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RESEARCH ARTICLE

Formulation and Evaluation of Mouth Dissolving Tablets of Zolmitriptan

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ABSTRACT:
The objective of present study was to formulate mouth dissolving tablets of Zolmitriptan. Zolmitriptan is a 5-HT receptor agonist. It is used in the treatment of migraine. Six different formulations of Zolmitriptan mouth dissolving tablets were prepared by using direct compression technique by using different concentrations of AC-Di-Sol, Avicel pH 101 and strlac. Tablets were evaluated for different precompression and post compression parameters of tablets were carried out and the results satisfies according to the pharmacopoeia specifications. Other parameters such as drug-excipients compatibility were also evaluated through IR and DSC study.IR and DSC studies revelled that there is no interaction between drug and different excipients used in formulation. Formulation F6 was selected as optimised formulation showing better dissolution results at 35 minutes.

KEY WORDS: Zolmitriptan, mouth dissolving tablets, Ac-Di-Sol, Antimigraine.

INTRODUCTION:
Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The more sophisticated delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system.

Tablets and hard gelatine capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake / diets have difficulties swallowing these dosage forms. Those who are travelling or have little access to water are similarly affected. For these reasons; tablets which can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention.

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Rapidly dissolving or disintegrating tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people .[1,2]

The growing importance of mouth dissolving tablet was underlined recently when European Pharmacopoeia adopted the term "Orodispersible Tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing. Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, anti-allergic and drugs for erectile dysfunction.[1]

To overcome this weakness, scientist have developed innovative drug delivery system known as fast dissolving "melt in mouth" or mouth dissolve (MD) tablet. These are novel type of tablet that disintegrate dissolve/disperse in saliva.

There are two different types of dispersible tablet. One dosage form disintegrates instantaneously in the mouth, to be swallowed without the need for drinking water, while other tablet formulation can readily be disperse in water, to form dispersion, easy to ingest by the

patient.MDT is a solid dosage form that dissolves or disintegrates within a minute in the oral cavity without the need of water and has a pleasant taste. MDT is also known as orally disintegrating tablet, fast-dissolving tablet, fast-melting tablet, mouth melting tablet or fast-disintegrating tablet.[1]

Orally disintegrating tablets are also called as orodispersible tablet, quick disintegrating tabltes, mouth dissolving tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelt.

United State Food and Drug Administration (FDA) defined MDT as "a solid dosage form containing medicinal substance or active ingredients which disintegrate rapidly usually within a matter of second when placed upon the tongue. The disintegration time for MDTs ranges from several seconds to about a minute.[2]

Therefore, in the present study an attempt will be made to formulate mouth dissolving tablet of Zolmitriptan by direct compression method using different concentration of superdisintegrants like Avicel pH 101, Starlac and Crosscarmellose sodium (Ac-Di-Sol) with a view to obtain rapid disintegration when taken orally, permitting a rapid onset of action during acute migraine attack.

MATERIALS AND METHODS:

Materials:

The excipients croscarmellose sodium, microcrystalline cellulose, magnesium stearate, peppermint was obtained as gift sample from Maxheal Pharmaceuticals Pvt. Ltd, MIDC, Satpur, Nasik.

Methods:

Analytical Method for Estimation of Zolmitriptan:

Identification of drug was carried out by IR (Model ALPHA Bruker ECO-ATR) Standardization of the drug was carried out by using UV visible spectrophotometer (Labindia UV 3000^{+}).

i)Preparation of Standard Calibration Curve of Zolmitriptan in Distilled Water

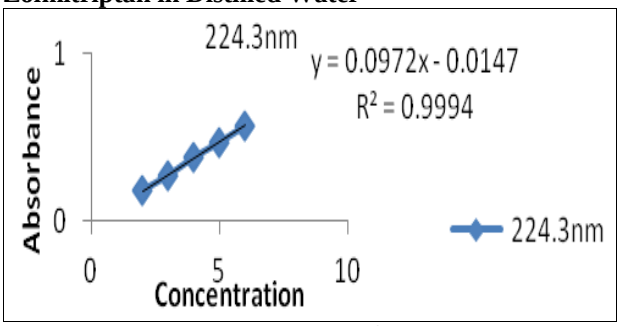


Figure 1: Standard calibration curve of Zolmitriptan in distilled water.

ii) Preparation of Standard Calibration Curve in 0.1 M HCl

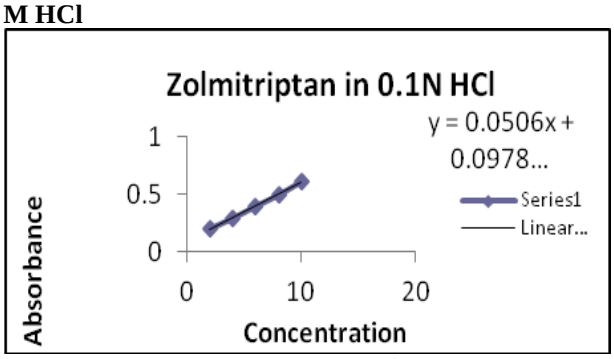


Figure 2: Standard Calibration Curve of Zolmitriptan in 0.1 N HCl

ii) Preparation of Standard Calibration Curve in phosphate buffer pH 6.8:

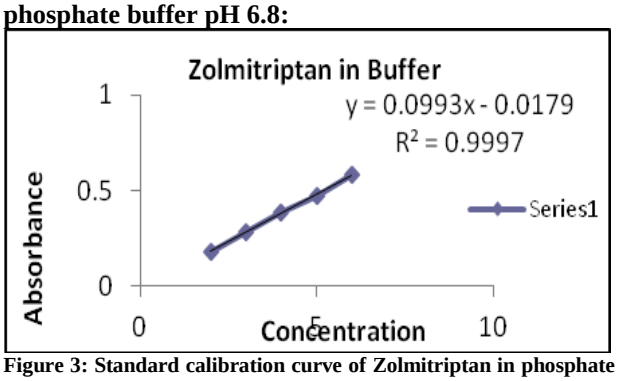


Figure 3: Standard calibration curve of Zolmitriptan in phosphate buffer pH6.8.

PRE-COMPRESSION PARAMETERS:

A) Angle of repose:

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

$$Tan\ \theta = h / r$$

$$\theta = tan^{-1}\ (h/r)$$

Where, **θ** is the angle of repose
h is height of pile
r is radius of the base of pile

Different ranges of flow ability in terms of angle of repose are given below

Table 1: Relation between Angle of Repose and Flow Properties

Angle of Repose (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Method:

A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph sheet was

taken to measure the area of pile, thereby evaluating the flow ability of the granules. Height of the pile was also measured.

B) Bulk Density:

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

Method:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of accurately weighed powder (bulk) from each formula, previously shaken to break any agglomerates formed was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec interval. The taping was continued until no further change in volume was noted. LBD and TBD were calculated using following formula;

$$LBD = \frac{\text{Weight of the powder}}{\text{Volume of the packing}}$$

$$TBD = \frac{\text{Weight of the powder}}{\text{Tapped volume of the packing}}$$

C) Tapped Density:

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (pt) was calculated using the following formula.

$$\rho t = \frac{M}{Vt}$$

D) Hausner Ratio:

Hausner ratio is an indirect index of ease of power flow. It is calculated by the following formula.

$$\text{Housner ratio} = \frac{\rho t}{\rho d}$$

Where, ρ_t is tapped density and ρ_d is bulk density. Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

F) Carr's compressibility index:

The compressibility index of the granules was determined by Carr's compressibility index. (%) Carr's Index can be calculated by using the following formula

$$\text{Carr's Index (\%)} = \frac{TBD - LBD}{TBD} \times 100$$

Table 2: Grading of Powders for Their Flow Properties according to Carr's Index[10]

Carr's Index (%)	Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Very very poor

DRUG EXCIPIENTS INTERACTION STUDIES

IR STUDIES:

IR spectra for pure drug and formulations were recorded in an infrared (IR) spectrophotometer (Model: Shimadzu) (Fig.) show the identical peak with excipients. There is no interaction with excipients.

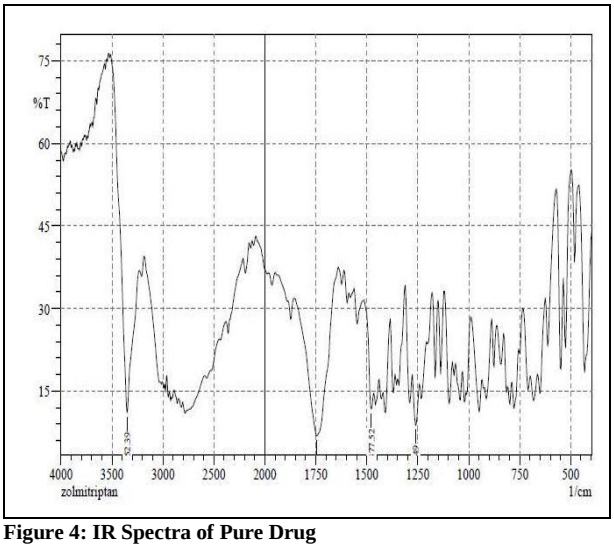


Figure 4: IR Spectra of Pure Drug

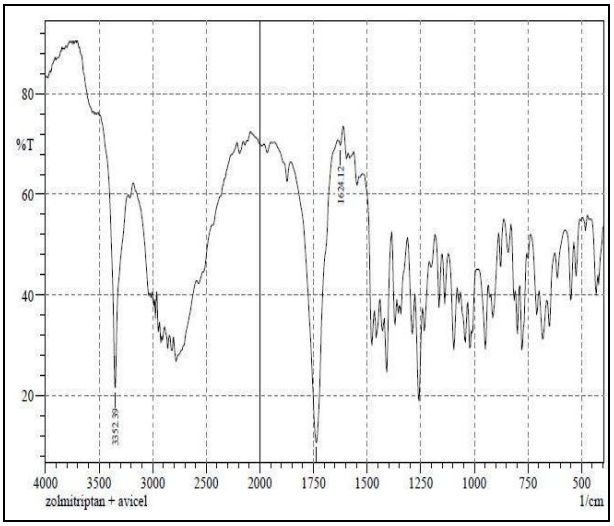


Figure 5: IR Spectra Drug and Avicel

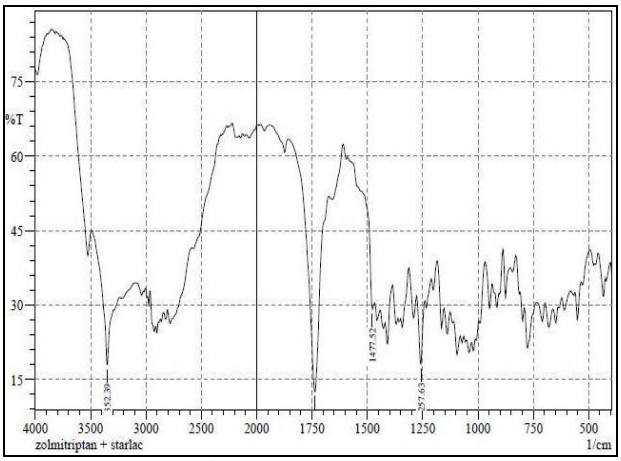
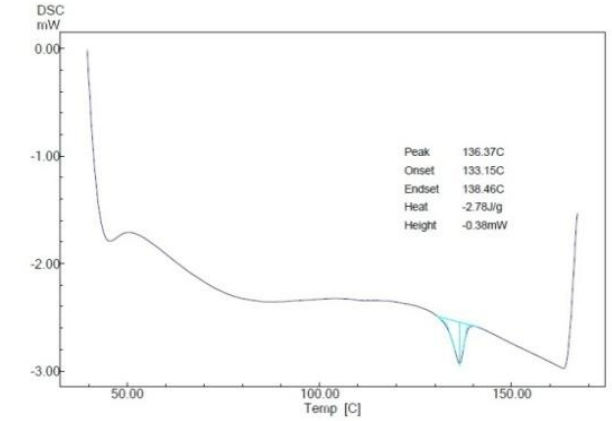


Figure 6: IR Spectra of Drug and starlac

DSC STUDIES:

Differential scanning calorimetry (DSC) studies of drug-excipients mixtures were performed using a detector to determine the drug excipients compatibility study. Thermograms of pure Zolmitriptan showed sharp endothermic peak at136.37°C.Similar peaks were obtained in the prepared drug-excipients mixtures at 151°C. **(Fig.).** this clearly indicated the nil drug excipients interaction.



(a): DSC of Pure Drug

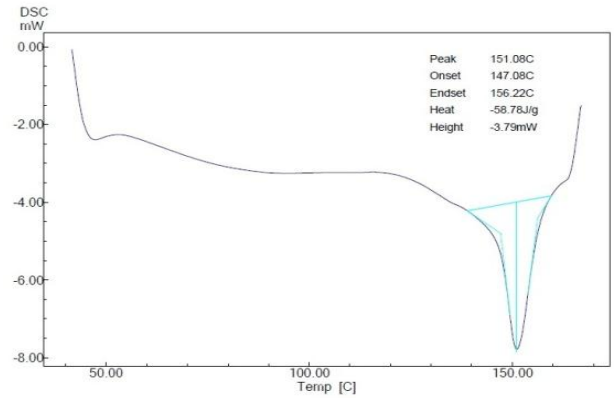


Figure 7 (b): DSC of drug and Excipients

Preparation of Mouth Dissolving Tablet by Direct Compression Technique:

Method:

Mouth dissolving tablet of Zolmitriptan were prepared by direct compression method according to the formula given in **Table 3.**

All the ingredients were passed through 60 mesh sieve separately. The drug and microcrystalline cellulose was mixed by small portion of both each time and blending it to get a uniform mixture kept aside. Then the ingredients were weighed and mixed in geometrical order and tablets were compressed of 8mm sizes flat round punch to get tablet using Multi Station rotary punch tablet compression machine.

Table 3: Formulation of Zolmitriptan Mouth Dissolving Tablet Prepared By Direct Compression Method

Ingredients	Formulation Code					
	F1	F2	F3	F4	F5	F6
Zolmitriptan	5	5	5	5	5	5
Ac-Di-Sol	2	2.5	3	2	2.5	3
Avicel pH 101	91.75	91.25	90.75	-	-	-
Starlac	-	-	-	91.75	91.25	90.75
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
Peppermint	0.25	0.25	0.25	0.25	0.25	0.25
Total Weight (Mg)	100	100	100	100	100	100

EVALUATION OF TABLETS[6, 10]:

1. Hardness
2. Friability
3. Weight variation.
4. Uniformity of thickness.
5. Drug content uniformity.
6. Wetting time.
7. Water absorption ratio.
8. *In vitro* disintegration time.
9. *In vitro* dissolution studies.
10. Stability studies.

Hardness test:

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm. Three tablets were randomly picked from each formulation and the mean and standard deviation 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 by using Electro lab, USP EF 2 friabilator. It is expressed in percentage (%). Four tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again. The percentage friability was then calculated by,

$$F = \frac{W\ initial - W\ final}{W\ initial} \times 100$$

% Friability of tablets less than 1% is considered acceptable.

Weight Variation Test:
The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Table 4: Percentage Deviation in Weight Variation

Average weight of a tablet	Percentage deviation
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
324 mg or more	5

In all the formulations the tablet weight was more than 99 mg and less than 100 mg, hence 10% maximum difference allowed.

Uniformity of Thickness:
The crown thickness of individual tablet may be measured with a Vernier Calliper, which permits accurate measurements and provides information on the variation between tablets. Other technique employed in production control involves placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding calliper scale. The tablet thickness was measured using screw gauge.

Drug Content Uniformity:
Four tablets weighted and crushed in a mortar then weighed powder contain equivalent to 10 mg of drug was taken and dissolved in 100 ml 0.1M HCL from this solution 1 ml of solution was diluted to 10 ml 0.1 M HCL again 1 ml solution from this diluted up to 10 ml with 0.1 M HCL and assayed for drug content at 237.5 nm.

Wetting Time:
The method was applied to measure tablet wetting time. A piece of tissue paper folded twice was placed in a small Petri dish (I.D. = 6.5 cm) containing 10 ml of water, a tablet was placed on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined.

Water Absorption Ratio:
A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation,

$$R = \frac{(Wa - Wb)}{Wb} \times 100$$

Where, Wb - weight of tablet before absorption
Wa - weight of tablet after absorption
Three tablets from each formulation were performed and standard deviation was also determined.

***In vitro* Disintegration Time:**
The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P specifications.

***In vitro* Dissolution Studies:**
Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rpm) using 900 ml of phosphate buffer pH (6.8) as dissolution medium. Temperature of the dissolution medium was maintained at37±0.5°C; aliquot of dissolution medium was withdrawn at every 5 min interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 225 nm and concentration of the drug was determined from standard calibration curve.

***In vitro* Drug Release Studies Details:**
Apparatus used : USP apparatus II dissolution test apparatus
Dissolution medium : 6.8 pH phosphate buffer solution.
Dissolution medium volume : 900 mL
Temperature : 37±0.5°C
Speed of basket paddle : 50 rpm
Sampling intervals : 5 min
Sample withdraw : 5 mL
Absorbance measured : 225nm

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 specifications.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of

environmental factors such as temperature, humidity an light and enables recommended storage conditions, re-test periods and shelf lives to be established. ICH specifies the length of study and storage conditions:

Long term testing 25°C ± 2°C / 60 % RH ± 5 % for 12 months Accelerated testing 40°C ±2 °C / 75 % RH ± 5 % for 6 months

In the present study, stability studies were carried out at 40°C / 75 % RH for a specific time period up to three months for the selected formulations.

RESULTS:

Table 5: characterization of pure drug (zolmitriptan)

Parameters	Experimental value	Standard value
Nature	Crystalline	Crystalline
Colour	White	White
Odour	Odourless	Odourless
Solubility	Soluble in 0.1 M HCL, Slightly soluble in water	Soluble in 0.1M HCL, Slightly soluble in water
Melting point	140^0 C	139^0-141^0C

Results of Pre-Compression Parameter for Prepared Tablet by Direct Compression Method:

Powder ready for compression containing drug and various excipients were subjected for pre-compression parameter to study flow property of granules to achieve uniformity of tablet weight. Results of all the pre-formulation parameter are given in **Table 6.**

Results of post compression tablet prepared by direct compression method:

Hardness:

The hardness of all the tablets prepared by both methods was maintained within the 2.5±0.264 kg/cm^2 to4.0±0.251 kg/cm^2. The mean hardness test results are tabulated in **Table 7.**

Friability test:

The friability was found in all designed formulations in the range 0.20±0.065 to0.90±0.072to be well within the approved range (< l %). The friability study results were tabulated in **Table 7.**

Thickness:

The mean thickness was (n=3) almost uniform in all the formulations and values ranged from3.28±0.155 mm to 3.47±0.265mm. The results of thickness for tablets were shown in **Table 7.**

***In vitro* dispersion time:**

The *in vitro* dispersion time is measured by the time taken to undergo uniform dispersion. Rapid dispersion within several minutes was observed in all the formulations. The *in-vitro* dispersion data is tabulated in the **Table 7.**

Table 6:Pre-Compression Parameters for Prepared Tablet by Direct Compression Method

Formulation Code	Parameters				
	Bulk Density* (g/cc)	Tapped Density* (g/cc)	Angle of Repose* (Degree)	Carr's Index* (Percent)	Hausner's Ratio*
F1	0.38±0.021	0.4545±0.003	28.60±0.013	15.55±0.172	1.18±0.025
F2	0.39±0.028	0.4594±0.007	28.17±0.01	13.33±0.215	1.15±0.0208
F3	0.38±0.015	0.4513±0.004	29.98±0.1562	15.55±0.208	1.18±0.0208
F4	0.387±0.015	0.4285±0.008	28.17±0.025	9.52±0.0255	1.10±0.013
F5	0.401±0.012	0.4521±0.002	29.03±0.035	11.11±0.145	1.12±0.012
F6	0.402±0.026	0.4604±0.005	28.29±0.035	13.04±0.111	1.15±0.0152

**Mean ± S.D., n=3 (All the values are the average of three determination*

Table 7: Evaluation of Zolmitriptan MDT Formulations

Formulation code	Parameters			
	Hardness* (kg/cm^2)	Friability* (%)	Thickness* (mm)	*In vitro* Dispersion time* (sec)
F1	3.0±0.254	0.50±0.05	3.36±0.030	19±1.00
F2	3.0±0.285	0.40±0.084	3.35±0.055	22±1.527
F3	3.5±0.136	0.20±0.065	3.43±0.015	15±1.510
F4	2.5±0.264	0.90±0.072	3.47±0.265	35±2.516
F5	4.0±0.251	0.30±0.076	3.28±0.155	30±1.023
F6	3.5±0.201	0.50±0.076	3.38±0.065	45±2.081

** Mean ± S.D., n=3 (All the values are the average of three determination)*

Weight variation test:

The weight variation was found in all designed formulations in the range 100.12±0.405 to 100.28±0.475mg. The mean weight variation test results are tabulated in **Table 8.**

Wetting time:

The results of wetting time are shown in **Table 8.** The wetting time of Zolmitriptan tablets prepared by direct compression was found to be in the range of 40.59±0.675 and69.10±0.269 sec respectively, which facilitate the faster dispersion.

Water absorption ratio:
The values of water absorption ratio shown in **Table 8.**

Drug Content:
The drug content uniformity was performed for all the 6 formulations and results are tabulated in **Table 8.** Three trials from each batch were analyzed spectrophotometrically. The average value and standard deviations of all the formulations were calculated.

Table 8: Evaluation of Zolmitriptan MDT formulations

Formulation Code	Parameters			
	Wetting Time*(sec)	Water Absorption Ratio*(%)	Percent Drug Content*	Weight Variation*
F1	69.1±0.269	51.95±1.571	97.62±0.582	100.28±0.475
F2	50.79±0.503	44.35±1.023	98.88±0.612	100.18±0.440
F3	58.71±0.518	48.33±0.675	100.4±0.632	100.28±0.447
F4	54.72±0.475	57.16±0.944	98.77±0.290	100.12±0.405
F5	50.89±0.320	63.86±0.490	99.30±0.172	100.18±0.472
F6	40.59±0.675	71.42±1.156	100.21±0.405	100.13±0.486

** Mean ± S.D., n=3 (All the values are the average of three determination)*

Release profile of Zolmitriptan

Table 9: Release Profile of Zolmitriptan mouth dissolving tablets by direct compression method

Time Interval (Minutes)	F1*	F2*	F3*	F4*	F5*	F6*
5	59.42%±0.01	60.05%±0.18	59.52%±0.02	54.57%±0.27	58.99%±0.12	64.99%±0.42
10	67.65%±0.35	68.56%±0.28	68.01%±0.49	62.78%±0.31	66.92%±0.42	74.00%±0.15
15	71.15%±0.26	72.73%±0.37	72.46%±0.19	66.22%±0.51	71.88%±0.30	77.19%±0.16
20	78.66%±0.33	80.25%±0.10	79.60%±0.28	73.40%±0.28	78.26%±0.25	84.47%±0.25
25	84.96%±0.48	87.07%±0.37	86.65%±0.10	79.78%±0.28	84.94%±0.35	92.19%±0.28
30	89.64%±0.20	91.53%±0.49	90.95%±0.31	89.17%±0.27	91.38%±0.31	97.52%±0.21
35	93.41%±0.33	95.67%±0.12	96.26%±0.24	92.03%±0.49	94.14%±0.51	99.17%±0.12

** Mean ± S.D., n=3 (All the values are the average of three determination)*

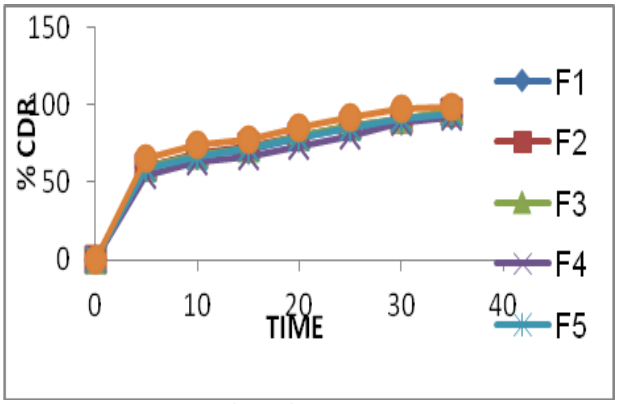


Figure11: Release Profile of Zolmitriptan MDT by Direct Compression Method

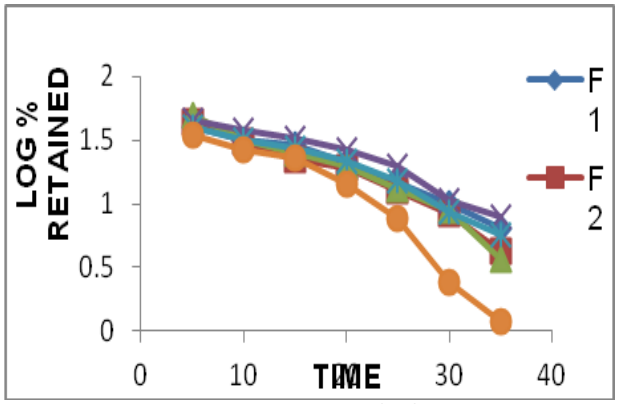


Figure 13: comparative First order plots for formulations F1-F6

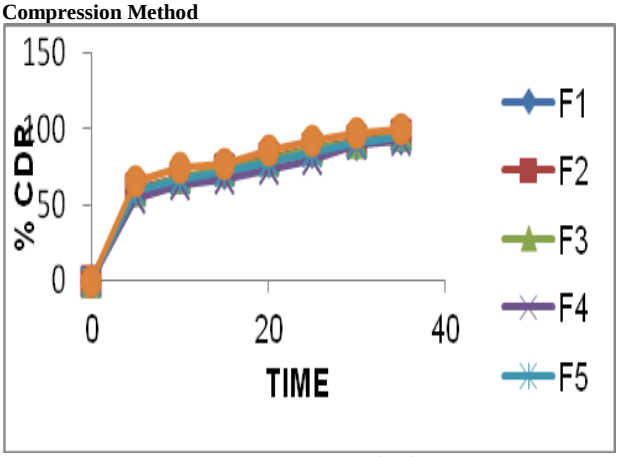


Figure 12: comparative Zero order plots for formulations F1-F6

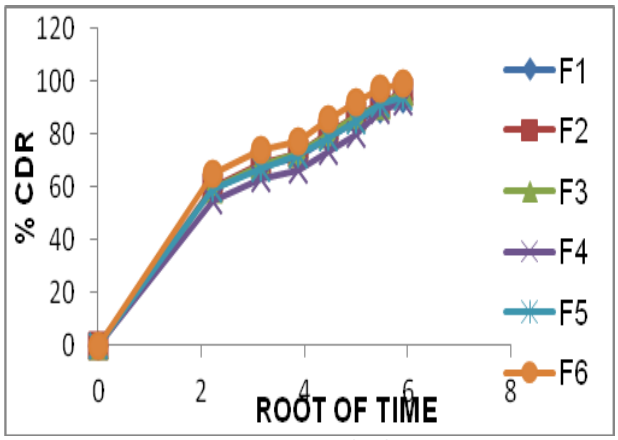


Figure 14: comparative Higuchi plots for formulations F1-F6

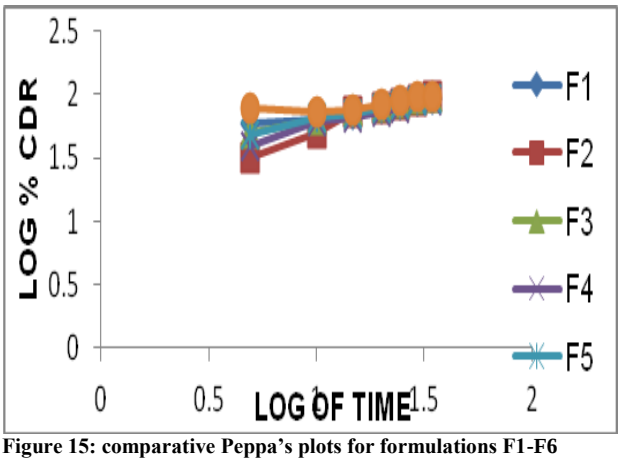


Figure 15: comparative Peppa's plots for formulations F1-F6

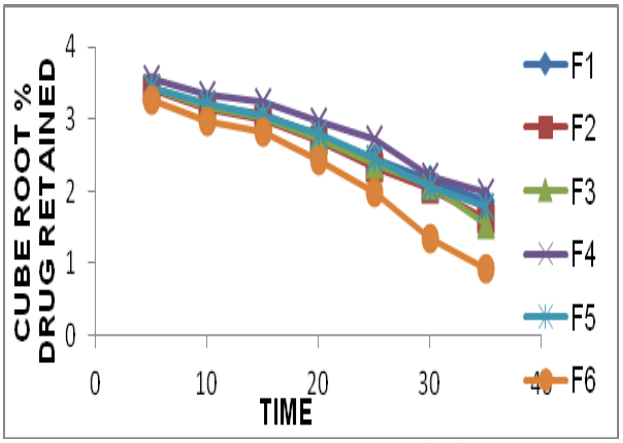


Figure 16: comparative Hixen Crowell plots for formulations F1-F6

DISCUSSION:

The intention of the development of present research is to study the effect of superdisintegrants on the dissolution rate of zolmitriptan.

In this study mouth dissolving tablets were prepared using Ac-Di-Sol, Avicel pH 101, starlac and evaluated for different parameters. Before going to formulation, the possibilities for drug-excipients interactions were studied using FTIR study and the results proved that there was no interaction between zolmitriptan and excipients. Then the tablets were prepared by direct compression method and evaluated for different parameters. The prepared tablets were studied for hardness, friability, weight variation and drug content and they were complied with Pharmacopoeial limits.
Among all formulations, formulation F6 shows disintegration time of 45 seconds and drug release up to 99.17% at 35 minutes.

CONCLUSION:

In the present work mouth dissolving tablets of Zolmitriptan were prepared by direct compression method using superdisintegrants such as croscarmellose sodium and microcrystalline cellulose. All the tablets of Zolmitriptan were subjected to weight variation, hardness, friability, *in vitro* dispersion, drug polymer interaction, drug content uniformity, water absorption ratio, wetting time, and *in vitro* drug release.

Based on the disintegration time, formulation 6(F6) co-processed mixtures of Ac-Di-Sol and Starlac was found to be promising and showed a dispersion time of 45 sec, wetting time of 40.59sec.The *in vitro* drug release from fast dissolving tablets of Zolmitriptan prepared by direct compression methods were found to be 99.17% within 35 minute. The stability study shows that no significant changes in drug content after three month study.

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