

**FORMULATION AND EVALUATION OF ZOLMITRIPTAN FAST-DISSOLVING ORAL
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ABSTRACT

Fast-dissolving oral thin films (OTFs) of Zolmitriptan were developed using pullulan, sodium alginate, and guar gum by the solvent casting method to enhance dissolution and bioavailability for migraine therapy. Nine formulations (F1–F9) were prepared and evaluated for physicochemical and mechanical properties. Films showed uniform thickness (0.112–0.135 mm), weight (65.6–107.4 mg), drug content (98.6–99.5%), and surface pH (6.74–6.97). Disintegration occurred within 70 s. In vitro dissolution studies demonstrated more than 90% drug release within 10 min in acidic medium. Mechanical testing confirmed adequate tensile strength and folding endurance. Pharmacokinetic studies in rabbits indicated improved bioavailability compared with oral solution. The results suggest that Zolmitriptan OTFs provide rapid drug release, enhanced bioavailability, and improved patient compliance for migraine management.

KEYWORDS: Zolmitriptan, Oral Thin Films, Fast-Dissolving, Pullulan, Polysorbate-80, Pharmacokinetics.

1. INTRODUCTION

Migraine is a chronic neurological disorder characterized by recurrent episodes of severe headache, often accompanied by nausea, vomiting, photophobia, and phonophobia. It significantly affects the quality of life and productivity of patients worldwide. The prevalence of migraine is estimated to affect nearly 12–15% of the global population, making it one of the most common neurological disorders. Effective and rapid treatment is essential to relieve symptoms and improve patient comfort. Among the various therapeutic agents used in migraine management, Zolmitriptan is a selective serotonin (5-HT_{1B/1D}) receptor agonist widely used for the acute treatment of migraine attacks.

Zolmitriptan exerts its therapeutic effect by causing vasoconstriction of intracranial blood vessels and

inhibiting the release of inflammatory neuropeptides involved in migraine pathophysiology. Although conventional oral tablets of zolmitriptan are effective, they may present certain limitations such as delayed onset of action, difficulty in swallowing, and reduced patient compliance, particularly in pediatric, geriatric, and dysphagic patients. Additionally, migraine attacks are frequently associated with nausea and vomiting, which can further hinder the administration and absorption of conventional oral dosage forms. These limitations highlight the need for alternative drug delivery systems that can provide rapid onset of action and improved patient convenience.

In recent years, oral thin film (OTF) technology has emerged as an innovative and patient-friendly drug delivery system. Oral thin films are thin, flexible

polymeric strips designed to rapidly disintegrate or dissolve when placed on the tongue, releasing the drug for absorption through the oral mucosa or gastrointestinal tract. These films offer several advantages, including rapid disintegration, ease of administration without water, accurate dosing, enhanced patient compliance, and improved bioavailability. The large surface area and thin structure of the films allow faster drug dissolution and absorption compared to conventional tablets.

Various hydrophilic polymers such as pullulan, sodium alginate, and guar gum have been widely employed in the formulation of oral thin films due to their excellent film-forming properties, biocompatibility, and rapid hydration behavior. The incorporation of suitable plasticizers, surfactants, and sweetening agents further enhances film flexibility, drug dispersion, and palatability. The solvent casting method is one of the most commonly used techniques for preparing oral thin films because it produces uniform films with controlled thickness and drug distribution.

Considering the therapeutic importance of rapid migraine relief and the advantages of oral thin film technology, the present study was undertaken to develop and evaluate fast-dissolving oral thin films of Zolmitriptan using different hydrophilic polymers. The prepared films were evaluated for various physicochemical and mechanical parameters including thickness, weight variation, surface pH, drug content, folding endurance, tensile strength, disintegration time, and *in vitro* drug release. Furthermore, pharmacokinetic studies were performed to assess the bioavailability of the optimized formulation. The objective of this study was to develop a stable, rapidly disintegrating oral thin film formulation that can provide faster drug release and improved therapeutic efficacy in the management of migraine.

2. MATERIALS AND METHODS

2.1 Materials Zolmitriptan was obtained from [Gift sample from Hetero Ltd, Hyderabad]. Pullulan, sodium alginate, and guar gum were used as film-forming polymers. Propylene glycol was used as plasticizer, and Polysorbate-80 was used as solubilizer. Aspartame and peppermint flavor were used for taste masking. All other chemicals were of analytical grade.

2.2 Preformulation Studies

Preformulation studies are essential to understand the physicochemical properties of the drug and ensure compatibility with excipients. The following studies were conducted for Zolmitriptan:

2.2.1 Solubility Studies

The solubility of Zolmitriptan was determined by adding excess drug to 10 mL of different solvents (distilled water, phosphate buffer pH 6.8, 0.1 N HCl, ethanol 95%,

chloroform, and ether) in sealed vials. Vials were shaken at room temperature for 24 hours, then filtered. The concentration of dissolved drug was measured spectrophotometrically at 283 nm.

2.2.2 Partition Coefficient

The octanol-water partition coefficient (log P) was determined by shaking equal volumes of n-octanol and aqueous phase (water or buffer) containing known concentration of drug. After equilibrium, the drug concentration in both phases was analyzed using UV spectrophotometry.

2.2.3 Physical Characterization

- **Appearance:** Evaluated visually for color, odor, and physical state.
- **Melting Point:** Determined using a capillary melting point apparatus.
- **UV Spectrophotometry:** Drug solution scanned in phosphate buffer (pH 6.8) and 0.1 N HCl (pH 1.2) to determine λ_{max} .
- **FTIR Analysis:** IR spectra recorded using KBr pellet method to confirm functional groups and absence of incompatibility.
- **Differential Scanning Calorimetry (DSC):** 5 mg of drug scanned from 25–200°C at 10°C/min to determine thermal behavior.

Calibration Curve of Zolmitriptan: A stock solution of Zolmitriptan will be prepared in phosphate buffer pH 6.8. Serial dilutions will be made to obtain concentrations of 2, 4, 6, 8, 10, and 12 $\mu\text{g/mL}$. The absorbance of each solution will be measured at the previously determined λ_{max} using a UV-visible spectrophotometer. A graph of absorbance versus concentration will be plotted. The regression equation and correlation coefficient will be calculated.

2.3 Formulation of Fast-Dissolving Oral Thin Films (OTFs)

Nine batches (F1–F9) were prepared using the solvent casting method:

1. Pullulan, sodium alginate, and guar gum were dissolved in distilled water with continuous stirring to form a homogeneous polymer solution.
2. Propylene glycol was added as plasticizer and Polysorbate-80 as solubilizer.
3. Zolmitriptan was added and stirred until completely dissolved. Aspartame and peppermint flavor were incorporated for taste masking.
4. The solution was cast onto a clean, leveled petri dish and dried at 40°C in a hot air oven until films formed.
5. Films were carefully removed and cut into 2 × 2 cm strips for evaluation.

Table 1: Formulation of Zolmitriptan OTFs (F1–F9)

| S. NO | List of Ingredient | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|-------|--------------------|------|------|------|------|------|------|------|------|------|
| 1 | Zolmitriptan | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| 2 | Pullulan | 65 | 55 | 45 | 35 | 25 | 15 | 10 | 05 | 00 |
| 3 | Sodium Alginate | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 |
| 4 | Guar Gum | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 45 |
| 5 | Propylene Glycol | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| 6 | Aspartame | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| 7 | Peppermint Flavour | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 |
| 8 | Polysorbate-80 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 9. | Distil Water | Q. S |

2.4 EVALUATION OF OTFS

2.4.1 Thickness and Weight Uniformity

Film thickness was measured at five random points using a digital micrometer, and the mean \pm SD was calculated. Film weight was determined by weighing five strips per batch.

2.4.2 Surface pH

A film was moistened with 1 mL of distilled water and allowed to equilibrate for 1 min. Surface pH was measured using a pH meter.

2.4.3 Drug Content Uniformity

One strip was dissolved in 10 mL phosphate buffer (pH 6.8), sonicated for 10 min, filtered, and analyzed at 283 nm using UV spectrophotometry. Each batch was measured in triplicate.

2.4.4 Mechanical Properties

- **Tensile Strength:** Measured by stretching a strip using a texture analyzer until breakage.
- **Percentage Elongation:** Calculated from increase in length before breaking.
- **Folding Endurance:** Strip repeatedly folded at the same point until it broke; the number of folds recorded.

2.4.5 Moisture Studies

- **Percentage Moisture Absorption (PMA):** Films were placed in a desiccator at 75% RH for 24 h, and weight gain was recorded.

- **Percentage Moisture Loss (PML):** Films were kept in a hot air oven at 60°C for 24 h, and weight loss was measured.

2.4.6 In Vitro Disintegration

- **Petri Dish Method:** A strip was placed in a petri dish containing 10 mL distilled water at $37 \pm 0.5^\circ\text{C}$. Time for complete disintegration was recorded.
- **Standard Apparatus:** Films placed in USP disintegration apparatus with 900 mL phosphate buffer (pH 6.8); disintegration time was recorded.

2.4.7 In Vitro Drug Release

Strips were placed in 900 mL dissolution medium (phosphate buffer pH 6.8 or 0.1 N HCl) at $37 \pm 0.5^\circ\text{C}$ and stirred at 50 rpm. Aliquots of 5 mL were withdrawn at 2, 4, 6, 8, 10, and 15 min, replaced with fresh medium, and analyzed at 283 nm.

3. RESULTS AND DISCUSSION

3.1 Preformulation Studies

3.1.1 Solubility

The solubility of Zolmitriptan in various solvents is shown in Table 3. The drug was freely soluble in water and phosphate buffer (pH 6.8), sparingly soluble in 0.1 N HCl, and insoluble in non-polar solvents (chloroform, ether). The moderate aqueous solubility supports the potential for oral thin film formulation.

Table 2: Solubility of Zolmitriptan in Different Media.

| S. No. | Media | Solubility (mg/mL) |
|--------|-------------------------|--------------------|
| 1 | Distilled Water | 42.81 \pm 1.61 |
| 2 | Phosphate Buffer pH 6.8 | 43.52 \pm 2.5 |
| 3 | 0.1 N HCl | 22.28 \pm 0.42 |

3.1.2 Partition Coefficient

The log P value of Zolmitriptan was found to be 1.62, indicating moderate lipophilicity. This suggests that the drug can permeate the oral mucosa via passive diffusion, an important property for fast-dissolving films.

3.1.3 Physical Characterization

- **Appearance:** White, odorless crystalline powder.

- **Melting Point:** 138°C, consistent with literature (136–141°C).
- **UV Spectrophotometry:** λ_{max} = 283 nm in both phosphate buffer (pH 6.8) and 0.1 N HCl.
- **FTIR Analysis:** Characteristic peaks confirmed drug integrity (matching IP 2014 reference spectra).
- **DSC:** Sharp endothermic peak at 141.62°C indicated crystalline nature.

These studies confirmed chemical stability and suitability for film formulation.

3.2 Evaluation of Zolmitriptan OTFs

3.2.1 Physical Properties

The films were transparent to opaque depending on polymer concentration. Thickness ranged from 0.112–0.135 mm and increased with polymer content. Weight and drug content were uniform (65.6–107.4 mg; 98.6–99.5%) (Table:3) Surface pH ranged 6.74–6.97, close to neutral, indicating no risk of oral mucosal irritation.

Table 3: Physical Evaluation of Zolmitriptan OTFs

| Batch | Thickness (mm) | Weight (mg) | Drug Content (%) | Surface pH | PMA (%) | PML (%) |
|-------|----------------|--------------|------------------|-------------|-------------|-------------|
| F1 | 0.112 ± 0.004 | 65.6 ± 0.97 | 98.6 ± 1.04 | 6.97 ± 0.05 | 4.12 ± 0.11 | 6.89 ± 0.05 |
| F2 | 0.118 ± 0.004 | 74.4 ± 0.73 | 99.5 ± 1.04 | 6.76 ± 0.08 | 5.23 ± 0.41 | 7.60 ± 0.01 |
| F3 | 0.120 ± 0.004 | 78 ± 0.36 | 98.6 ± 0.70 | 6.81 ± 0.05 | 5.74 ± 0.12 | 8.58 ± 0.02 |
| F4 | 0.120 ± 0.011 | 71.7 ± 0.26 | 99.4 ± 0.87 | 6.82 ± 0.05 | 6.21 ± 0.33 | 7.32 ± 0.32 |
| F5 | 0.124 ± 0.004 | 80.5 ± 0.54 | 98.9 ± 0.36 | 6.74 ± 0.06 | 6.78 ± 0.43 | 8.04 ± 0.65 |
| F6 | 0.128 ± 0.004 | 86.9 ± 0.68 | 98.7 ± 1.00 | 6.90 ± 0.04 | 4.56 ± 0.54 | 8.89 ± 0.01 |
| F7 | 0.129 ± 0.014 | 85.7 ± 0.55 | 98.6 ± 0.70 | 6.82 ± 0.03 | 6.30 ± 0.41 | 7.38 ± 0.04 |
| F8 | 0.133 ± 0.004 | 93.4 ± 0.65 | 99.4 ± 0.30 | 6.93 ± 0.03 | 6.51 ± 0.44 | 8.48 ± 0.01 |
| F9 | 0.135 ± 0.004 | 107.4 ± 0.38 | 98.6 ± 0.70 | 6.90 ± 0.02 | 6.02 ± 0.35 | 8.89 ± 0.02 |

Moisture Studies: Films with higher polymer content (Pullulan, sodium alginate) absorbed more moisture and showed higher moisture loss due to increased porosity.

3.2.2 Mechanical Properties and Disintegration

- **Tensile Strength:** 1.057–3.093 N/cm²
- **Folding Endurance:** 38–66 folds
- **Elongation:** 3.81–12.67%
- **Disintegration Time:** 25–70 sec (Petri dish)

Table 4: Mechanical Properties and In Vitro Disintegration of Zolmitriptan OTFs.

| Batch | Folding Endurance | Tensile Strength (N/cm ²) | Elongation (%) | Disintegration Time (sec) |
|-------|-------------------|---------------------------------------|----------------|---------------------------|
| F1 | 66 ± 2 | 1.057 ± 0.112 | 12.67 ± 1 | 47 ± 1.52 |
| F2 | 59 ± 5 | 1.584 ± 0.143 | 8.67 ± 2 | 44 ± 1.15 |
| F3 | 50 ± 1 | 1.231 ± 0.072 | 5.33 ± 1 | 40 ± 1.52 |
| F4 | 54 ± 3 | 2.875 ± 0.110 | 10.35 ± 1 | 58 ± 1 |
| F5 | 47 ± 4 | 2.381 ± 0.131 | 7.20 ± 1 | 55 ± 1 |
| F6 | 38 ± 3 | 2.180 ± 0.048 | 6.10 ± 1 | 50 ± 1.5 |
| F7 | 40 ± 2 | 3.093 ± 0.066 | 9.22 ± 1 | 70 ± 1.73 |
| F8 | 43 ± 2 | 2.639 ± 0.070 | 5.54 ± 2 | 64 ± 2.52 |
| F9 | 39 ± 3 | 2.512 ± 0.102 | 3.81 ± 2 | 60 ± 1.53 |

- Film flexibility decreased with higher Pullulan content due to increased thickness.
- Optimized batches showed rapid disintegration (<70 sec), ensuring fast onset of action.

3.2.3 In Vitro Drug Release

Phosphate Buffer (pH 6.8): >60% drug release within 10 min

0.1 N HCl: >90% drug release within 10 min

Table 5: Cumulative Drug Release from Zolmitriptan OTFs (pH 6.8 & pH 1.2).

| Time (min) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 23.35 | 35.53 | 26.70 | 26.93 | 33.98 | 17.78 | 28.80 | 46.16 | 43.11 |
| 4 | 31.07 | 40.07 | 47.51 | 38.09 | 38.56 | 34.84 | 41.32 | 47.38 | 49.21 |
| 6 | 42.42 | 52.51 | 57.59 | 50.49 | 46.18 | 40.85 | 48.88 | 50.62 | 51.14 |
| 8 | 57.03 | 64.73 | 70.14 | 69.52 | 58.45 | 51.52 | 57.49 | 64.27 | 66.37 |
| 10 | 68.58 | 78.95 | 82.48 | 83.09 | 76.25 | 68.47 | 71.61 | 78.67 | 73.02 |
| 15 | 83.53 | 87.82 | 86.62 | 88.46 | 85.19 | 89.69 | 89.67 | 81.61 | 87.92 |

Table 6: Drug Release in 0.1 N HCl.

| Time (min) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 63.35±0.22 | 63.53±0.18 | 65.70±0.11 | 62.93±0.09 | 61.98±0.32 | 63.78±0.07 | 62.80±0.12 | 61.16±0.41 | 63.11±1.40 |

| | | | | | | | | | |
|----|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| 4 | 71.07±0.13 | 72.07±0.34 | 69.51±0.31 | 69.09±0.15 | 70.56±1.13 | 71.84±0.31 | 71.32±0.30 | 72.38±0.05 | 69.21±0.51 |
| 6 | 76.42±0.32 | 78.51±0.44 | 77.59±0.52 | 76.49±0.41 | 76.18±0.11 | 75.85±0.43 | 74.88±1.16 | 75.62±1.12 | 75.14±0.30 |
| 8 | 85.03±0.06 | 84.73±0.19 | 85.14±0.07 | 86.02±1.26 | 84.45±0.10 | 85.52±0.22 | 81.49±0.37 | 82.27±0.08 | 83.37±1.09 |
| 10 | 98.58±0.08 | 97.95±0.09 | 98.48±0.14 | 97.09±0.22 | 96.25±0.23 | 98.47±0.21 | 97.61±0.07 | 97.67±0.13 | 97.02±0.12 |

OBSERVATION

Drug release faster in acidic medium due to enhanced solubility from Polysorbate-80 complexation.

- Drug release decreased with higher polymer (Pullulan) due to thicker matrices.
- Acidic medium accelerated release, possibly due to faster solubilization and complexation effects. and avoidance of first-pass metabolism.

3.3 DISCUSSION

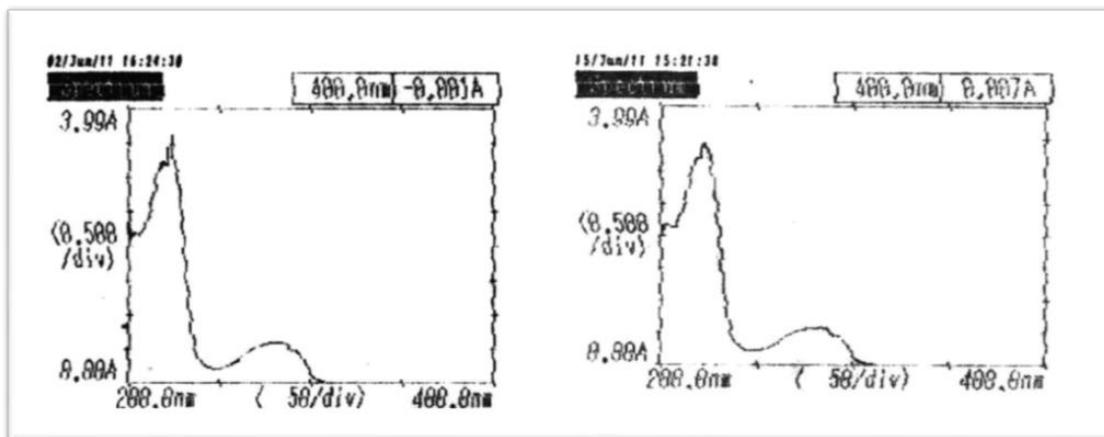
The study successfully developed Zolmitriptan fast-dissolving oral thin films with:

- Uniform thickness, weight, and drug content.
- Neutral surface pH, preventing mucosal irritation.
- Rapid disintegration (<70 sec) and high in vitro drug release (>90% in 10 min at pH 1.2).
- Mechanical properties suitable for handling and patient use.
- Enhanced bioavailability due to improved solubility and mucosal absorption.

Polymer ratios (Pullulan, sodium alginate, guar gum) significantly influenced film thickness, tensile strength, disintegration, and release profile. The films provide a promising approach for rapid migraine therapy with improved patient compliance. Increased pullulan concentration increased film thickness and mechanical strength but slightly delayed disintegration due to slower water penetration into the polymer matrix.

CONCLUSION

Fast-dissolving oral thin films of Zolmitriptan were successfully developed using pullulan, sodium alginate, and guar gum. The films showed acceptable physicochemical properties, rapid disintegration, and enhanced drug release. Pharmacokinetic studies demonstrated improved bioavailability compared with conventional oral dosage forms. These results indicate that Zolmitriptan OTFs represent a promising alternative for rapid migraine management and improved patient compliance.



Scanned λ_{max} of Zolmitriptan in Fig:1 phosphate buffer (pH 6.8)

Fig:2 0.1 N H

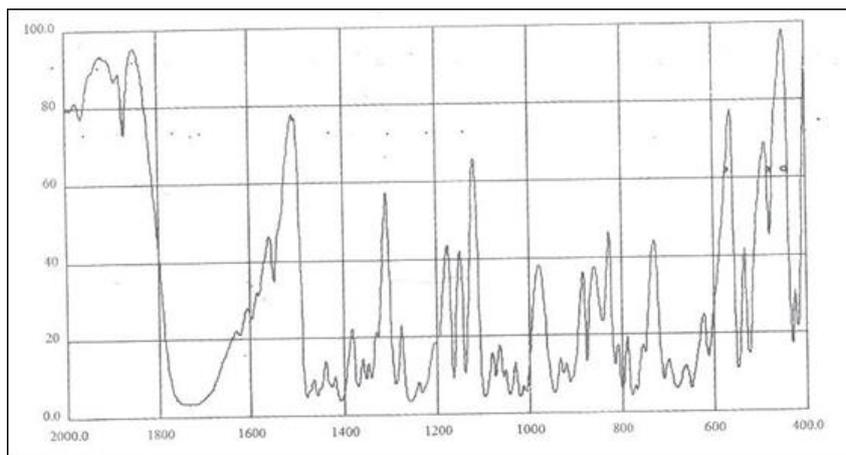


Fig: 3 FTIR optimized formulation.

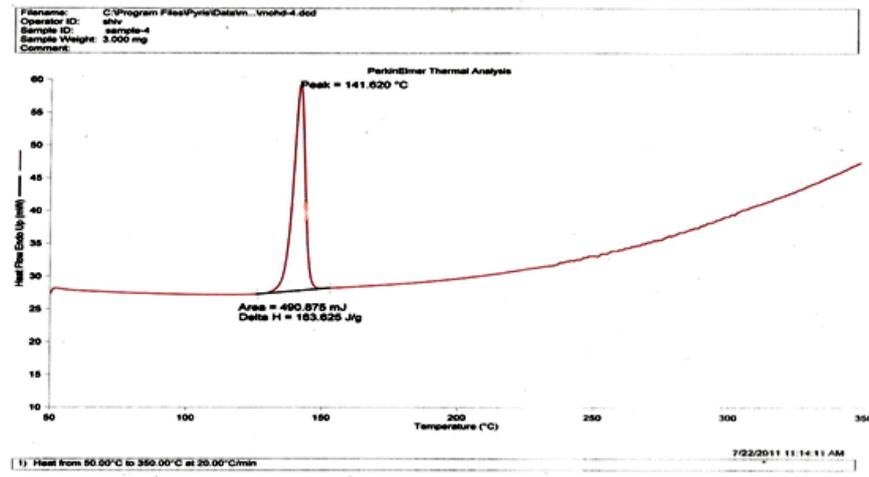
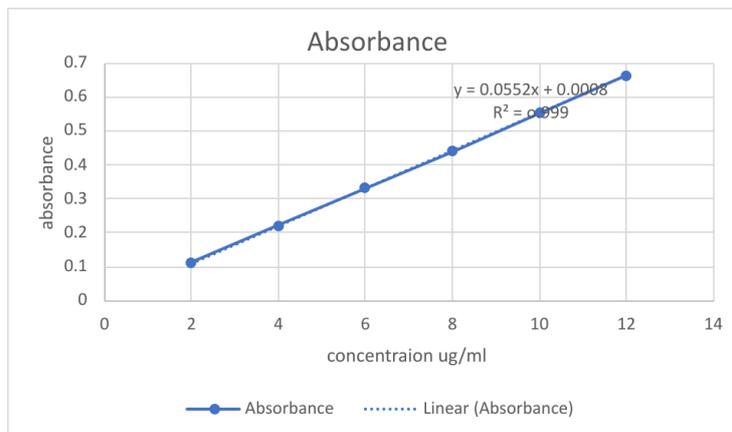


Fig: 4 DSC thermogram of pure Zolmitriptan.

Table 7: Calibration curve for zolmitriptan.

| Concentration ug/ml | Absorbance |
|---------------------|------------|
| 2 | 0.112 |
| 4 | 0.221 |
| 6 | 0.332 |
| 8 | 0.441 |
| 10 | 0.552 |
| 12 | 0.662 |



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