

## RESEARCH ARTICLE

# Formulation Development and *In Vitro* Characterization of Zolmitriptan Controlled Release Drug Delivery Systems

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**Abstract: Background:** Zolmitriptan is an artificial tryptamine, employed for the acute cure of migraine attack with or exclusive of aura and cluster headaches.

**Objective:** It is an attempt to develop the extended release (ER) of Zolmitriptan matrix (ZMT) tablets to treat migraine safely and effectively.

**Methods:** All formulations were prepared with natural polymers or gums like guar gum, xanthan gum, karaya gum through direct compression method using 6mm punch.

**Results:** Powder blend of all formulations (F1 - F12) using different ratios of the above mentioned gums (5%, 10%, 15% and 20%) were characterized with pre-compression parameters (angle of repose, bulk density, tapped density, compressibility index, hausner ratio, compatibility studies) and post-compression parameters (weight variation, thickness, friability, hardness, assay, *in vitro* dissolution studies). F1 - F4 formulations were prepared with gum karaya and compared with remaining gums; gum karaya shows more retardance capacity. F9 - F12 (with guar gum) formulations were unable to produce the desired release, whereas F5 - F8 formulations containing with xanthan gum exhibited more retarding effect with increasing concentration of polymer.

**Conclusion:** All prepared formulations (F1 - F12) were characterized and F3 formulation was optimized (97.3% drug released in 8 hours). All prepared formulations (F1 - F12) showed good flow properties and release patterns. Hence, formulations of ZMT matrix tablets have a promising delivery system which will enhance bio-availability and achieve greater therapeutic efficacy.

**Keywords:** Zolmitriptan, controlled release, direct compression, bio-availability, therapeutic efficacy.

## 1. INTRODUCTION

The majority and trendy route is the oral route of administration, and still, it is a most commonly used dosage form due to their uninterrupted pioneering ideas to overcome the drawbacks [1]. Drug release from the dosage form is of two types, one is immediate release and another one is extended release (ER) [2]. In an immediate release, the drug released immediately after administration for the most part within 30 min. In ER formulations there are two types of

drug release one is controlled release (CR) and another one is sustained release (SR). In CR there are two parameters to consider those are time and rate of release. In SR time is the key parameter to consider and there is no control over the drug release [3]. These CR systems release drug in a predetermined rate for a specific period of time. We can achieve both local and systemic delivery of drugs [4]. CR systems indicate release at predetermined and predictable in a controlled manner [5]. This system is able to make available authentic therapeutic controls whether be it of

sequential or spatial life or both. In addition, the system makes an attempt to supply the steady-state concentration to target sites or tissues [6]. Oral controlled drug delivery system (CRDDS) is an essential step for successful performance and the drug should have good absorption throughout the gastrointestinal tract (GIT) [7]. Design of CRDDS is to be modified in such a way that it should have more gastric residence time in the stomach to release the drug before the absorption window [8]. To overcome conventional dosage problems, it is mandatory to distribute a single dose for a prolonged period of time [9]. Thus, it is a suitable candidate for the development of extended delivery systems such as CR and SR [10]. Zolmitriptan (ZMT) is a 5-hydroxytryptamine selective serotonin receptor agonist used for acute migraine treatment of 1B and 1D subtypes with or without aura [11-14]. ZMT is a white powder, slightly soluble in water and significantly soluble in acidic medium (0.1N hydrochloric acid [HCl]) and it belongs to biopharmaceutical classification system III drug. It is having 40% bioavailability and the doses range from 1.25 mg (i.e., recommended) to 5 mg (i.e., maximum dose with 2–3 times a day). Direct compression has compensation over the other techniques (i.e. wet and dry granulations), is cost-effective, and reduces the preparation cycle time [15].

The intention of the present works to prepare and assesses ZMT matrix tablets with natural polymers such as guar gum, xanthan gum, and karaya gum.

## 2. MATERIALS AND METHODS

### 2.1. Materials

ZMT received as a gift sample from M/s. Aurobindo Pharma Ltd., Hyderabad, India. Gum karaya, xanthan gum, and guar gum were from DOW chemical company, USA. Microcrystalline cellulose, talc, and magnesium stearate were purchased for S.D. Fine Chem. Ltd., Mumbai, India. HCl is purchased from Merck Specialties Pvt. Ltd., India.

### 2.2. Methods

#### 2.2.1. Evaluation of Zmt Matrix Tablets

##### 2.2.1.1. Pre-Compression Characterization of Zmt Matrix Tablets

The different physical properties were evaluated for powder blend of ZMT formulations (F1–F12) [16].

##### 2.2.1.2. Drug-Excipient Compatibility Studies

Fourier-transform infrared spectroscopy (FTIR) was carried out to find out the presence of interaction among drug and excipients. Pure drug (5 mg) and optimized formulations (F3), i.e., a drug with the polymer (5 mg+15 mg) are subjected to the analysis. Using KBr press about 1–2 mg of sample was mixed with dried potassium bromide and compressed to form a KBr disk. The samples were scanned from 4000 to 400  $\text{cm}^{-1}$  [17].

##### 2.2.1.3. Construction of Calibration Curve of ZMT

Prepare different concentrations are ranging from 2 to 10  $\mu\text{g/ml}$  ZMT with acidic (0.1N HCl) and basic medium (6.8 pH phosphate buffer) and observe the maximum wavelength ( $\lambda_{\text{max}}$ ) for acidic and basic mediums with 298 nm and 299 nm, respectively, then calculated regression coefficient ( $R^2$ ) by plotting graph between concentration on X-axis and absorbance on Y-axis.

### 2.3. Preparation of ZMT Matrix Tablets

ZMT matrix tablets were prepared by the direct compression using multi-stations of 6 mm. Drug and all ingredients except lubricant (magnesium stearate), weighed accurately as mentioned in Table 1, and sifted through sieve #24. The ZMT (drug) was mixed with the required quantities of natural polymers such as guar gum, xanthan gum, and karaya gum (1:1, 1:2, 1:3, and 1:4) and Avicel PH200 in geometric proportions. The earlier weighed mixture was lubricated with magnesium stearate and finally subjected to compression

**Table 1. Pre-compression evaluation of ZMT formulations**

Code	Bulk density ( $\text{g/cm}^3$ )	Tapped density ( $\text{g/cm}^3$ )	Carr's index (%)	Hausner's ratio	Angle of repose ( $\Theta$ )
F1	0.42±0.124	0.58±0.912	19.62±1.025	1.83±0.03	27.91±1.228
F2	0.44±0.365	0.49±0.127	16.72±0.983	1.25±0.91	28.692±0.983
F3	0.48±0.736	0.56±0.957	18.79±0.938	1.35±0.18	29.29±0.124
F4	0.42±0.901	0.55±0.561	16.86±0.864	1.21±0.65	28.90±0.542
F5	0.51±0.287	0.42±0.915	14.13±0.796	1.19±0.23	22.28±0.338
F6	0.50±0.912	0.57±0.629	15.12±0.619	1.16±0.19	27.65±0.526
F7	0.49±0.291	0.53±0.527	16.45±0.191	1.19±0.14	28.78±0.878
F8	0.48±0.228	0.58±0.553	18.61±1.604	1.18±0.10	27.81±0.846
F9	0.49±0.873	0.48±0.692	19.10±0.936	1.20±0.13	28.10±0.663
F10	0.46±0.916	0.50±0.690	19.43±0.336	1.21±0.15	29.98±0.912
F11	0.50±0.694	0.52±0.910	17.29±0.853	1.18±0.12	28.90±0.032
F12	0.48±0.195	0.44±0.628	16.48±0.676	1.18±0.11	27.18±0.099

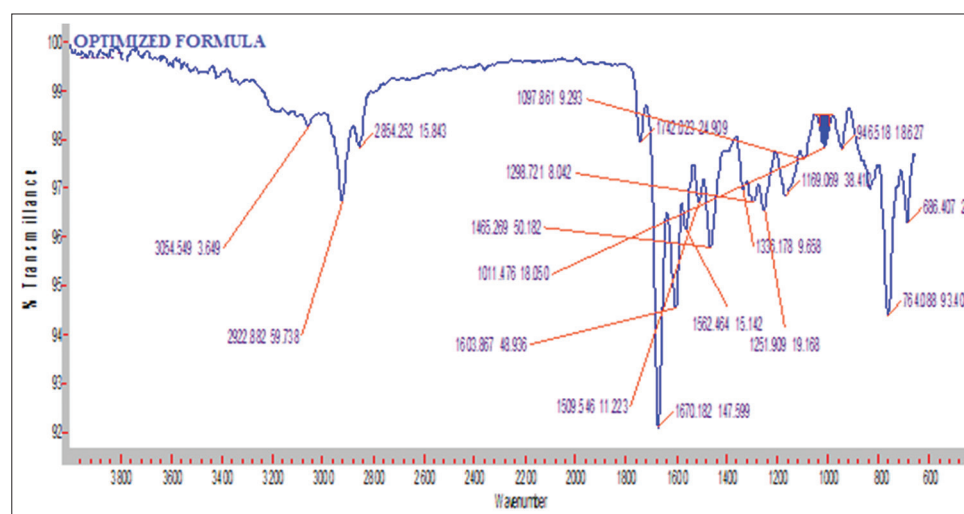
ZMT: Zolmitriptan



**Table 3. Post-compression evaluation of ZMT formulations**

Code	Weight variation (mg)	Hardness (Kg/cm <sup>2</sup> )	Thickness (mm)	Friability (%)	Assay (%)
F1	104±0.22	4.5±1.5	2.3±0.13	0.43	98.23±1.32
F2	104±0.18	4.3±1.7	2.3±0.11	0.34	96.45±1.39
F3	100±0.16	4.1±1.9	2.2±0.29	0.49	99.26±0.93
F4	105±1.21	4.1±1.5	2.4±0.18	0.47	96.34±0.10
F5	102±0.17	4.3±1.9	2.6±0.15	0.49	98.16±1.93
F6	98±2.16	4.2±1.4	2.3±0.11	0.34	96.55±2.01
F7	100±1.11	4.4±1.5	2.5±0.14	0.49	99.26±2.73
F8	104±0.16	4.5±1.3	2.4±0.15	0.34	95.85±1.96
F9	96±2.18	4.6±1.2	2.2±0.14	0.34	98.35±0.99
F10	101±0.89	4.4±1.7	2.3±0.17	0.43	96.41±0.94
F11	102±0.64	4.7±1.9	2.3±0.17	0.54	97.92±2.06
F12	104±0.90	4.5±1.6	2.2±0.11	0.43	98.12±2.11

ZMT: Zolmitriptan

**Fig. (2). Fourier transforms infrared spectra of optimized formulation (F3).**

0.912), bulk density ( $0.42 \pm 0.124$ – $0.51 \pm 0.287$ ), tapped density ( $0.42 \pm 0.915$ – $0.58 \pm 0.912$ ), compressibility index ( $14.13 \pm 0.796$ – $19.62 \pm 1.025$ ), Hausner ratio ( $1.16 \pm 0.19$ – $1.83 \pm 0.03$ ), and compatibility studies. The obtained values indicating that the flow properties of the drug have been increased when mixed with different excipients. Moreover, all ZMT formulations (F1–F12) were found within the pharmacopeial limits, and all the results were shown in Table 1.

### 3.2. Drug-excipient Compatibility Studies

The FTIR spectroscopy spectrum of the pure drug was found to be similar to the reference standard IR spectrum of ZMT. The IR spectrum of the pure drug (Fig. 1) ZMT has indicative of the presence of absorption peak due to an occurrence of N-H of the lactam is  $3054.55 \text{ cm}^{-1}$ , as well as resulting amine absorption, suggesting that these functionalities are here in the drug molecule. The aromatic and aliphatic C-H absorption are noticed from  $2854.2588 \text{ cm}^{-1}$  to  $2922.88 \text{ cm}^{-1}$ . Based on FTIR studies confirmed

that the absence of chemical interaction between drug and other excipients utilized in the formulations (F1–F12) and the results were shown in Figs. 1 (i.e., pure drug) and 2 (i.e., optimized formulation).

### 3.3. Construction of Calibration Curve of ZMT

Calibration curve of ZMT in pH 6.8 phosphate buffer and pH 1.2 (0.1N HCl) was performed. The graph was linear, and it obeys Beer Lambert's law, based on the standard graph of ZMT, had good reproducibility and a good correlation was obtained with  $R^2$  values of 0.9985 ( $y = 0.0636x + 0.0751$ ) and 0.9982 ( $y = 0.0595x + 0.083$ ) for acidic and basic mediums, respectively.

### 3.4. Post-compression Evaluation of ZMT Formulations

Post-compression parameters of all formulations (F1–F12) were found to be weight variation ( $96 \pm 2.18$  to  $105 \pm 1.21 \text{ mg}$ ), hardness ( $4.1 \pm 1.5$ – $4.7 \pm 1.9 \text{ kg/cm}^2$ ), friability ( $0.34$ – $0.54\%$ ), and thickness ( $2.2 \pm 0.11$ – $2.6 \pm 0.15 \text{ mm}$ ), and

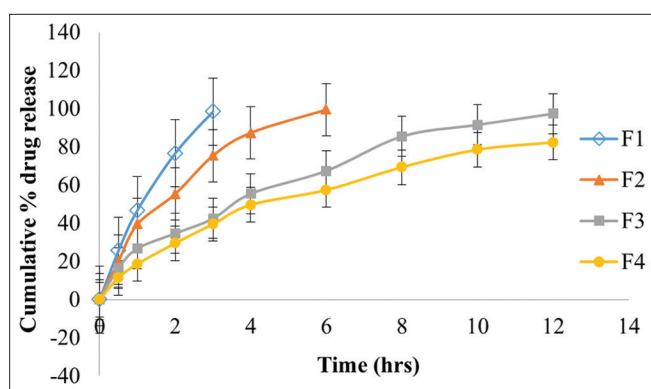


Fig. (3). Dissolution profiles of zolmitriptan prepared with gum karaya polymer.

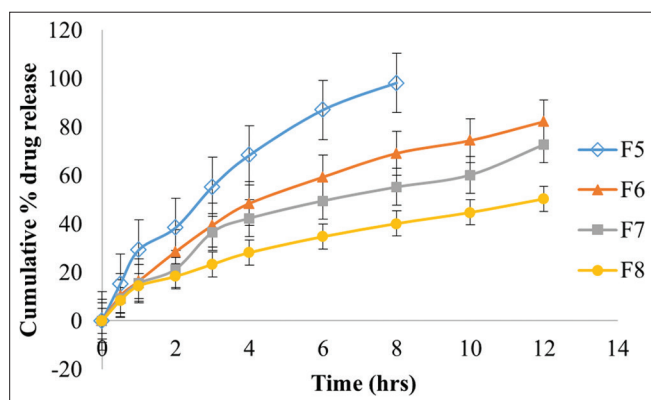


Fig. (4). Dissolution profiles of zolmitriptan prepared with xanthan gum polymer.

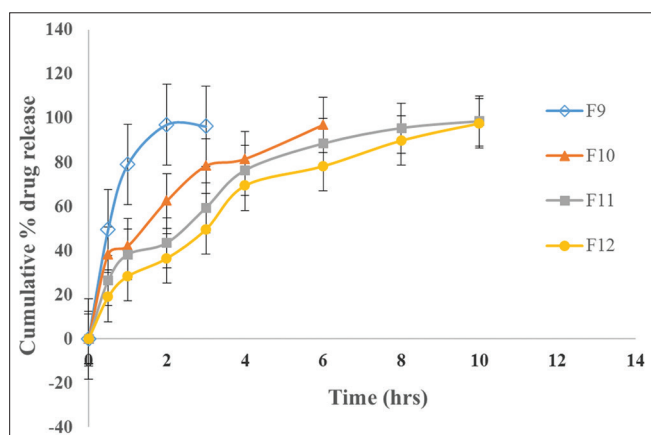


Fig. (5). Dissolution profiles of zolmitriptan prepared with guar gum polymer.

assay ( $95.85 \pm 1.96\%$ – $99.26 \pm 2.73\%$ ) and all results were shown in Table 3. The standard deviation values indicated that all the prepared ZMT matrix tablet formulations within the range and all the formulations are having good mechanical strength.

### 3.5. *In Vitro* Dissolution Study

*In vitro* studies were performed (10 h) using the acidic medium (for 2 h) and basic medium (8 h). The dissolution

profiles were shown in Fig. 3 (with gum karaya formulations, i.e., F1–F4), Fig. 4 (with xanthan gum formulations, i.e., F5–F8), and Fig. 5 (with guar gum formulations, i.e., F9–F12). Drug release from the prepared formulations increased with time and the effect of different gums on drug release was observed.

Based on the values of percentage drug releases and other characteristics (i.e., pre- and post-compression parameters) of all prepared ZMT matrix formulations, F3 was the most promising formulation to compare with other ZMT formulations (F1–F12) due to its drug release and other characteristics.

### 3.6. Mechanism of Drug Release and Kinetics

ZMT formulations (F1–F12) drug release data were fitted to different kinetic models to know the mechanism and from the data it is evident that the optimized formulation (F3) was following zero-order.

## 4. CONCLUSION

The CR matrix tablets of ZMT were developed using three different natural polymers such as gum karaya, xanthan gum, and guar gum as release retardants with different ratios such as 5, 10, 15, and 20%’s. In the prepared 12 formulations (F1–F12) of ZMT matrix tablets, based on the pre- and post-compression characterization one of the formulations (F3) was found to be the best formulation. The optimized formulation (F3) shows desire drug release and dissolution statistics was subjected to release kinetics. Moreover, the curve fitting analysis shows that the optimized F3 formulation follows zero-order kinetics. Thus, the results of the current study clearly indicated that the ZMT CR matrix tablets have the most promising potential dosage form and used as an alternative to the conventional dosage form.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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