DEVELOPMENT AND OPTIMIZATION OF ORAL FAST DISSOLVING FILMS OF ZOLMITRIPTAN

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ABSTRACT

An analysis of relationship between clinical end points and satisfaction found that more than 90% of patients who were pain free 2 hours somewhat satisfied with treatment, but satisfaction was dependent on relatively rapid pain relief. By assessing physician preference and practices, degree of pain relief and rapid onset were identified as the most important attributes of acute therapy. Based on results from preference studies of triptans,50% of patients more rapid pain relief as the most important determinant of treatment preference.

Triptans are the family of tryptamine- based drugs for the treatment of migraines and cluster headaches. They were first introduces in the 1990's.Their actions is attributed to their agonist effects on serotonin 5-Hydroxy tryptamine(5-HT)1 Band 5-HT1 D in Cranial blood vessels and subsequent inhibition of pro-inflammatory neuropeptide release. Evidence is accumulating these drugs are effective because they act on serotonin receptors in nerve endings as well as the blood vessels. This leads to a decrease in the release of several peptides, including Calcitonin, gene related peptide(CGRP) and substance P.

For purposes of this research invention, Zolmitriptan can be administered as the base or as any pharmaceutically acceptable salt than demonstrates adequate stability upon storage and bioavailability upon administration .Taste masked fast dissolving oral films of Zolmitriptan are more palatable form without need of water during administration.

Introduction

For the last two decades there has been an enhanced demand for more patient-compliant dosage forms. As a result there are now approximately 350 drug delivery corporations and 1000 medical device companies. The demand for their technologies was approximately 14–20 billion in 1995 and according to industry reports; this is expected to grow to 60 billion annually.

The novel technology of oral fast-dispersing dosage forms is known as fast dissolve rapid dissolve rapid melt and quick disintegrating tablets. However the function and concept of all these dosage forms are similar. By definition a solid dosage form that dissolves or disintegrates quickly in the oral cavity resulting in solution or suspension without the need for the administration of water is known as an oral fast-dispersing dosage form. Difficulty in swallowing (dysphasia) is common among all age groups especially in elderly and is also seen in swallowing conventional tablets and capsules. An estimated 35% of the general population and an additional 30–40% of elderly institutionalized patients and 18–22% of all persons in long- term care facilities suffer from dysphasia. This disorder is associated with many medical conditions including stroke Parkinson's AIDS thyroidectomy head and neck radiation therapy and other neurological disorders including cerebral palsy

.One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets. The most common complaint was tablet size followed by surface form and taste. The problem of swallowing tablets was more evident in geriatric and pediatrics patients as well as travelling patients who may not have ready access towater.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. To overcome the difficulties experienced by geriatric and pediatric patients in swallowing conventional oral dosage forms oral fast dissolving films were develope . They are ultra thin postage stamp size films prepared using hydrophilic polymers with an active agent and other pharmaceutical excipients.

Current Oral Fast-Dispersing Dosage Form Technologies:

Several methods are employed in the preparation of oral fast- dispersing tablets such as modified tabulating systems floss or Shear form formation by application of centrifugal force and controlled temperature and freeze drying.

Classification Of Fast Dissolve Technology:

For ease of description fast-dissolve technologies can be divided in to three broad groups:

- Lyophilized systems
- Compressed tablet-based systems
- Thin filmstrips

The lyophilized systems:

This system has been by far the most successful among them in terms of sales value sales volume and number of worldwide product approvals. The technology around these systems involves taking a suspension or solution of drug with other structural excipients and through the use of a mould or blister pack forming tablet-shaped units. The units or tablets are then frozen and lyophilized in the pack or mould. The resulting units have a very high porosity which allows rapid water or saliva penetration and very rapid disintegration. Dose-handling capability for these systems differs depending on whether the active ingredients are soluble or insoluble drugs with the dose capability being slightly lower for the former than for some tablet based systems. The units are capable of incorporating a range of taste-masked materials and have more rapid disintegration than tablet-based systems.

Compressed tablet-based systems

This system is produced using standard tablet technology by direct compression of excipients. Depending on the method of manufacture the tablet technologies have different levels of hardness and friability. These results in varying disintegration performance and packaging needs which can range from standard HDPE bottles or blisters through to more specialist pack designs for product protection for example The speed of disintegration for fast-dissolve tablets compared with a standard tablet is achieved by formulating using water soluble excipients or super- disintegrate or effervescent components to allow rapid penetration of water into the core of the tablet. The one exception to this approach for tablets is Biovail's Fuisz technology.

Oral Thin Films (OTF):

Oral films also called oral wafers in the related literature are a group of flat films which are administered into the oral cavity. Although oral film systems the third class have been in existence for a number of years they have recently become the new area of interest in fast- dissolve pharmaceutical drug delivery. Dissolvable oral thin films (OTFs) or oral strip (OS) evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for trans dermal drug delivery capitalized on the opportunity to transition this technology to OTF formats. Today OTFs are a proven and accepted technology for the systemic delivery of APIs for over-the-counter (OTC) medications and are in the early- to mid-development stages for prescription drugs.

This is largely as a result of the success of the consumer breath freshener products such as Listerine PocketPaks in the US consumer market. Such systems use a variety of hydrophilic polymers to produce a 50-200 mm film of material. This film can reportedly incorporate soluble insoluble or taste-masked drug substances. The film is manufactured as a large sheet and then cut into individual dosage units for packaging in a range of pharmaceutically acceptable formats**.**

Classification of Oral Film:

There are three different subtypes

- Flash release
- Mucoadhesive melt-away wafer
- Mucoadhesive sustained-release wafers

These three types of oral films are differentiated from each other in following table 2.

Table 1: Types of wafers and their properties

Property/Sub Type	Flash release water	Mucoadhesive melt-away wafer	Mucoadhesive sustained release wafer
Area (cm^2)	2-8	2-7	2-4
Thickness(µm)	20-70	50-500	50-250
Structure	Film: single layer	Single or multilayer System	Multi layer system
Excipients	Soluble highly hydrophilic polymers	Soluble hydrophilic Polymers	Low/Non-soluble Polymers
Drug phase	Solid solution	Solid solution or suspended drug particles	Suspension and/or solid solution
Application	Tongue(upper palate)	Gingival or buccal Region	Gingival (other region in the oral cavity)
Dissolution	Maximum 60 seconds	Disintegration in a few minutes forming gel	Maximum 8-10 hours
Site of action	Systemic or local	Systemic or local	Systemic or local

Advantages of Oral Thin Film

This dosage form enjoys some distinct advantages over other oral formulations such as-

- Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.
- The disadvantage of most ODT is that they are fragile and brittle which warrants special package for protection during storage and transportation. Since the films are flexible they are not as fragile as most of the ODTs. Hence there is ease of transportation and during consumer handling and storage.
- As compared to drops or syrup formulations precision in the administered dose is ensured from each of the strips
- Pharmaceutical companies and consumers alike have embraced OTFs as a practical and accepted alternative to traditional OTC medicine forms such as liquids tablets and capsules. OTFs offer fast accurate dosing in a safe efficacious format that is convenient and portable without the need for water or measuring devices.

Disadvantage of Oral Strip

The disadvantage of OS is that high dose cannot be incorporated into the strip. However research has proven that the concentration level of active can be improved up to 50% per dose weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone perstrip**.**

PHARMACOPOEIAL STATUS OF ORAL FILM:

Monographs of common dosage forms are provided by the pharmacopoeias (e.g. Ph. Eur. USP). Even though dosage forms for application in the oral cavity such as Medicated chewing gums Oromucosal preparations Orodispersible tablets or oral Lyophilisates are included monographs and specifications for oral films of diverse dissolution kinetics has not yet been established. There are inadequate pharmaceutical technical procedures for analysis in development and quality control of oral films as well. For instance disintegration and dissolution testing procedures may be provided but the recommended conditions such as volumes of media do not reflect the natural conditions in the oral cavity.

MATERIALS AND METHODS

1	Zolmitriptan	Chandra labs Hyderabad India.
2	Guar gum	Research-lab fine Chem industries Mumbai.
3	Aloevera	Research-lab fine Chem industries Mumbai.
4	Sodium alginate	Research-lab fine Chem industries Mumbai.
5	Poly ethylene glycol 400	Research-lab fine Chem industries Mumbai.
6	Sodium starch glycolate	Research-lab fine Chem industries Mumbai.
7	Vanillin	Research-lab fine Chem industries Mumbai.
8	Sodium Saccharine	Research-lab fine Chem industries Mumbai.

METHODOLOGY:

Preparation of fast dissolving oral films Film was prepared by using specified polymer by solvent casting method. The specified amount of polymer was weighed and dissolved in specified amount of water for overnight to get a uniform dispersion of different % (w/v) solutions. Drug sodium starch glycolate vanillin were dissolved in specific amount of water in a beaker. The drug solution was added to the polymer solution and mixed using magnetic stirrer for 1 hour. The resulting solution was degassed so as to remove any bubbles formed.

The bubble free solution was casted on to a Petri dish of surface area 28.26 cm2. It was dried for 24 hours at room temperature. The film was removed from the Petri dish very carefully and observed for any imperfections. Film that was clear and bubble free was selected for further studies. Film of area 2.25 cm2 (1.25 X 1.25) was cut and stored in a butter paper covered with aluminum foil and stored in desiccators.

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 formingpolymer
- Propylene glycol as aplasticizer
- Citric acid as saliva stimulatingagent
- Sodium saccharin as a sweeteningagent
- 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 byadding sufficient amount ofwater
- Then both the solution was mixed together. Initially stirring was carried out at lowRPM and later at higherspeed
- The required quantity of plasticizer was added drop wise. The solution was casted on to Petri dish (area of 64 cm2) within inverted funnel and allowed to dry overnight at room temperature.
- The films were removed carefully and an area of 4 cm2 was punched out so that each film contained 2.5 mg of thedrug
- The dried films were wrapped in butter paper then cover with aluminum foil and keptin desiccators

Preformulation studies:

Preformulation involves the application of pharmaceutical principles to the physicochemical properties of drug substance and is characterized with the goal of designing optimum drug delivery system.It pays a significant role in anticipating the formulation problems. Several formulation trails are made in order to obtain a good film by varying the ratios of HPMC PG and SSG. HPMC used between 2% to 8% PG used between 1% to 5% and SSG used between 1% to 6%.

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.

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.

Weight variation of the film:

- Two centimeter square of the film was cut at three different places in the castefilm
- The weight of each filmstrip was taken and the weight variation wascalculated

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.

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.

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.

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.

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.

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 0C 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.

Invitro dissolution rate:

Invitro dissolution studies were carried out in USP type I apparatus (basket) 900 ml of phosphate buffer pH 6.8 was used as dissolution media at 37+0.5oC. 2×2cm2 OFDF’s was placed in dissolution basket. Dissolution was carried out by withdrawing aliquot of 5ml samples at regular time intervals 1 2 3 4 and 5min time intervals and the fresh medium was replaced.Samples were filtered and diluted suitably and analysed by using a UV spectrophotometer at 223nm.

FTIR studies:

As a part of the preformulation studies drug-polymer interaction study was performed by using Fourier Transform Infrared Spectroscopy [FTIR].[18] The FTIR spectra of Zolmitriptan HPMC E5 and their physical mixture were recorded individually. The samples were scanned in the range of 400-4000cm-1.

Differential scanning calorimetry (DSC):

Pure zolmitriptan and the prepared film subjected to DSC studies using TA instruments Q20 model. Empty Aluminium sample pan was used as reference material. Samples are scanned at the rate of 100 C/ min from room temperature to 300° C where in nitrogen gas is used as purge gas at a flow rate of 50mL/min.

Powder X-ray diffraction (XRD) studies:

Pure zolmitriptan and the prepared film were subjected to XRD studies. The scanning rate employed was 2° per min and samples were analysed between 2θ angles 10-80° a voltage of 40kB and a current of 30aM.

Percentage moisture loss:

All the eight formulations are subjected to the percentage moisture loss studies in order to know the amount of moisture present in the oral films after complete drying which alters the stability of films.
Amount of moisture loss was calculated and the values are shown.

Invitro disintegration time:

The disintegration time was calculated by petri dish method. The disintegration time for all eight formulations ranged from 8 to 16sec as shown in table-2. From the results it is evident that at higher concentration of superdisintegrant the film takes less time to disintegrate. Thus addition of superdisintegrant helps the faster breakdown of the film and hence fast release is obtained.

In vitro dissolution study:

The dissolution of Zolmitriptan oral fast disintegrating films were carried out in USP I basket type apparatus. Dissolution study for all eight formulations was performed for 5 min. The results wereshown graphically in figures 1. From the results it can be said that as the concentration of polymer and plasticizer increases drug release decreased.

Folding endurance:

Folding endurance gives an indication of brittleness of the film. The value depends upon the hydrophilic polymer and plasticizer concentrations used. Folding endurance for all eight formulations was found to be more than 200 times as shown in table-2.As the concentration of plasticizer increases folding endurance also increases. But from the contour plot it is clear that as the concentration of PG increases disintegration time increases and as a result drug release decreases.

Surface pH:

The prepared formulations are analysed for surface pH and all the formulations showed pH between 6.6 to 7 indicates there will not be much change in mouth feel.

Fourier Transform Infra-Red spectroscopy (FTIR):

The FTIR spectra of pure zolmitriptan displayed bands at 3329.43 cm-1 due to N- H stretch at 1751.83 cm-1 due to C=O stretching at 1430.36 cm-1 due to heterocyclic C=C stretching. The spectra also showed bands at 1317 cm-1 due to C-H bending. The FTIR spectrum of film containing zolmitriptan exhibited characteristic bands consistent with the molecular structure of zolmitriptan such as bands at 3322.43 cm-1 due to N-H stretch at 1741 cm-1 due to C=O stretching at 1423.36 cm-1 due to heterocyclic C=C stretching at 1314 cm-1 due to C-H bending.

RESULTS AND DISCUSSION

Composition of various fast dissolving oral films formulations

S. No	Ingredients (mg/film)	F1	F2	F3	F4	F5	F6	F7	F8
1	Zolmitriptan	5	5	5	5	5	5	5	5
2	Guar gum*	0.4	0.7	-	-	-	-	-	-
3	Xanthan gum*	-	-	0.4	0.7	-	-	-	-
4	Sodium alginate*	-	-	-	-	1.5	2	-	-
5	Aloevera*	-	-	-	-	-	-	1.5	2
6	SSG	2	2	2	2	2	2	2	2
7	PEG 400**	20	20	20	20	20	20	20	20
8	Vanillin	1	1	1	1	1	1	1	1
9	Sodium saccharine	1	1	1	1	1	1	1	1
10	Water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

*=Expressed as %w/v

** = Expressed as %w/w of the polymer

Stability Studies

S.NO	Time (Days)	Appearance	*In-vitro* Disintegration Time (Sec)	% CDR
1	Initial (0 Days)	Transparent and Acceptable	33.33 ± 3.05	98.5%
2	1 month (30 Days)	Transparent and Acceptable	32.05 ± 2.85	98%
3	3 months (90 Days)	Transparent and Acceptable	30 ± 2.0	97.6%

Figure3.FastdissolvingoralfilmsofAloevera1.5% Aloevera(2%

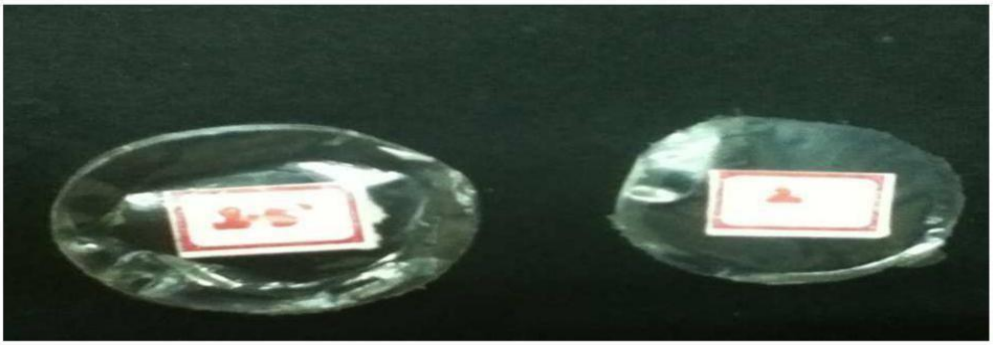


Figure4. Fastdissolvingoralfilmsofsodiumalginate1.5%and2%

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

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 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	-	-

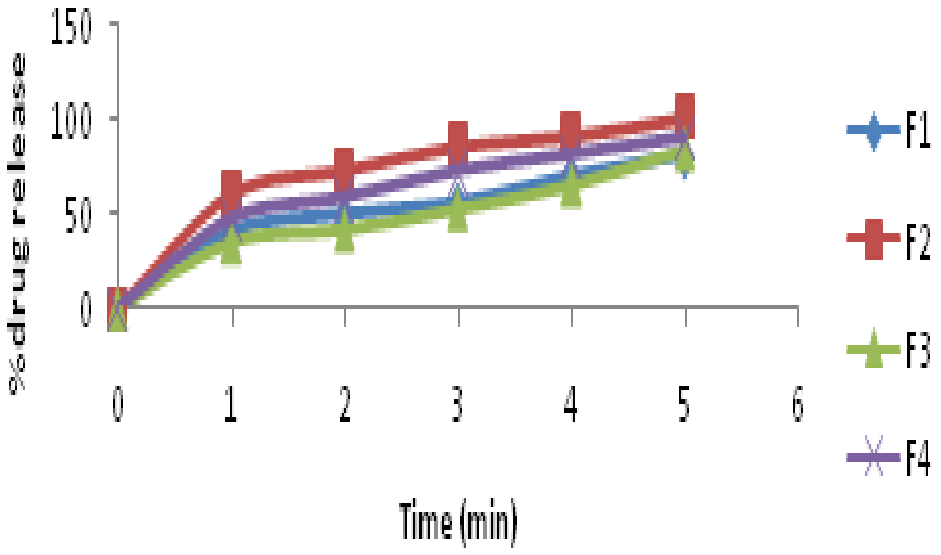
Stability studies for F-4

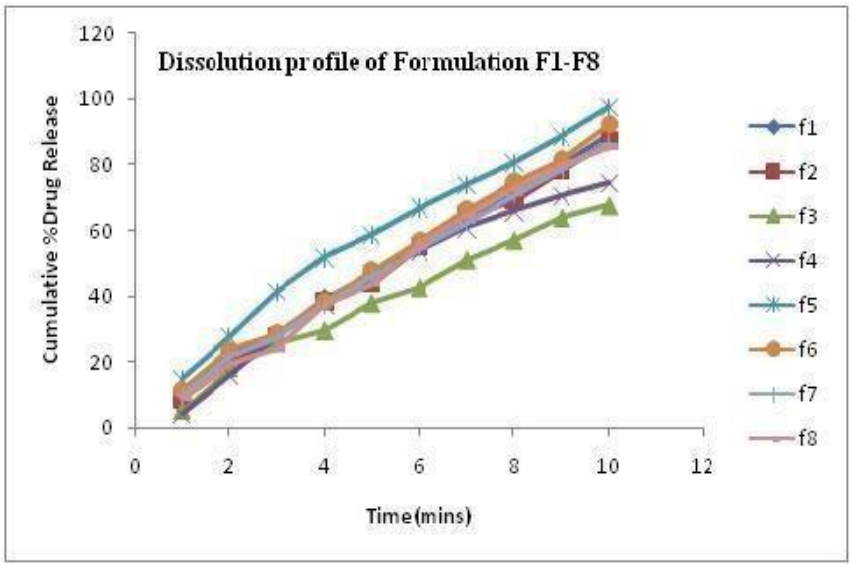
Parameters	Stability data	
	Initial	3 months (40^0C±75%RH)
Thickness(mm)	0.54±0.07	0.52±0.008
Folding endurance	21±0.01	20±0.01
Tensile strength(gm/cm^2)	59.3	57
Invitro disintegration(sec)	18	20
In vitro dissolution (%)	99.4	99.1

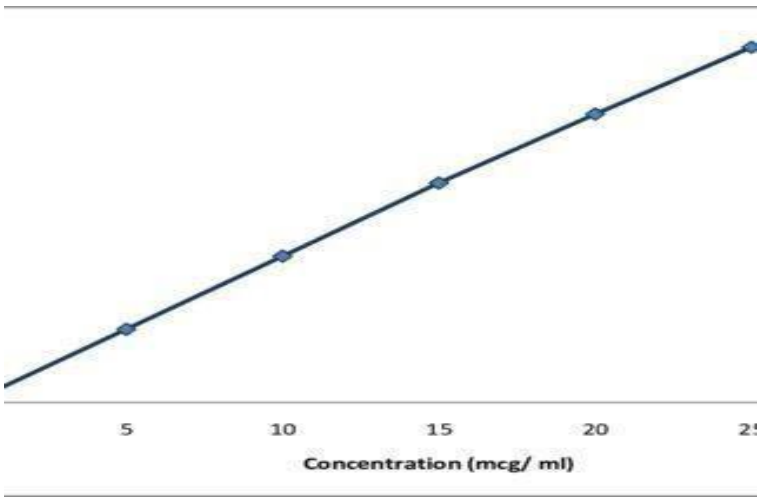
Stability studies for F7

Parameters	Stability data	
	Initial	3 months(40^0C±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

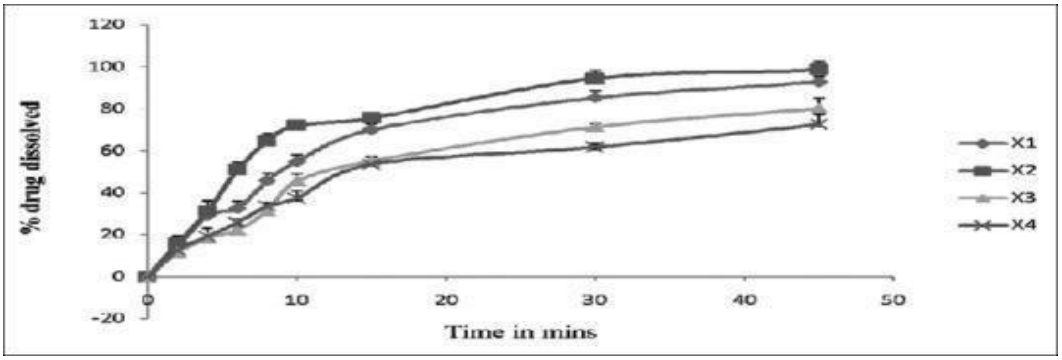
Invitro release studies of fast dissolving oral films of Zolmitriptan:



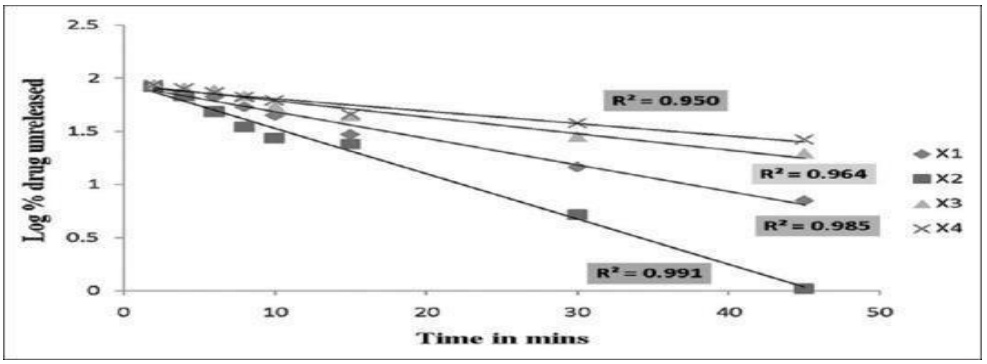




Standard graph using 0.1NHCL



A plot of cumulative percent drug released versus time (*n* = 3 mean ± standard deviation)

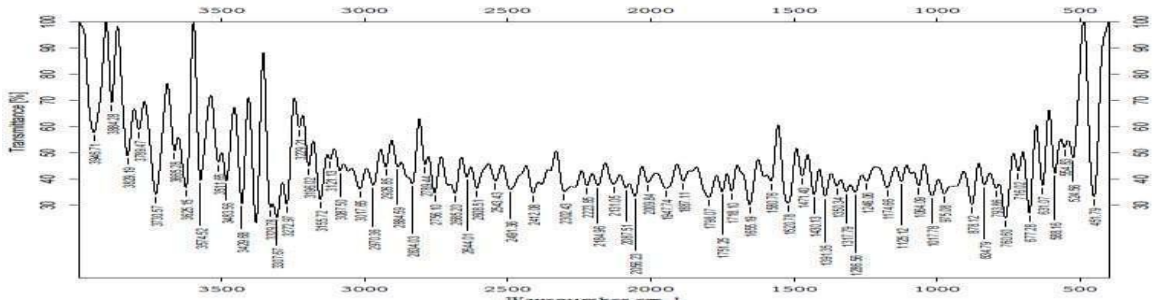


Log percent drug unreleased as a function of time (*n* = 3 mean ± standard deviation)

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

FTIR: spectra of zolmitriptan pure drug



Comparative evaluations of *In-vitro* dissolution profiles of fast dissolving oral films

Time in min	Cumulative % of drug release							
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
1	10 %	8.2%	9.3%	10.6%	26%	21%	8.4%	8%
2	26 %	22.6%	22%	21%	45%	41%	15%	13.6%
3	41 %	34.3%	39.8%	30%	60.3%	53.5%	32%	28%
4	53.3%	45.9%	49.3%	39.8%	77.3%	69.3%	44%	39%
5	67.6%	60%	60%	46%	90.8	80%	53%	47%
6	78.3%	71%	69%	56%	98.5%	90.9%	60%	56%
7	86.3%	79.3%	74.3%	70%	98.5%	94.8%	69%	63%
8	93.2%	85.3%	80%	81%	98.5%	96.8%	76%	70%
9	95.3%	89.3%	90.9%	88%	98.5%	96.8%	84%	78%
10	96.3%	92%	92.4%	92.4%	98.5%	96.8%	91%	89%
11	96.8%	93.1%	93%	95%	98.5%	96.8%	93.8%	92%
12	97.3%	93.9%	94.5%	96%	98.5%	96.8%	94.9%	93.8%
13	97.8%	94.6%	95.6%	96.9%	98.5%	96.8%	96.3%	94.5%
14	98.4%	94.9%	97%	97.3%	98.5%	96.8%	96.3%	96.3%
15	98.6%	95.4%	97%	98%	98.5%	96.8%	96.3%	97%
16	98.6%	96.1%	97%	98%	98.5%	96.8%	96.3%	97.6%
17	98.6%	96.8%	97%	98%	98.5%	96.8%	96.3%	98%
18	98.6%	97.2%	97%	98%	98.5%	96.8%	96.3%	98%
19	98.6%	97.6%	97%	98%	98.5%	96.8%	96.3%	98%
20	98.6%	98	97%	98%	98.5%	96.8%	96.3%	98%

DISCUSSION

Drug polymer compatibility studies:

FTIR studies conducted on pure drug and mixture of drug and excipients showed that there is no marked interaction between drug and excipients selected. The graphs obtained indicate that the drug is compatible with the excipients used.

Physical characterization of fast dissolving oral films:

The physical characterization of the formulated oral films were done by various techniques mentioned and the results were tabulated in Table-2 for various parameters like

- Weight variation of the films
- Thickness of the films

- Tensile strength of the films
- Folding endurance of the films
- Disintegration time
- Mouth dissolving time
- Drug content uniformity of films
- In-vitro dissolution

Weight variation varies from 41.4 ± 0.43 to 56.16 ± 0.87 mg as the polymer concentration increases the thickness folding endurance and disintegration time of the film also increases. The formulation F5 shows 33 Sec (disintegration time). The formulation F_2 shows the maximum value of tensile strength 4.32 ± 0.02 and folding endurance was 181 this might be due to the formation of strong hydrogen bonds between polymer and plasticizer there by imparting flexibility to withstand rupture. The *In-vitro* drug release from the formulation f_5 was 98.5% within 7 mins of time.

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.

CONCLUSION

The Zolmitriptan is a serotonin (5-HT1) agonist used for the treatment of migraine with or without aura. The half-life of Zolmitriptan is 2.5 to 3 hrs and it undergoes hepatic metabolism the absolute oral bioavailability is about 40 to 50%. So in order to improve the bioavailability and efficacy we have prepared fast dissolving films of Zolmitriptan.

Pre-formulation study involving FTIR study showed no interaction between drug and polymer. Fast dissolving films prepared in the study exhibited good film characteristic features as indicated by thickness measured folding endurance and mouth dissolving time tensile strength and drug content.

The prepared films were found to be uniform flexible and 98.5% of drug was released from F_5 film within 6 minutes which was desirable for fast absorption. Later stability studies of this formulation were indicating that there was no degradation of the formulation at high temperature and humidity conditions. It was indicating that this formulation was stable.

From the present investigation it can be concluded that oral thin film formulation can be a potential novel drug dosage form for pediatric geriatric and also for general population.

Hence fast dissolving films of Zolmitriptan were found to be suitable for eliciting better therapeutic effect in the treatment of migraine.

REFERENCES

1. Priyanka Nagar Iti Chauhan and Mohd Yasir. Insights into Polymers: Film Formers in Mouth Dissolving Films. *Drug Invention Today* 2011; 3(12):280-289.
2. Rajni Bala Pravin Pawar Sushi Khanna and Sandeep Arora. Orally dissolving strips: A new approach to oral drug delivery system. *International Journal of Pharmaceutical Investigations* April 2013; 3:67-76.
3. Ishikawa T Koizumi N and Mukai B Pharmacokinetics of acetaminophen from rapidly disintegrating compressed tablet prepared using microcrystalline cellulose (PHM06) and spherical sugar granules. *Chem Pharm Bull* (Tokyo) 2001; 49:230-32.
4. Price TM Blauer KL Hansen M Stanczyk F Lobo R and Bates GW. Single dose pharmacokinetics of sublingual versus oral administration of micronized 17 beta estradiol. *ObstetGynecol*1997; 89: 34045.
5. Lea L. Sublingual Administration. *Colon Health* 1996;13.
6. Kaur Mandeep A.C. Rana and Seth Nimrata. Fast Dissolving Films: An Innovative Drug Delivery System. *International Journal of Pharmaceutical Research & Allied Sciences* 2013; 2(1):14-24.
7. Rawda Khalifa Ali A. R. Shabaraya and Mohd Azharuddin. Design and Evaluation of Fast Dissolving Oral Films of Granisetron Hydrochloride. *American Journal of PharmTech Research* 2012; 2(6):590-601.
8. DesaiPandBasuB.DesignandEvaluationofFastDissolvingOralFilmsofDomperidone. International Research Journal of Pharmacy 2012; 3(9): 134-145.
9. Bhupinder Bhyan Sarita Jangra Mandeep Kaur and Harmanpreet Singh. Orally Fast Dissolving films: Innovation in formulation and technology. International journal of pharmaceutical science review and research 2010; 9(2):50-57.
10. Shivani Singh Satyam Gangwar Garima Garg Vipin Garg and P. K. Sharma. Formulation and evaluation of rapidly disintegrating film of Levocetrizine Hydrochloride. Scholars Research Library Der Pharmacia Lettre 2010; 2(2):434-439.
11. Bankim Chandra Nandy A. K. Gupta A. Mittal and Mohd. Zakir Khan. Design and Development of Solid Dispersion System of Zolmitriptan. Journal ofBiomedical and Pharmaceutical Research 2013; 2 (5):07-13.
12. Kapoor D1 Vyas RB1 Lad C1 Patel M1 Tyagi BL2 Frabrication and characterization of oral thin films of leukotriene receptor antagonist (LTRA) Journal of Drug Delivery & Therapeutics 20155 (2);77-82.
13. Farhana sultana Mohammad Arafat SaifulIPathan Preparation and evaluation of fastdissolving oral film of caffeineIJPBS 2013 3 (1);153-161.
14. Aggarwaljyothi Jindal khesav Singh grupreet Formulation and evaluation of oral fastdissolving films of Granisetron hydrochloride using different polymersIRJP 20156 (10); 724-728.
15. Vijayakuchana DeepthiKammila SumathiSampathi amuSandhya Amareshwar S Preparation and invitro evaluation of buclizine oral thin film strips IJPIR 20144(2);63-68.
16. NGN Swamy and S Shiva kumarFomulation and evaluation of fast dissolving oral filmsofPalonosetron hydrochloride using HPMC E5 IJPCS 20143 (1);145-150.
17. UdhanRavindhraRadhakisan Vijayalaxmichavan NithinTribhuvan Mouth dissolving

filmand their patent: an overview IRJP 20123(9);39-42.

18. ShrutiCPrabhuet.al'Areviewonfastdissolvingsullingualfilmsforsystemicdrugdelivery'**IntJrPh &CheSci**2014v0l3(2)p.no501511.
19. **NishiThakuret.al**'overview"A novel approach of fast dissolving films and their patients" **Adv inBioRes** 2013vol7(2)p.no 50-58.
20. **BhupinderBhyanet.al**'oral fast dissolving films: innovations in formulation and technology'**I nt JrPh SciRev&Res**2011 vol9(2)p.no50-57.
21. **PallaviPatilet.al**'fastdissolvingoralfilms: aninnovativedrugdelivery systems' **Int JrSci&Res**2014vol 3(7)p.no 2088-2093.
22. **ArunAryaet.al**'fast dissolving oral films:an innovative drug delivery system and dosageform'**IntJrChemTechRes**2010vol2(1)p.no576-583.
23. **ChonkarAnkita.Det.al**'Anoverviewonfastdissolvingoralfilms'**AsiJrPhTech**2015vol5(3)p.no 129-137.
24. **Nagasowjanyajuluruet.al**'Fastdissolvingoralfilms'**IntJrAdvPhBio&Che**2013vol2(1)p.no10 8-112.
25. **G.KadheandR.EArasan**'Advancesdrugdeliveryoforalhypoglycemicagents'**Current science**vol83 (12) 2002p.no 1539-1543.
26. **HelenMcolham**et.al'primarypreventionofcardiovasculardiseasewithatorvastatinintype2diabet esinthecollaborativeatorvastatindiabetesstudy' **Fast trackarticles**2004vol364(9435)p.no685-696.
27. **Jigishapatelet.al**'Dyslipedimiaindiabetesmellitus'**BMJclinicalevidence**2008.
28. **Dysphagia**:Merck manual of patientsymptomsintheMerckmanualsonlinemedicallibrary.
29. ExpertcommitteeontheDiagnosisandclassificationofdiabetes mellitus.Reportoftheexpertcommitteeonthediagnosisandclassificationofdiabetesmellitus.**Diabe tescare**1997vol.20:1183-1197.
30. **Huang.cet.al**cellularbasisofdiabeticnephropathy:II. ThetransforminggrowthfactorbetasystemanddiabeticnephropathylesionsintypeIdiabetes.**Diabe tes**2002p.no972-977.
31. **SalimBastakiet.al**'Reviewondiabetesmellitusanditstreatment'**IntJrdiabetes mellitus**2005vol.13p.no997-999.
32. **MentleinR.et.al**Dipeptidyl-peptidaseIV(CD26)-RoleintheinactivationofregulatorypeptidesRegulpept**pubMed**1998vol85p.no 9-24.
33. **DruckerDJet.al**'theefficiencyandsafetyofincretinsystem:glucoganlikepeptide-Ireceptoragonistsanddipeptidase-4inhibitorsintype2diabetes2006vol36p.no695-705.
34. **WaleKiranKet.al**'Formulationdevelopmentandin-vitroevaluationofimmediatereleasetablet ofsitagliptinphosphatemonohydrate**WJPR**2014vol3 (3) p.no 4945-4957.
35. **AbbarajuPrasannaLakshmiet.al**'Formulationandevaluationoftastemaskedorallydisinte gratingtabletsofsitagliptinphosphatemonohydrate'**Int ReJr Ph**2012vol 3(9) p.no 305-308.
36. **HemanthKumarGet.al**'Formulationandin-vitroevaluationofbilayerfloatingtabletsofmetformin hydrochlorideand sitagliptinphosphate'**Ini J AdPh**2012 vol2 (2) p.no 64-81.
37. **GnanachaithanyaNet.al**'Formulationandevaluationoffastdisintegratingtabletsofsitagliptinpho sphate'**IntJPhWRes**2012vol3 (3)p.no 1-12.
38. Handbook of pharmaceuticalexcipientsby**RaymondCRowe**.

39. **Bentley'sRawlins**EAtextbookofpharmaceutics8thedition2003270-281.
40. **LachmanL**theoryandpracticeofindustrialpharmacyvargheesepublicationhouse1990vol3p.no317-319.
41. **AultonMEWellsTI**pharmaceutics:thescienceofdosagefromdesign.LondonEngland:churchil;livingstone;1998.