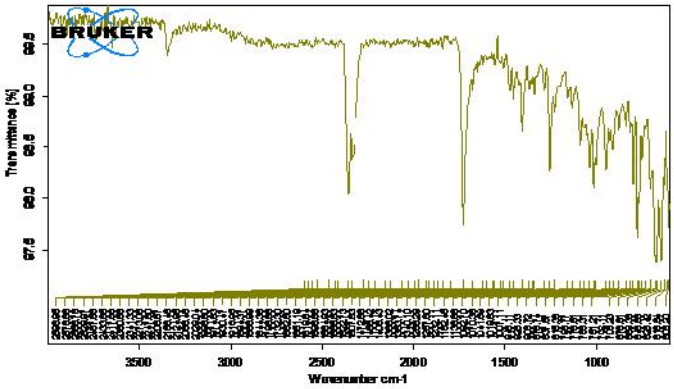

Figure 2: IR spectra of Zolmitriptan + HPMC K4M

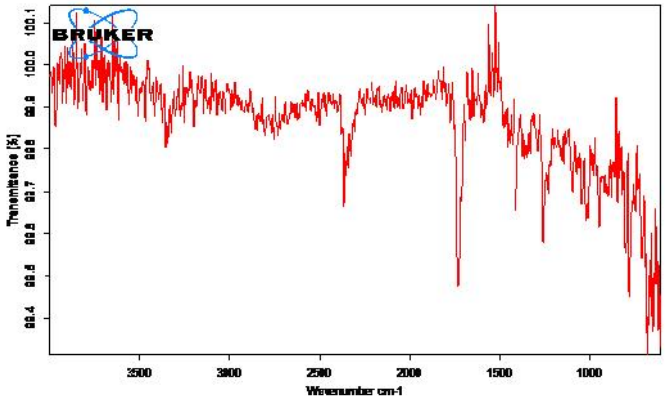

Figure 3: IR spectra of Zolmitriptan + PVA

Appearance

The appearance of all the films was uniform having transparent in appearance and having smooth surface.

Thickness uniformity

Thickness of the films was found to be between 0.126±0.01 mm to 0.148±0.01 mm. A very low standard deviation values indicates that the method used for the formulation of film is reproducible and give film of uniform thickness and hence dosage accuracy in each film can be ensured. The results are shown in Table 2.

Weight variation of the film

All batches do not have uniform amount of ingredient in it, so their weight was varied. Weight uniformity of the films was found to be between 39.66±0.573 mg to 63.66±1.525 mg. The results are shown in Table 2.

Folding endurance

Folding endurance measurement gives an indication of brittleness of the film. The value depends on hydrophilic polymer as well as plasticizer concentrations used. Folding endurance test result indicated that the film would not break and would maintain their integrity. Folding endurance for all the formulation was found to be more than 150 which was satisfactory to reveal good film property. Folding endurance of the films was found to be between 158.3±3.5 to 198.3±6.2. The results are shown in Table 2.

Surface pH

The surface pH of the films was ranging from 6.71±0.2 to 6.85±0.2. 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.

Drug content:

All the formulations of Zolmitriptan containing HPMC K4M and PVA polymers show uniform drug content as seen in Table 2.

Disintegration Time

The disintegration time of films was found to be decreased with increase in the concentration of the polymer. When placed over the tongue, the film dissolved instantly. The disintegration time of formulation F5 film was lowest, so they release drug faster than other formulation.

In-vitro dissolution studies

In vitro drug release study was carried out using USP dissolution apparatus, type-I. Comparative dissolution profile of all batches is given in Figure 4. Being the fast disintegrating formulations the release rates of all the formulations were very rapid. Formulation F5 released Zolmitriptan completely faster. This may be due to HPMC K4M and

propylene glycol that result in increase wettability and penetration of water into the film matrices and hence increased diffusion of the drug. Whereas release rates of other formulation were comparatively slowest.

Table 2: Evaluation parameters of Zolmitriptan films

Formulation code	Thickness (mm±SD)	Wight uniformity (mg±SD)	Folding endurance	Surface pH	Disintegration time	% drug content
F1	0.127±0.01	39.66±0.573	185.3±3.1	6.73±0.1	44.3±1.5275	93.84
F2	0.141±0.01	54±1.4142	172.6±2.8	6.73±0.3	45.3±1.5275	91.53
F3	0.133±0.01	45.33±0.573	174.3±6.0	6.71±0.2	50.6±1.5275	85.38
F4	0.151±0.01	63.66±1.525	158.3±3.5	6.72±0.1	53.3±1.5275	86.92
F5	0.126±0.01	40.33±0.575	198.3±6.2	6.85±0.2	32.3±1.5275	98.15
F6	0.144±0.02	52.66±0.573	182±3	6.78±0.1	37.6±1.5275	96.15
F7	0.129±0.05	46.33±1.5275	175±3	6.81±0.01	40.3±1.1547	93.07
F8	0.148±0.01	60.33±1.5275	167±2.64	6.82±0.03	42.3±0.5773	91.61

Table 3: Result of *In Vitro* Drug Release Studies of Formulation

Time(min)	Percentage drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
1	10.1535	8.76921	5.07693	4.15386	14.7693	11.5386	9.69238	8.76921
2	22.7842	19.5307	18.0842	16.2238	27.4762	23.7307	21.3921	19.5307
3	28.2386	27.7	25.7693	27.5693	41.3158	28.7386	27.2842	24.0079
4	39.3158	38.3079	29.4238	37.2535	51.6842	38.4386	37.4238	37.7842
5	46.8762	44.0079	37.7465	46.6307	58.5238	47.8307	45.8762	43.9386
6	55.9386	55.3307	42.5079	53.8465	66.8465	56.9079	54.4614	55.7238
7	63.7535	64.5238	51.0307	60.7079	73.9079	66.1238	62.2535	64.4614
8	72.1465	69.2386	56.9158	65.8238	80.6079	74.5535	70.6238	72.8693
9	79.7386	78.1693	63.8079	70.5465	88.7842	81.7238	78.1921	80.0158
10	89.282	87.237	67.5693	74.40769	97.53846	92.22308	86.33077	85.41538

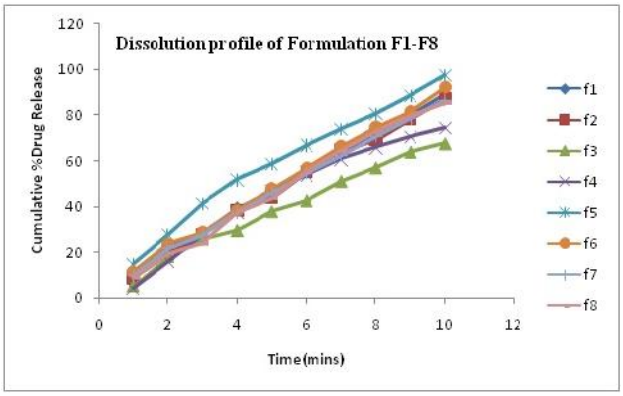

Fig. 4: In vitro release profile of Zolmitriptan in simulated salivary fluid

Stability studies

Films of formulation F5 were stored at storage condition 40 0C / 75% RH. Each film was wrapped in butter paper followed by aluminum foil. The films were evaluated for appearance, weight, drug content and in vitro drug release initially and after storage for 30days, 60days and 90 days. In vitro drug release after stability studies was compared with the drug release before the stability studies to identify any change in the drug release. There were no physical change in appearance and flexibility and result were shown table 4 that there were no major changes in disintegration time, drug content and in vitro drug release. Hence the formulation was found to be stable.

Table 4: Stability study of the A5 Formulation

Sr.No.	Time period (days)	Storage Condition	Disintegration time (sec)	% Drug Content	%CDR (at 10 min)
1.	0	40^0C and 75 % RH	32.3±1.5275	98.15	97.53
2.	30	400C and 75 % RH	33±1.7320	97.92	97.07
3.	60	400C and 75 % RH	33.3±1.5275	97.69	96.61
4.	90	400C and 75 % RH	33.6±1.1547	97.07	96.18

4. Conclusion

It can be concluded that formulation F5 containing, 400 mg of HPMC K4M and 25 % w/w propylene glycol was considered to be the optimized formulation. Increase in polymer concentration was found to influence in all the aspects of physicochemical and mechanical properties of the films. FTIR studies revealed that there is no interaction between drug and excipients. Formulation F5 shows minimum disintegration and dissolution time in comparison to other formulation. F5 was the best formulation showed 97.53% drug release in 10 min. *In vitro* stability evaluation of optimized formulation F5 with different environmental conditions, confirms the potential of films for longer storage. Hence, Zolmitriptan can be conveniently administered orally in the form of films.

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