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RESEARCH ARTICLE

Formulation and *In-Vitro* Evaluation of Sustained Release Matrix Tablets of Zolmitriptan

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ABSTRACT

The aim of the present research work is to Formulate & *in-vitro* evaluation studies of sustained release matrix tablets of Zolmitriptan using Locust bean gum, Xanthan gum, HPMC K 100 and Ethyl cellulose. Tablets were prepared by wet granulation method. Zolmitriptan is an anti-migraine drug. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose. The developed tablets were subjected to various tests for physical parameters such as thickness, hardness, friability, drug content and *in vitro* release studies. Release kinetics was evaluated by using United States Pharmacopeia USP type II dissolution apparatus. The *in vitro* dissolution study was carried out for 12 hrs. For first 2hrs in 0.1 N hydrochloric acid (pH 1.2) followed by using phosphate buffer pH 6.8for the remaining 10 hrs. The results of dissolution studies indicated that formulations containing Xanthan gum showed better dissolution than synthetic gums (HPMC K-100, Ethyl cellulose). The dissolution study proved enhanced sustained release when Xanthan gum was used as a matrix forming material.

KEYWORDS

Sustained release matrix tablet, Zolmitriptan, Locust bean gum, Xanthan gum, HPMC K-100, Ethyl cellulose

INTRODUCTION

Oral drug delivery system is the most preferred and suitable option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. Normally conventional dosage form gives wide range of fluctuation in drug concentration in the bloodstream and tissues with consequent undesirable toxicity and poor efficiency. The maintenance of concentration of drug in plasma within therapeutic index is very critical for effective treatment.

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These factors as well as factors such as repetitive dosing and unpredictable absorption lead to the concept of oral Sustained release drug delivery systems. Developing oral sustained release matrix tablets for drug with constant release rate has always been a challenge to the pharmaceutical technologist. Drug release through matrix system is determined by Water penetration, Polymer swelling, Drug dissolution, Drug diffusion, Matrix erosion have been utilized as formulation approaches.[1]

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug

levels in the blood or target tissue, it is considered as a controlled-release system.[2]

Migraine is a recurrent incapacitating neurovascular disorder characterized by attacks of debilitating pain associated with photophobia, phonophobia, nausea and vomiting. Migraine affects a substantial fraction of world population and is a major cause of disability in the work place. Though the pathophysiology of migraine is still unclear three major theories proposed with regard to the mechanisms of migraine are vascular (due to cerebral vasodilatation), neurological (abnormal neurological firing which causes the spreading depression and migraine) and neurogenic dural inflammation (release of inflammatory neuropeptides). The modern understanding of the pathogenesis of migraine is based on the concept that it is a neurovascular disorder.[3]

Zolmitriptan is 5-HT1B/1D receptor agonists which have well established efficacy in treating migraine. It is derivative of tryptamine. After oral administration, Zolmitriptan is rapidly and completely absorbed from the gastrointestinal tract. Linear kinetics over the dose range of 2.5 to 50 mg. Mean absolute bioavailability is approximately 40%. The mean apparent volume of distribution is 7.0 L/kg. Plasma protein binding of zolmitriptan is 25% over the concentration range of 10- 1000ng/mL.[4,5,6]

MATERIAL AND METHODS

Zolmitriptan was obtained as gift sample from Apotex Research Pvt. Ltd Bangalore. Locust bean gum, HPMC K 100, Ethyl Cellulose were purchased from Research-lab Fine Chem Industries, Mumbai. Xanthan gum was purchased from Hi media Lab Pvt Ltd, Mumbai. Magnesium stearate was purchased from Loba Chemicals Pvt. Ltd. Mumbai. Talc, PVP K 30, Lactose were purchased from SD Fine chemicals Ltd, Mumbai.

Methods

Formulation of Sustained Release Matrix Tablets

Tablet formulations were prepared by wet granulation method. Non-aqueous granulation process was adopted to prepare Zolmitriptan SR matrix tablets. Proportion of excipients with drug was as given in Table no 1. All ingredients were sifted through sieve no.60. The sifted ingredients were mixed thoroughly in a polybag for 15min. PVP K30 was dissolved in isopropyl alcohol and used for wet granulation of the final blend. To get the desired wet mass. This wet mass was passed through sieve # 16. The prepared granules were dried at 60^0C for 1 hour in hot air oven. Dried granules were sized by passing it through sieve no.20 and lubricated with magnesium stearate and Talc for 1 minutes. Finally tablets were compressed at 200 mg weight on a 10 station mini rotary tableting machine (Shakti Pharma tech Pvt. Ltd, Ahmedabad) with 8 mm flat-shaped punches.

Evaluation of Granules[7,8,9]

Angle of Repose

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the powder cone.

Bulk Density

Both loose bulk density and tapped bulk density were determined and calculated by using the following formulas.

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index (%) = [TBD-LBD] X 100 / TBD

Where, TPD is Tapped bulk density

LBD is Loose bulk density

The physical properties of granules were shown in Table 2.

Evaluation of Tablets[7,8,9]

Post Compression Parameters

Thickness and Diameter

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm

Hardness

The Mansanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.

Friability (F)

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets.

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} \times 100$$

Weight Variation

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated.

The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double the percentage limit.

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods shown in Table 3.

Uniformity of Drug Content

Weigh and powder 20 tablets. Weigh accurately a Quantity of the powder equivalent to 100 mg of Zolmitriptan, transfer to a 250 ml volumetric flask. Add about 150 ml of 0.1N HCL, shake well and sonicate it for 25-30 min. Make up the volume up to 250 ml with 0.1N HCL. Filter the solution, take 10 ml of filtrate in 100 ml volumetric flask and make up the volume with 0.1N HCL. Measure the absorbance, of the resulting solution at the maxima at about 222 nm spectrophotometrically. Measure the concentration of drug in tablet powder using following equation:

$$Cu/Cs = Au/As * \text{dilution factor}$$

Cu = Concentration of unknown sample,

Cs = Concentration of Standard sample

Au = Absorbance of unknown sample &

As= Absorbance of standard sample[10].

In-Vitro Dissolution Study

Dissolution tests were performed in a USP Dissolution Test Apparatus II (Paddle method) at 37 ± 0.5°C. The Paddles were rotated at a speed of 50 rpm. The prepared tablets of (Zolmitriptan) tablets were placed in the dissolution vessel containing 0.1 N HCl solutions (pH 1.2) for 2 hrs. These were then transferred to phosphate buffer (pH 6.8) and continue dissolution.5 ml of solution were withdrawn at different time intervals, filtered through 0.45 µm filter paper and the content of Zolmitriptan was determined spectrophotometrically at a wavelength of 222nm. At each (hour) time of Withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask. On the basis of release studies the formulation which gave desired once a day release of Zolmitriptan was chosen as the optimized formulation. The dissolution profiles of different formulations are shown in Figure 14,15. The drug release from the formulations were sustained in the following manner F1 > F2 > F5. In all the formulations, it has been observed that by increase the concentration of polymers in the formulations there by

respectively retard the drug release form the matrices.

Drug Release Kinetics

To determine the mechanism of drug release from this formulation, the drug release data of *in-vitro* dissolution study was analyzed with various kinetic equations. Various kinetic equations. The data were treated according to:

1. Zero order kinetic model – Cumulative % drug released versus time.
2. First order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus log time.

Stability Study

The optimized formulation was subjected to stability at 25^0C± 2^0C / 60% ± 5% RH, 30^0C ± 2^0C / 65% ± 5% RH and40^0C ± 2^0C / 75% ± 5% RH for period of 90 days. After each month tablet sample was analyzed for physical characteristics and drug release profile.[11]

Table 1: Composition of matrix tablet of Zolmitriptan

Ingredients	Formulation code (in mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zolmitriptan	5	5	5	5	5	5	5	5	5
Locust Bean Gum	150	180	210	-	-	-	-	-	-
Xanthan Gum	-	-	-	150	180	210	-	-	-
HPMC K 100	-	-	-	-	-	-	150	180	210
Lactose	124	94	64	124	94	64	124	94	64
PVP K 30	12	12	12	12	12	12	12	12	12
Magnesium stearate	6	6	6	6	6	6	6	6	6
Talc	3	3	3	3	3	3	3	3	3

RESULTS AND DISCUSSION

Table 2: Evaluation of Pre-Compression Parameters

Formulations	Bulk Density* (g/ml)	Tapped bulk* density (g/ml)	Carr's index (%)	Angle of repose*
F1	0.289 ± 0.002	0.302 ± 0.001	11.34±1.41	27.66±1.42
F2	0.284 ±0.005	0.266 ± 0.006	8.6±1.02	26.62±1.25
F3	0.288 ± 0.003	0.292 ± 0.003	9.71±1.32	27.12±1.12
F4	0.291 ±0.008	0.302 ± 0.001	11.24±1.44	26.58±1.32
F5	0.286 ± 0.006	0.266 ± 0.006	9.49±1.41	28.03±1.86
F6	0.290 ±0.005	0.292 ± 0.003	11.5±1.39	27.17±1.61
F7	0.302 ± 0.001	0.325 ± 0.016	7.07±1.39	27.33±1.74
F8	0.266 ± 0.006	0.294 ±0.011	10.20±1.44	26.71±1.14
F9	0.292 ± 0.003	0.326 ± 0.013	10.42±1.36	27.33±1.15

*The values represent mean ± SD, n=3.

Table 3: Evaluation of Zolmitriptan SR tablets

Formulations	Thickness* (mm)	Hardness* (kg/cm^2)	Friability* (%)	Drug content (%)
F1	3.55±0.08	6.2±0.09	0.26±0.09	99.83
F2	3.54±0.13	6.3±0.1	0.26±0.22	99.26
F3	3.53±0.15	6.6±0.06	0.29±0.10	99.10
F4	3.54±0.01	5.9±0.18	0.31±0.16	99.32
F5	3.55±0.09	6.2±0.20	0.30±0.13	99.45
F6	3.55±0.14	6.4±0.06	0.27±0.116	98.90
F7	3.55±0.06	6.7±0.11	0.33±0.19	99.26
F8	3.54±0.02	6.3±0.08	0.32±24	99.19
F9	3.56±0.07	6.6±0.06	0.31±0.10	99.30

*The values represent mean ± SD, n=3

Table 4: Correlation coefficients of different mathematical models for formulations F1 to F9

Formulation Code	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas- model	
				R^2	Slope n
F1	0.995	0.660	0.984	0.997	0.850
F2	0.987	0.954	0.983	0.969	0.773
F3	0.983	0.975	0.992	0.995	0.674
F4	0.969	0.934	0.979	0.977	0.845
F5	0.990	0.636	0.962	0.989	0.847
F6	0.991	0.692	0.943	0.987	0.874
F7	0.986	0.706	0.932	0.946	0.734
F8	0.968	0.971	0.990	0.961	0.782
F9	0.995	0.982	0.975	0.988	0.920

FTIR Spectroscopy

The FT-IR Spectrum of pure Zolmitriptan and its physical mixture with polymers and different excipients are shown in Figure: 1-9.

Functional group vibrations	Zolmitriptan [RS] (cm^{-1})	Optimised formulation F-6 (cm^{-1})
N-H Stretching	3346.553	-
C-H Stretching	2924.180	2917.129
C=O Stretching	1730.010	-
C-N Stretching	1368.767	1377.465
C-O Stretching	1257.267	-

The FT-IR Spectrum of drug & polymers filer and formulations were shown in figures below. In the formulations characteristic peaks of the drug were observed in the spectra of mixture of drug and polymer, however the intensity of the peaks were reduced this might be due to very low concentration of drug in the mixture this indicates that there is no interaction between the drug and polymer mixtures.

Perusal to the FT-IR spectra from Figures 1-9 shows that there was no interaction between drug and different polymer mixtures. Hence these release retarding materials were selected for formulation of sustained release tablets.

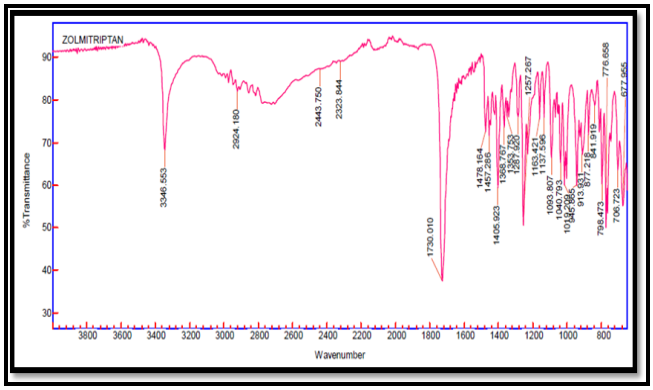

Figure 1: FT-IR of Zolmitriptan

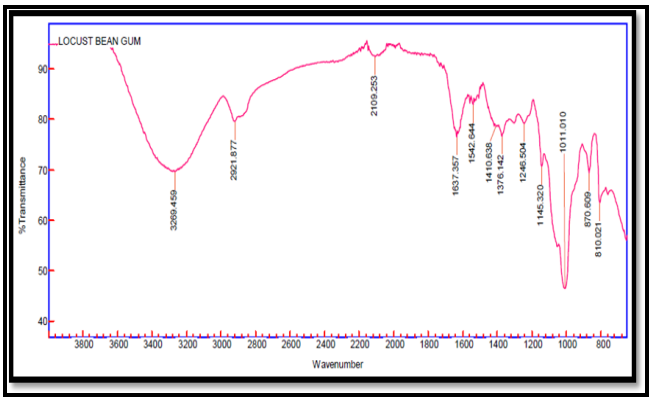

Figure 2: FT-IR of Locust bean gum

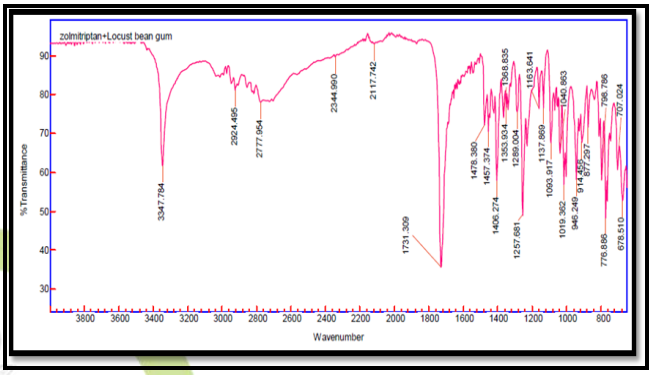

Figure 3: FT-IR of Zolmitriptan +Locust bean gum

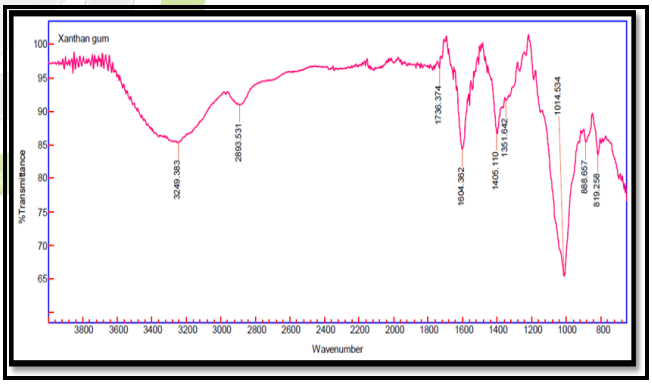

Figure 4: FT-IR of Xanthan gum

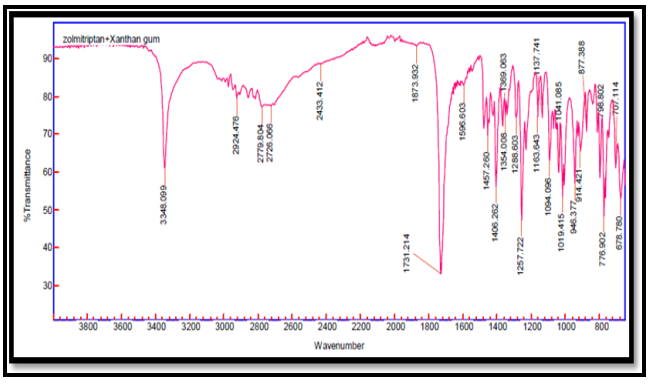

Figure 5: FT-IR of Zolmitriptan + Xanthan gum

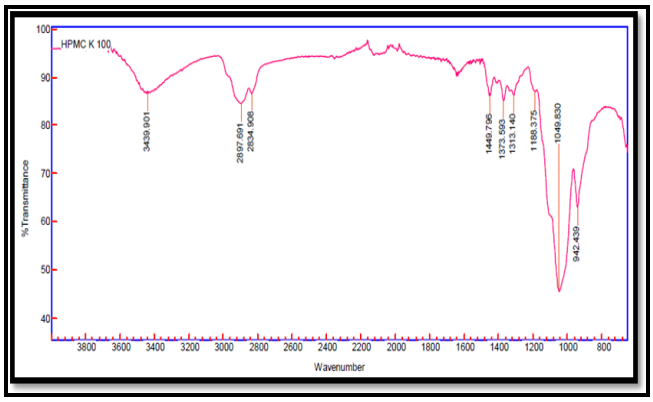

Figure 6: FT-IR of HPMC K 100

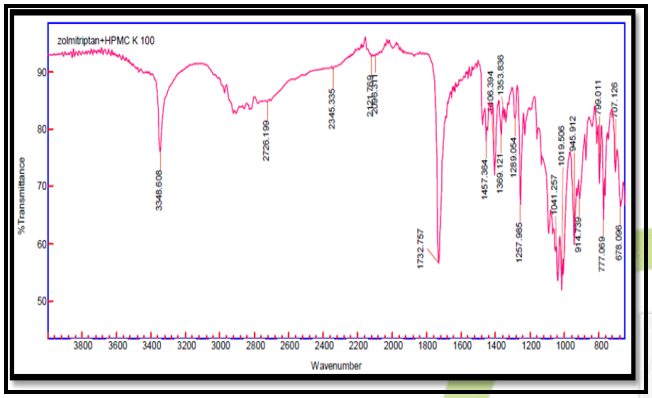

Figure 7: FT-IR of Zolmitriptan + HPMC K 100

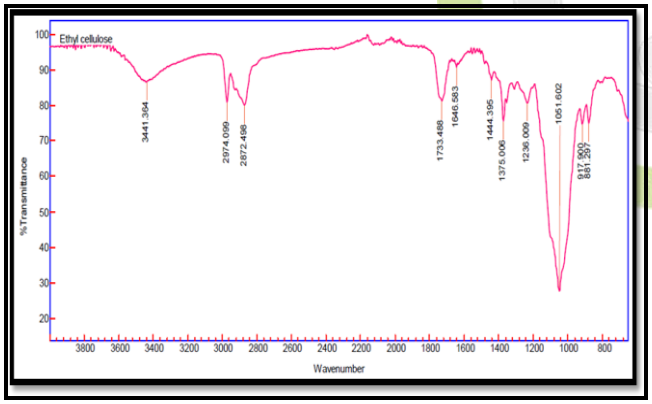

Figure 8: FT-IR of Ethyl cellulose

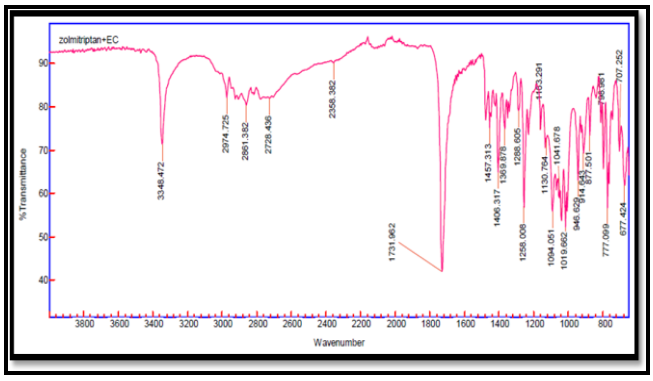

Figure 9: FT-IR of Zolmitriptan + Ethyl cellulose

Scanning Electron Microscopy (SEM) of the Optimized Formulation

SEM photomicrograph of the matrix tablet taken at different time intervals after the dissolution experiment showed that matrix was intact and pores had formed throughout the matrix. SEM photomicrographs with graphs of tablet surface at different time intervals also showed that erosion of matrix increased respect to time indicated by the photomicrographs at 2nd, 6th, and 12thhrs revealing pores with increasing diameter. These photomicrographs also revealed formation of gelling structure indicating, the formation of both pores and gelling structure on tablet surface indicates the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of Zolmitriptan from formulated matrix tablets. As shown in (Figure 10 a, b, c).

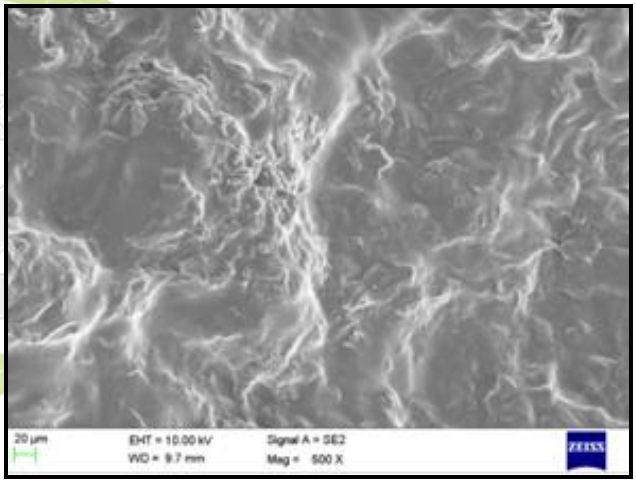

Figure 10 (a): 2ndhrs

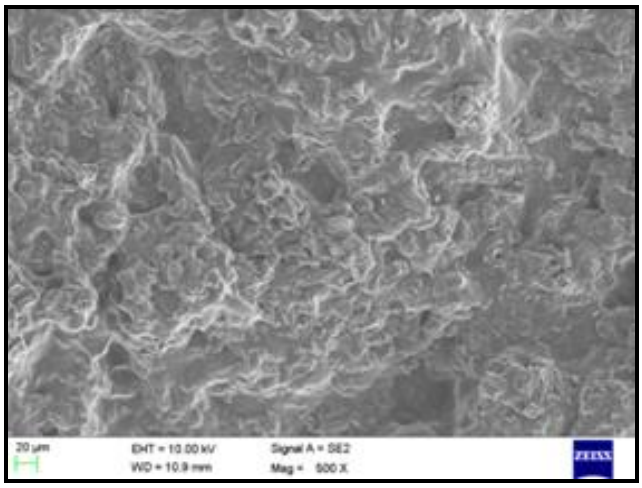

Figure 10 (b): 6thhrs

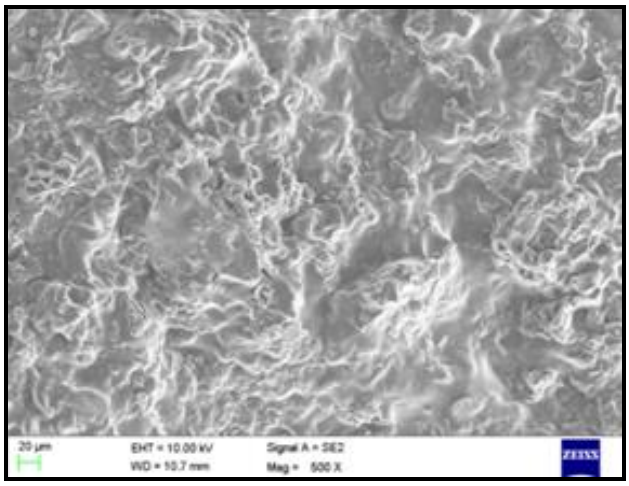

Figure 10 (c): 12thhrs

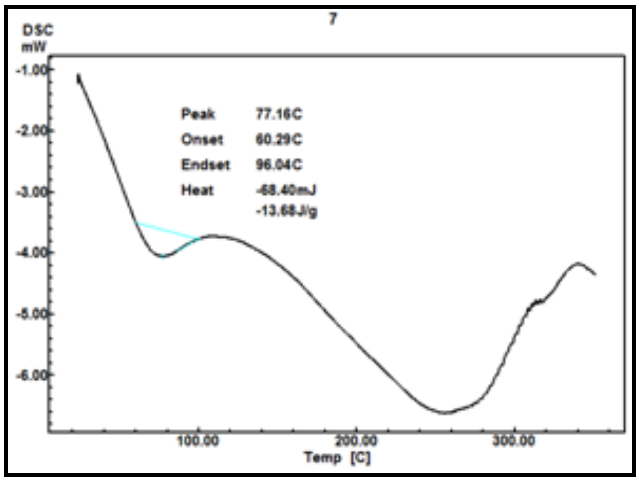

Figure 12: DSC of pure locust bean gum

Differential Scanning Calorimetry

Thermogram of Zolmitriptan is shown in the Fig. 13 which indicates the melting point of pure drug is 139.68^{0}C and the melting peak of optimized formulation (F-6) is at 151.93^{0}C was observed in the Figure 13 Change in temperature is due to various concentrations of drug and other excipients in physical mixture.

This shows that there is no interaction between drug and optimized formulation F-6. DSC studies revealed that there was no much shift in the melting point of the drug in the physical mixture compared to the pure drug, this indicates that there is no interaction between drug and matrix materials.

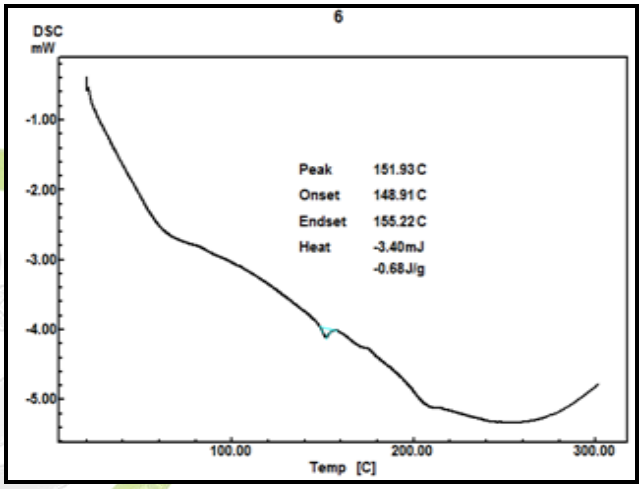

Figure 13: DSC of Zolmitriptan and locust bean gum

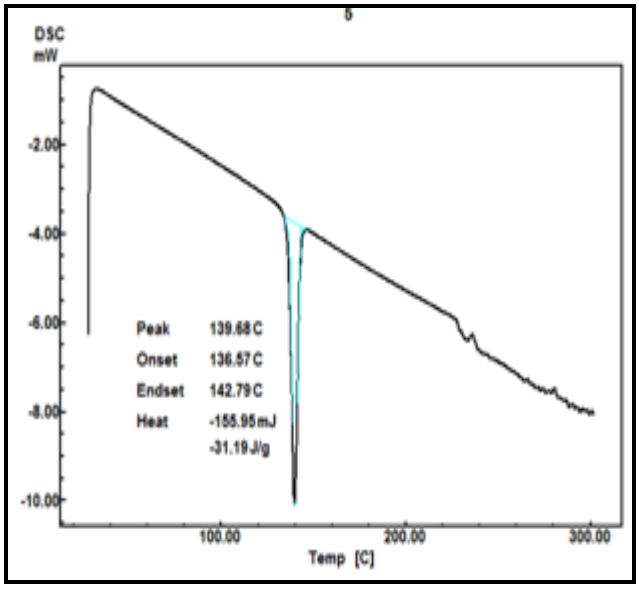

Figure 11: DSC of Zolmitriptan

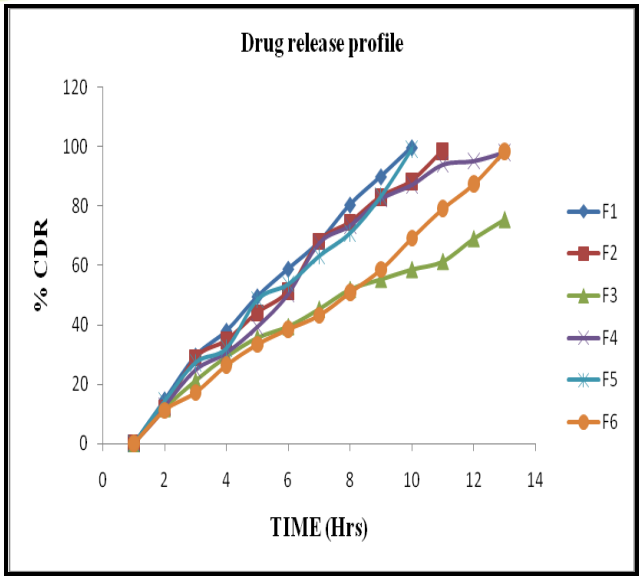

Figure 14: *In Vitro* Dissolution Profile of F1 to F3 Formulations

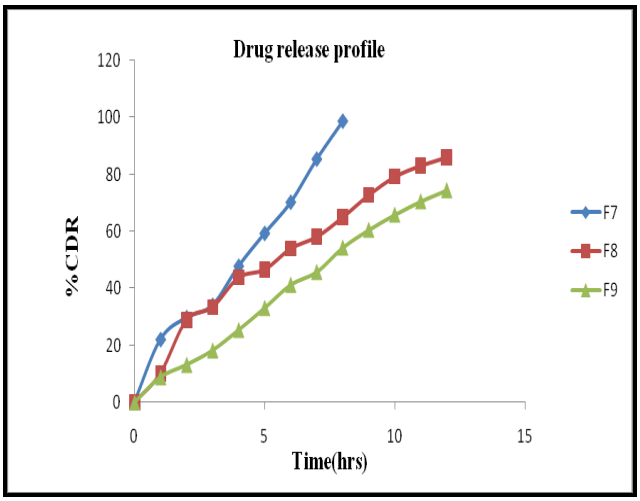

Figure 15: *In Vitro* Dissolution Profile of F4 to F9 Formulations

All the tablet formulations showed acceptable quality control properties like hardness, friability, thickness, weight variation, drug content uniformity etc. Complied with in the specifications for tested parameters. From the formulations F1 to F3, the release rate was decreased in the following order: F1 > F2 > F3. When the polymer concentration of Locust bean gum increased the drug release rate was reduced from the above formulations. The rate of release was faster in F1 and slower in F3. This result showed that as the proportion of mucilage increased, the overall time of release of the drug from the matrix tablet increased. Drug release from swellable and erodible hydrophilic matrices can be attributed to polymer dissolution, drug diffusion through gel layer, or a combination of both.

From formulation F4 to F6 increase in drug release was observed with higher concentration of polymers okra gum. Rate drug release was faster in F6 and slower in F4, as the concentration of polymer increases the drug release become fasters. The highest release of drug from formulation F6 Shows 98.5% drug release after 12 hours, and F4 & F5 shows 86.4 %, 92.2% drug release after 12 hrs respectively. The rate of drug release was optimized in matrix tablets of F6 formulation (i.e 98.5 %) up to 12 hrs.

Appears to be suitable for use as a release retardant in the formulating sustained release matrix tablets because of its compatibility, good swelling, good flow properties and drug release characteristics.

Formulation F7 to F9, the release rate decreases with increases in polymer concentration in following order F7 > F8 > F9. This result shown that as the proportion of HPMC K 100increased, the overall time of release of the drug from the matrix tablet was also increased (release retarding).

Stability studies were conducted for the optimized formulations as per ICH guidelines.

There was not much variation in matrix integrity of the tablets at all the temperature conditions. There were no significant changes in drug content, physical stability, hardness, friability and drug release for the selected formulation F3 after 90 days.

CONCLUSION

Matrix tablet of Zolmitriptan can be prepared successfully by using wet granulation method, using Locust bean gum, Xanthan gum, HPMC K 100 and ethyl cellulose polymers as retardant and by using lactose as filler. From the above observations it was concluded that slow and controlled release of Zolmitriptan over a period of 12 hours was obtained from matrix tablets F6. It was found that increase in the polymeric concentration in polymeric ratio increases the drug release. The results suggest that the developed sustained-release tablets of Zolmitriptan might achieve better than conventional dosage forms, leading to improve efficacy and patient compliance.

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