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Formulation And InVitro Evaluation Of Oral Fast Dissolving Tablet Using Antimigraine Drug

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Abstract:

The main objective of this research work was to formulate and evaluate fast dissolving tablet of Zolmitriptan for the treatment of migraine. In this study, fast dissolving tablet were prepared by Direct Compression Method by using croscarmellose sodium, Crospovidone and sodium starch glycolate as Fast Disintegrating Polymers or superdisintegrant. Mannitol is used as a binder. The designed tablets were subjected to various assessment parameters like friability test, hardness test, disintegration test, wetting time, in vitro drug release and drug content. All the prepared formulations were subjected to various assessment parameters, and the findings obtain within the prescribed limit. The calibration curve of pure drug using various solvents like distilled water, phosphate buffer pH 6.8, 0.1 N HCL was plotted. The disintegration time of three formulations (F1-F3) was good passes of the reference of book. But the above remaining formulation (F4-F9) was in the range. % Drug Release of Fast dissolving tablet (F1-F9) was found to be range (92.33±0.015) to (101.17 ±0.5661). It was observed that Cumulative % Drug release of dissolving tablets depend on concentration of polymer (Croscarmellose, crospovidone, Sodium starch glycolate). The results obtained in the research work clearly showed a promising potential of fast dissolving tablets containing a specific ratio of croscarmellose sodium and sodium starch glycolate as superdisintegrants for the effective treatment of hypertension.

Keywords: *Fast dissolving tablet, Zolmitriptan,, Superdisintegrants, Direct Compression method.*

1. INTRODUCTION

Oral administration of drugs is preferred due to its ease of swallowing, distress avoidance, versatility and most significantly, patient compliance. The large number of patients finds it difficult to swallow tablets and capsules, and do not take their medicines as prescribed. It is estimated that 50 % of the population affected by this problem, which finally results in a higher chance of noncompliance and ineffective therapy. For these reasons, tablets that can disintegrate in the oral cavity have attracted enormous attention. Solid dosage forms as oral tablets have the most considerable place among the entire pharmaceutical formulations. Taste-masking is a crucial step in the formulation of an acceptable fast dissolving/disintegrating tablet. Traditional tablet formulations generally do not solve the issues related to taste masking, because it is supposed that the dosage form will not disintegrate until it passes through the oral cavity. To eliminate the bitterness, the tablet can be prepared by adding flavors and sweetening agent or by sugar coating on the tablets. Many fast dissolving tablet technologies combine unique types of taste masking as well. Fast dissolving tablets technology, which makes tablets dissolve or disintegrate in the oral cavity without any additional water intake, has drawn a great deal of attention. Fast dissolving tablets are a solid dosage form that provides the rapid disintegration or dissolution of solid to present as suspension or solution form even when placed in the mouth under limited bio-fluid. Orally disintegrating tablets are known by various names such as orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, fast or rapid dissolving tablets, porous tablets, mouth dissolving tablets and rapid-melts. The excipients used in fast dissolving tablet technology are usually hydrophilic in nature and can be selected on the basis of drug's physicochemical properties like hydrophobicity or hydrophobicity. If the active pharmaceutical ingredient is hydrophobic in nature, then dosage form is called disintegrating tablet whereas, if it is hydrophilic, then the dosage form is called fast dissolving tablet. The fast dissolving tablet formulation defined by the Food and Drug Administration as “a solid dosages form containing medicinal

substances which disintegrates rapidly, usually within a matter of seconds when placed upon the tongue". The aim of this article is to review the advantages, limitations, formulation challenges, manufacturing techniques, patented technologies, marketed formulations and evaluation tests of fast dissolving tablets. [1-5]

Advantages of orally fast dissolving Tablet

1. Ease of administration for those patients who have difficulty in swallowing tablet.
2. No need of water to swallow the dosage form**.**
3. These tablets are useful for pediatric, geriatric and psychiatric patients.
4. Have acceptable taste masking property.
5. Achieve increased bioavailability through absorption of drugs from mouth, pharynx and esophagus as saliva passes down.
6. Have a pleasant mouth feel and leave minimal or no residue in the mouth after drug administration.
7. Have rapid dissolution and absorption of the drug which will produce quick onset of action.
8. Cost effective. [6-11]

Disadvantages of fast dissolving Tablet

1. The tablets commonly have insufficient mechanical strength. Hence, conscientious handling is necessary.
2. The tablets may leave unpleasant taste and/or grittiness in mouth if not formulate Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
3. Patients who simultaneously take anti-cholinergic drugs are not suitable candidates for fast dissolving tablets.
4. Patients who are traveling and do not have immediate access to water.
5. Rapid dissolution and absorption of the drug, which will produce quick onset of action. [12-14]

Ideal Characteristics of Fast Dissolving Tablet:

1. Utilizes cost effective production method.
2. Require no water for oral administration.
3. Dissolve / disperse/ disintegrate in mouth in a matter of seconds.
4. Have a pleasing mouth feel and taste masking.
5. Less friable and have sufficient hardness.
6. Leave minimal or no residue in mouth after administration.
7. Manufacturing using conventional manufacturing method.[15-16]

2. MATERIALS AND METHODS

Zolmitriptan were received as gift sample from Macleods Pharma, Mumbai, India. Crosscarmellose Sodium, Crospovidone and Sodium Starch Glycolate (Concept Pharma, Aurangabad, India), Mannitol (Zim laboratories Ltd, Nagpur.) All other chemicals were commercially available and used as received.

Tablet Manufacturing methods

Many techniques have been reported for the formulation of Fast dissolving tablets or Oro-dispersible tablets.

1. Freeze drying / lyophilization
2 . Spray drying
3. Tablet Moulding
4. Sublimation
5. Direct compression
6. Mass extrusion

1. Freeze Drying/ Lyophilization

Lyophilization means drying at low temperature under condition that involves the removal of water by sublimation. Drug in a water soluble matrix which is then freeze dried to give highly porous structure. The tablets prepared by lyophilization disintegrate rapidly in less than 5 seconds due to quick penetration of saliva in pores when placed in the oral cavity. Lyophilization is useful for heat sensitive drugs i.e. thermo-labile substances. Freeze drying process normally consists of three steps: Material is frozen to bring it below the eutectic point. Primary drying to reduce the moisture around 4% w/w of dry product. Secondary drying to reduce the bound moisture up to required final volume. [17-20]

Advantages: More rapid dissolution than other available solid products.
Disadvantages: High cost of the equipments & lack of physical resistance in blister packs.

2. Spray Drying

This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This then mixed with active ingredients and compressed into tablets. The formulations are incorporated by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating and an acidic material (e.g. citric acid) and / or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium. [21-22]
Advantages: Rapid disintegration of tablet.

3. Tablet Moulding

Tablets prepared by this method are solid dispersions. Molded tablets offer improved taste due to water soluble sugars present in dispersion matrix. Molding process is of two type's i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30○C under vacuum. [23-24]
Advantages: Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is, in general made from water soluble sugars.
Disadvantages: Moulded tablets do not possess great mechanical strength. Erosion & breakage occur during handling & opening of blister packages.

4. Sublimation

In this method a subliming material like is removed by sublimation from compressed tablets and high porosity is achieved due to the formation of many pores. Where camphor particles previously existed in the compressed tablets prior to sublimation of the camphor. A high porosity was achieved due to the formation of many pores where camphor particles previously existed in the compressed mannitol tablets prior to sublimation of the camphor. These compressed tablets which have high porosity rapidly dissolved within 15 seconds in saliva 30. [25-26]
Advantage: Tablets dissolve in 10-20 sec. and exhibit sufficient mechanical strength.

5. Mass Extrsuion

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shaped extrude which are finally cut into even segments using heated blade to form tablets. This process can also be used to coat granules of bitter drugs to mask their taste.[27-30]
Advantage: Mask bitter taste by coating the granules.

6. Direct Compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. [31]

Preformulation Studies:

FTIR spectroscopy studies:

The interaction between the drug was determined by using FTIR spectroscopy of Agilent equipment where infrared spectra of Zolmitriptan and other polymers were taken individually first and then compared with the spectra of the formulation combination; in which the drug was mixed with other ingredients. The scan range was from 4000 to 500 cm^{-1}. [32]

The Drug-Excipients Interaction studies:

DSC thermograms of pure drug Zolmitriptan and its physical mixture with polymer were carried out to investigate any possible interaction between the drug and polymer. The drug-excipients interaction study was carried out by using FTIR spectrophotometer and Differential scanning calorimetry.

Standard calibration curve of Zolmitriptan in 0.1 N HCL:

10 mg of drug was dissolved in 100 ml 0.1N HCl and then 20ml withdrawn from these stock solution and dilute 0.1N HCl upto 100ml. From this stock solution serial dilutions were made these aliquots are

1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 ml to obtain the solutions in concentrations ranging from 2-20µg/ml. The absorbance was measured at 216 nm using UV spectrophotometer.

Preparation of Fast Dissolving Tablet by Direct Compression method:

Different tablets formulations were prepared by direct compression technique. All powders were passed through 60 mesh. Required quantities of Zolmitriptan and polymers such as Croscarmallose, Crospovidone, and Sodium starch glycolate were mixed thoroughly Magnesium stearate was added as lubricant. Microcrystalline cellulose was used as diluent and Mannitol was used. Finally the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were evaluated for several tests. In all formulations, the amount of the active ingredient is equivalent to 2.5mg of Zolmitriptan to made upto 250mg of tablets.

Table 1: Formulation Batches of Fast Dissolving tablet.

Name of Ingredient	Formulation Code With Their Quantity								
Batch No	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zolmitriptan(mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Crosscarmellose sodium (mg)	20	20	20	30	30	30	40	40	40
Sodium Starch Glycolate (mg)	20	30	40	20	30	40	20	30	40
Mannitol (mg)	25	25	25	25	25	25	25	25	25
Microcrystalline cellulose (mg)	200.5	190.5	180.5	190.5	180.5	170.5	180.5	170.5	160.5
Magnesium stearate (mg)	2	2	2	2	2	2	2	2	2
Total	270	270	270	270	270	270	270	270	270

3. Evaluation Of Fast Dissloving Tablet. [33-35]

1. Hardness Test:

Hardness indicates the ability of a tablet to withstand mechanical shocks while packaging, handling and transportation. The hardness of the tablets was determined using Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet and a zero reading was taken. The upper plunger is then forced against a spring by turning threaded bolt until the tablet fractures. It is expressed in kg/cm^2. Three tablets were randomly picked and analyzed for hardness. The mean values were calculated.

2. Friability Test:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Normally, a pre-weighed tablet sample is placed in the friabilator. The friabilator was operated at 25 rpm, dropping the tablets a distance of six inches with each revolution for 4 minutes or run up to 100 revolutions. The tablets are then dusted and reweighed. [36]

3. Weight Variation Test:

The weight variation test was run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weight to the average weight .the tablets meet the IP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Table 2: Weight Variation and %Deviation

Average weight of a tablet(mg)	Percentage deviation

80 mg or Less	10
80-250	7.5
More than 250	5

4. Thickness and Diameter

Thickness of the 10 tablets was measure by using vernier caliper. It was expressed in **mm.**

5. Disintegration Time:

The In vitro disintegration time was determined using tablet disintegration tester, at 37°C ±2°C, containing 500ml of distilled water. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

6. *In-vitro* dissolution studies:

Dissolution was taken by using type-II apparatus of USP, by using 500ml of 0.1N HCl medium, the temperature of dissolution media was maintained at 37 $\pm 0.5^0$ C. The paddle rotation speed was kept at 50 rpm. Tablets was placed in the baskets containing 0.1N HCl and 5 ml samples were withdrawn predetermined time intervals and replaced with same dissolution media. This sample were withdrawn and analyzed by using UV spectrophotometer (Shimadzu 1800, Japan W 216 nm.) [37]

7. Stability Studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specification. A drug formulation is said to the stable if it fulfills the following requirements:

- It should contain at least 90% of the stated active ingredient.
- It should contain effective concentration of added preservatives, if any.
- It should not exhibit discoloration or precipitation, nor develops foul odor.
- It should not develop irritation or toxicity.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or a drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light, and enables recommended storage conditions, re-test periods and shelf lives to be established. International Conference on Harmonization (ICH) specifies the length of study and storage conditions.

In the present study, stability studies were carried out at (40 ± 2^0, 75±5% RH), (25 ± 2^0, 75±5% RH), (10 ± 2^0, 75±5% RH) for a specific time period up to 28 days for the optimized formulation. The optimized formulation was analyzed for the drug content study.

4. RESULT AND DISCUSSION

Drug-Excipient Interaction studies by FTIR:

The spectrum of zolmittriptan showed sharp peaks obtained in FTIR of pure drug for groups are found respective, Aromatic Compound 1450-1600 cm^{-1} stretching, RR' N-H 3310-3850 cm^{-1} stretching, C-N 1000-1400cm^{-1} Stretching.

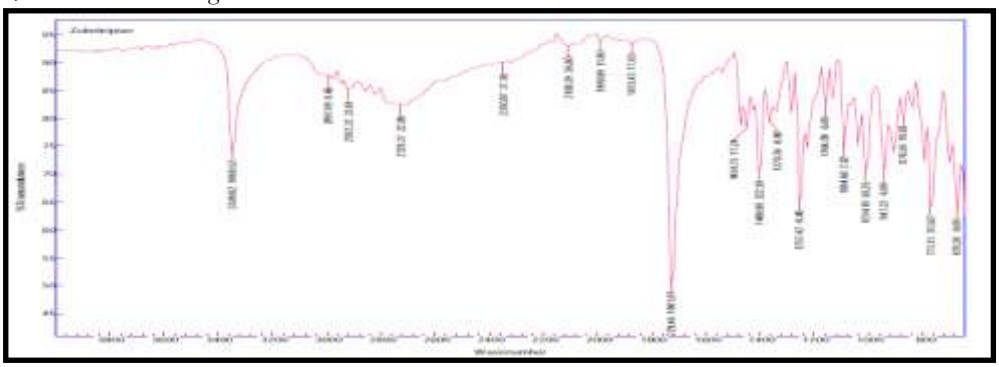

Figure 1: FTIR spectrum of Zolmitriptan

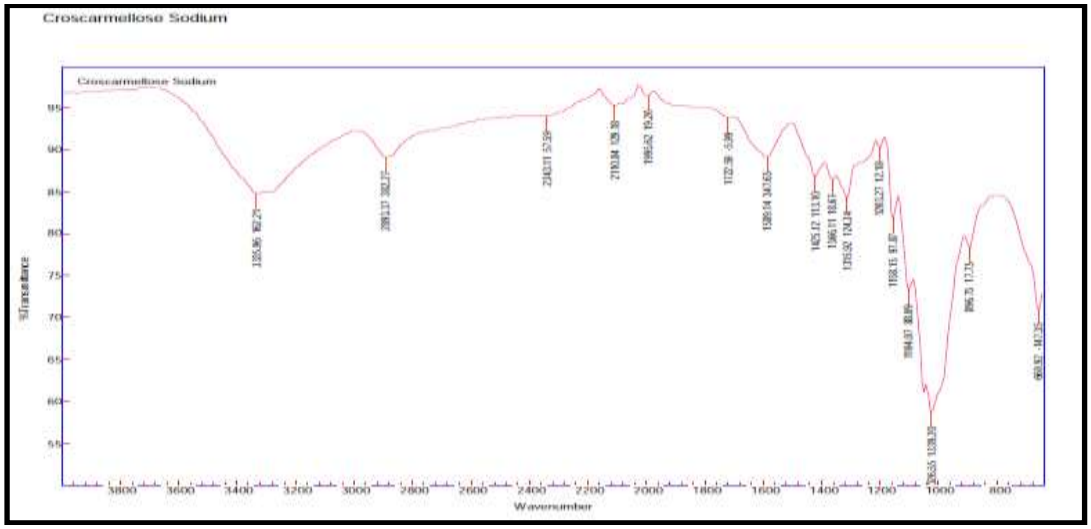

Figure 2: FTIR spectrum of Crosscarmellose Sodium

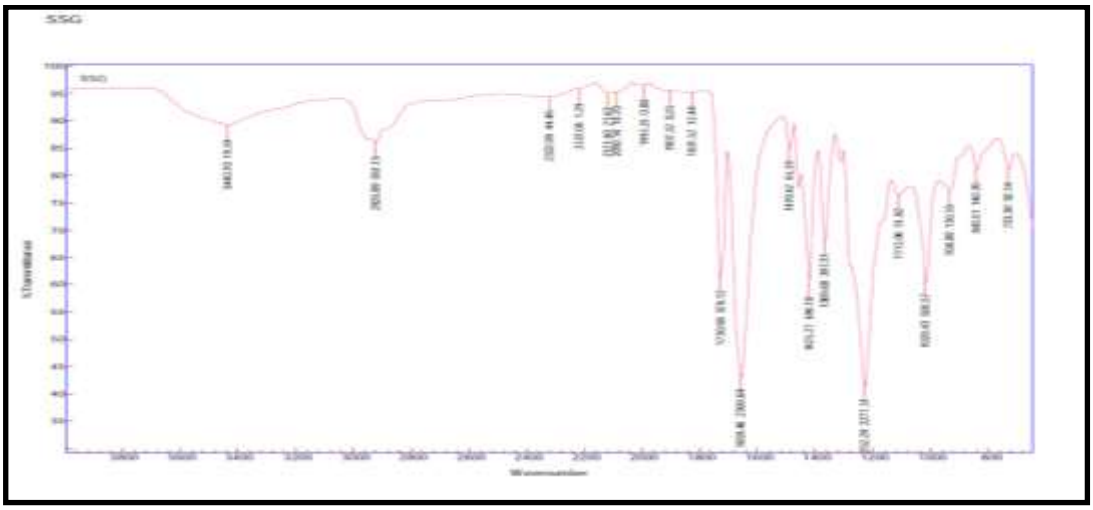

Figure 3: FTIR spectrum of Sodium Starch Glycolate

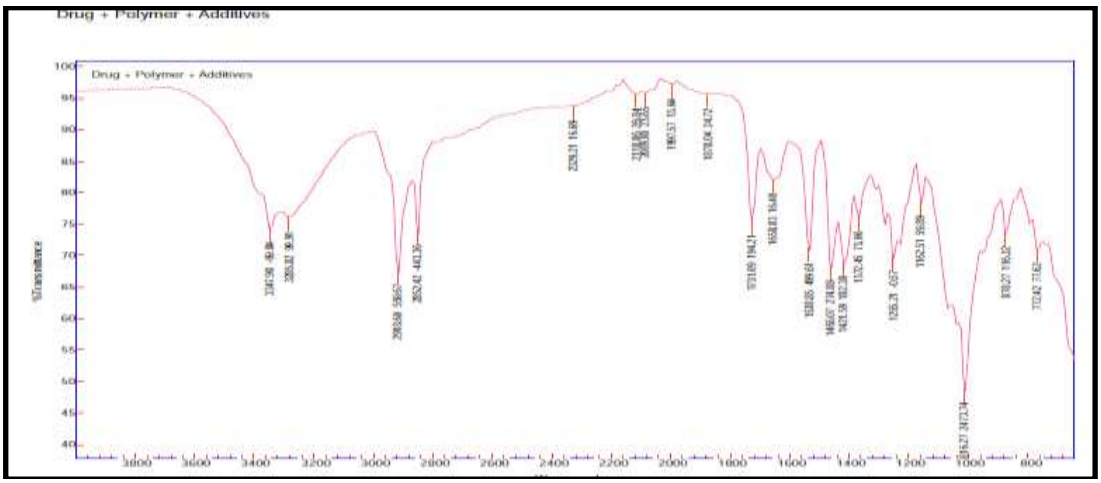

Figure 4. The Spectrum of Drug, Polymer and Additives

RESULT:

FTIR spectra of drug, polymer, and additives were shown in graph respectively. It was observed that principle peak of Drug was found in FTIR spectra of a drug as well as FTIR spectra of physical mixture of drug and excipients. It was suggested that there was no physical and chemical interaction between drug and polymers.

Calibration Curve of Zolmitriptan in 0.1N HCL:

Standard calibration curve of Zolmitriptan was plotted using UV visible Spectrophotometer at λ max 216 nm by using 0.1N HCL. A graph of absorbance verses concentration was plotted and was found to be linear, indicating its Compliance with Beer-Lambert's law

Equation, $y = 0.077x + 0.007$

$R^2 = 0.998$

Table 3: Calibration curve for Zolmitriptan

Sr. No.	Concentration	Absorbance
1	0	0
2	2	0.124
3	4	0.339
4	6	0.48
5	8	0.649
6	10	0.783
7	12	0.913
8	14	1.09
9	16	1.233
10	18	1.367
11	20	1.55

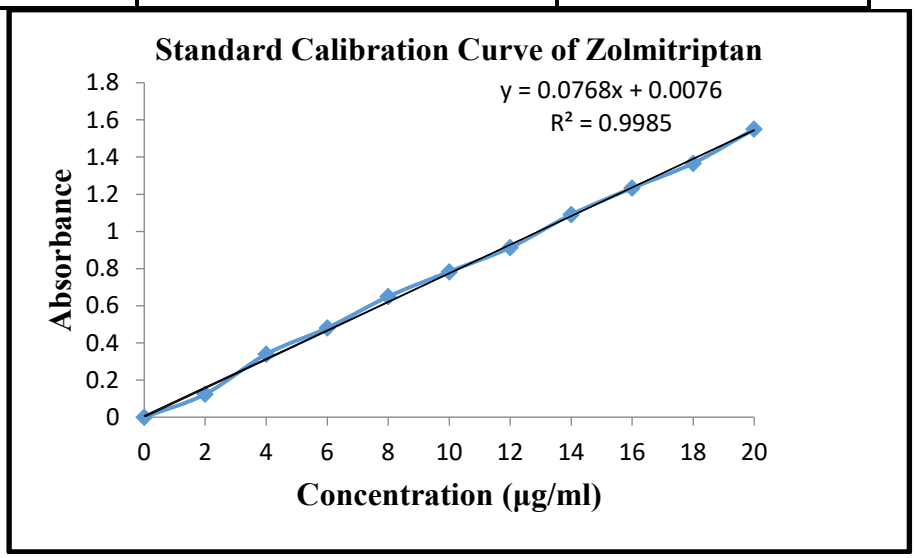

Figure 5 : Graph of Absorbance Versus Concentration

Table 4 :Evaluation of Fast Dissolving Tablet Formulation Batches F1 to F8 (Final Formulation)

Formulation code	Hardness(gm/cm3) ± S.D.	Friability (%) ± S.D.	Weight Variation (mg) ± S.D.	Thickness of Tablets (mm) ± S.D.
F1	5.64± 0.3551	0.567± 0.2269	269.25± 0.7968	4.73± 0.2081
F2	6.36± 0.6429	0.532± 0.1177	268.86± 2.1779	4.20± 0.3000

F3	6.73± 0.7371	0.505± 0.1354	269.58± 0.4650	4.23± 0.3511
F4	5.96± 0.1154	0.489± 0.1541	270.72± 1.3547	4.16± 0.1154
F5	5.70±5.7666	0.544± 0.1981	269.01± 1.8170	5.06± 0.2516
F6	5.80±0.1732	0.497± 0.0657	268.76± 2.3864	4.73± 0.2081
F7	4.66±0.2080	0.448± 0.0795	270.10± 2.0843	4.56± 0.4618
F8	4.93±0.1523	0.330± 0.1315	270.33± 1.1144	4.66± 0.4725
F9	5.86± 0.5859	0.341± 0.0791	268.52± 2.5951	3.96± 0.3055

Table Continue...

Formulation code	Drug content ± S.D	Disintegrating Time (seconds) ± S.D	Diameter (mm) ± S.D
F1	99.18± 1.5773	62.99± 2.6490	4.43±0.3511
F2	100.1± 2.6861	74.00± 3.6055	5.16±0.2516
F3	98.37± 1.7451	85.43± 3.9576	5.10± 0.5567
F4	99.78± 3.2949	42.76± 3.9156	5.20± 0.3605
FF5	98.85± 0.6438	54.55± 1.5236	4.90± 0.2000
FF6	101.1± 1.0445	59.81± 2.2050	5.23± 0.3511
FF7	100.0± 2.5106	29.28± 2.3725	5.13± 0.5773
FF8	98.14± 1.7856	34.20± 2.5272	4.03± 0.2309
FF9	99.38± 2.8953	40.07± 1.3298	5.63± 0.2516

Evaluation Parameter:

Hardness Test:

Hardness indicates the ability of a tablet to withstand mechanical shocks while packaging, handling and transportation. The hardness of the tablets was determined using Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet and a zero reading was taken. The upper plunger is then forced against a spring by turning threaded bolt until the tablet fractures. It is expressed in kg/cm^2. It was observed that, the hardness of formulation **(F1-F8)** is less but formulation **(F9)** has more hardness, so that disintegration time was more. The range of hardness in between 5-6 gm/cm^3. Three tablets were randomly picked and analyzed for hardness. The mean values were calculated**.**

Friability Test:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Normally, a pre-weighed tablet sample is placed in the friabilator. The friabilator was operated at 25 rpm, dropping the tablets a distance of six inches with each revolution for 4 minutes or run up to 100 revolutions. The tablets are then dusted and reweighed.

It was observed that, friability of tablet of all formulation **(F1-F9)** in the range of 0.23-1%. So that it resist chipping and abrasion during transportation. Weight variation of all formulation was passes good.

Weight Variation Test:

The weight variation test was run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weight to the average weight .the tablets meet the IP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. Weight variation of all formulation was passes good.

Thickness and Diameter

Thickness of the 10 tablets was measure by using vernier caliper. It was expressed in **mm.** It was observed that, Thickness of all formulation small. Hence that all formulation was not passes well.

Disintegration Time:

The In vitro disintegration time was determined using tablet disintegration tester, at 37°C ±2°C, containing 500ml of distilled water. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds. The disintegration time of all formulation **(F1-F9)** was good or passes.

***In-vitro* dissolution studies:**

Dissolution was taken by using type-II apparatus of USP, by using 500ml of 0.1N HCl medium, the temperature of dissolution media was maintained at 37 $\pm 0.5^0$ C. The paddle rotation speed was kept at 50 rpm. Tablets was placed in the baskets containing 0.1N HCl and 5 ml samples were withdrawn predetermined time intervals and replaced with same dissolution media. This sample were withdrawn and analyzed by using UV spectrophotometer (Shimadzu 1800, Japan W 216 nm.)

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5. CONCLUSION:

The present study has been a satisfactory attempt to formulate fast dissolving tablet of zolmitriptan with a view of improving its oral disintegration and giving a rapid release of the drug.

F1-F9 formulation showed best possible result and was selected as optimized batch.

Formulated tablet gives satisfactorily result for various evaluation of tablet like Hardness, friability, weight uniformity, thickness uniformity, disintegration time , Surface pH, Drug content uniformity, In vitro drug release. Formulation showed fairly acceptable values for all the evaluation test. From evaluation it was concluded that disintegration time of the film increased with increased in polymer concentration. Hence, finally it was concluded that the prepared tablet of zolmitriptan may prove to be potential candidate for safe and effective fast dissolving drug delivery.

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