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### TRANDOLAPRIL SUBLINGUAL TABLET FORMATION AND EVALUATION

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**Abstract:** The goal of the study was to develop a sublingual tablet containing  $\beta$ -cyclodextrin and trandolapril in a 1:1 dose ratio. Thickness, hardness, weight fluctuation, friability, disintegration time, wetting time, water absorption ratio, and drug content consistency were all examined after the tablet was kneaded. According to the study, trandolapril sublingual tablets are a blood pressure drug that works well and improves patient compliance. However, before they are put on the market, more clinical trials are required. The formulation's low water absorption ratio and wetting time support its efficacy.

**Keywords:** Trandolapril,  $\beta$ -cyclodextrin, Blood Pressure, Bioavailability

#### 1. INTRODUCTION

Oral drug administration refers to the oral delivery of pharmaceutical agents or substances.<sup>1</sup> The bulk of medical products are given orally because they have a beneficial systemic effect and reach many sections of the body through the blood.

Tablets are solid dosage forms that are

##### 1.1 Anatomical Structure of Oral Mucosa:

The oral mucosa is a unique environment in which the hard tissues of the teeth surround the mucosal epithelium and a growing commensal bacterium maintains balance. The oral cavity is a dynamic environment

compressed and contain pharmaceutical substances, either with or without excipients. This pharmaceutical product is made by compressing a medication or combination of medications, with or without diluents and excipients, to generate a solid dosage form with flat or biconvex circle-like patterns..<sup>1,2</sup>

that is subjected to mechanical stressors (from eating and talking), as well as modifications caused by the consumption of hot or cold meals, rapid changes in local pH, sensory changes such as pain, and distinct perceptions of taste and thirst.<sup>3</sup> Swallowing, retching, gagging, and salivating are all

reflexes that contribute to the tissue environment's complexity.

Drug distribution through the mucosa has inspired great interest in both local and systemic therapeutics. Mucoadhesive drug delivery techniques are linked to higher levels of compliance because of their low enzymatic activity, painless injections, ease of use, and capacity to target particular

### 1.2. Function of Oral Mucosa <sup>5,6</sup>

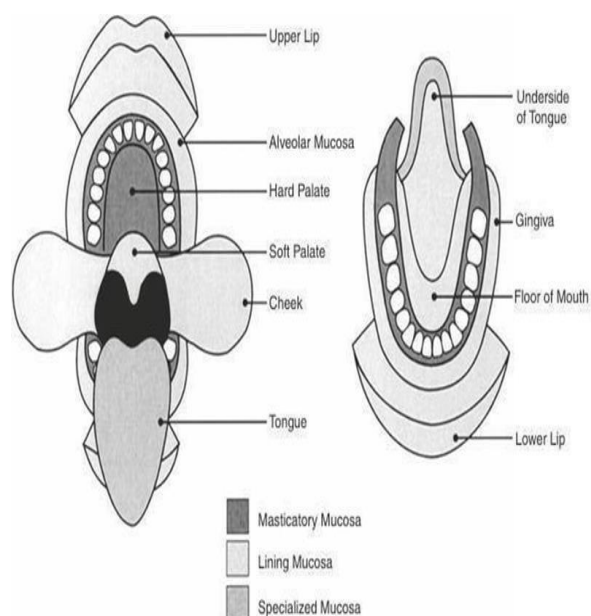
The oral cavity is constantly exposed to a potentially dangerous and ever-changing environment, and the oral mucosa's primary role is to protect and preserve the underlying tissues. This is accomplished through:

1. Providing resistance to mechanical injuries.
2. Preventing the spread of microbes.
3. Creating a barrier against harmful chemicals.

### 1.3 Permeability and Pathophysiology of Oral Mucosa <sup>7,8,9</sup>

Examining normal tissue in animal models aids in understanding the permeability and pathophysiology of the oral mucosa. <sup>10</sup> The

conditions. Unlike oral delivery, which is harsh on therapeutic proteins and peptides, mucosal administration provides a more gentle and secure environment for drug absorption.<sup>4</sup> Furthermore, the highly vascularized and thin mucosal epithelium permits medicinal compounds weighing up to 5,000 Da to reach the bloodstream directl



**Fig 1.2:- The general anatomy of the oral cavity**

permeability of altered and diseased human oral mucosa has not been well studied, and this review will only offer a limited amount of information on particular oral diseases, primarily concentrating on skin parallels..<sup>12</sup>

**Table: 1.1 Thickness and turnover time for human oral epithelium and epidermis**

| Layers    | Mean thickness 1 ( $\mu\text{m}$ ) | Median turnover time 2 (days) |
|-----------|------------------------------------|-------------------------------|
| Epidermis | 120                                | 27                            |

|                       |     |    |
|-----------------------|-----|----|
| Hard palate           | 310 | 24 |
| Buccal mucosa         | 580 | 14 |
| Floor of mouth mucosa | 190 | 20 |

#### 1.4 Biopharmaceutics of Buccal and Sublingual Absorption: <sup>11,13</sup>

Because it is comfortable, inexpensive, and simple to give, the oral route of pharmaceutical distribution is still the preferred method for giving patients medical supplies, which improves patient compliance. However, for traditional low molecular weight organic and peptide-based therapeutic compounds that are susceptible to either a high "first-pass" effect because of intestinal and/or hepatic extraction or extensive degradation and/or inactivation by gastric acid or gastrointestinal enzymes, as well as for patients who would not typically receive a drug orally because of age (paediatric) or a particular disease state (malabsorption syndrome, immediately following abdominal surgery, etc.). <sup>14,15</sup>

The oral transmucosal route is a safe and efficient way to distribute drugs. As a

result, a variety of dosage forms for inserting and delivering medicinal substances through the mouth cavity have been developed, including mucoadhesive tablets, gels, patches, ointments, and films, to name a few.<sup>17</sup> This chapter covers fundamental principles in the architecture and physiology of the oral mucosa, as well as their application to local and systemic oral transmucosal drug administration. <sup>16,19</sup> The advantages and disadvantages of oral transmucosal drug delivery, drug delivery routes, factors influencing drug delivery, the oral cavity's microenvironment (such as mucus, saliva, and salivary glands), and practical considerations of tissue irritation and/or harm when using this route of prescription drug administration are just a few of the topics covered.<sup>20,21</sup>

**TABLE 1.2: Postulated Mechanism For Polymer – Mucosal Adhesive Properties <sup>25,26</sup>**

| S.No. | Theory of Adhesion | Mechanism of Adhesion                                                                                                                                                     |
|-------|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1     | <b>Adsorption</b>  | Van der Waals forces, hydrophobic interactions, electrostatic attraction, and hydrogen bonds are the secondary chemical connections that exist between mucus and polymer. |
| 2     | <b>Diffusion</b>   | Entanglements of the chains of polymers in the mucus                                                                                                                      |

|   |                   |                                                                                                                                                                                                                                                                                                           |
|---|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|   |                   | networks.                                                                                                                                                                                                                                                                                                 |
| 3 | <b>Electronic</b> | The electron transport among polymer and mucus generates attractive forces across an electrical double layer.                                                                                                                                                                                             |
| 4 | <b>Wetting</b>    | Evaluates the capacity of the polymer to spread over the biological surface and determine the interfacial tension between them. The tension is proportional to $X^{1/2}$ , where X is the polymer-polymer interaction parameter. Low values of X indicate structural similarity and improved miscibility. |
| 5 | <b>Fracture</b>   | The force needed to separate two surfaces relates to adhesive bond strength and is used to calculate fracture strength of adhesive bonds.                                                                                                                                                                 |

### 1.5 Sublingual Tablet

Sublingual pharmaceutical administration may be safer and more efficient than oral drug delivery since it avoids hepatic metabolism.<sup>22</sup> Certain drugs are made to have a quick onset of pharmacological activity, especially those used to treat acute illnesses. Sublingual pills dissolve rapidly; for dosage form breakdown and enhanced dissolution and bioavailability, a small amount of saliva is typically adequate.<sup>29</sup> Sublingual drug delivery is a technique for delivering medication under the tongue so that it can passively diffuse via lipoidal membranes and reach the oral mucosa.

#### Advantages of Sublingual Tablets:<sup>22</sup>

Sublingual drugs have an instantaneous systemic effect because they are rapidly absorbed through the mucosal lining of the mouth beneath the tongue.

- Dose decreases.
- Quick impact onset.

Compared to enteral and parenteral delivery, this approach has several advantages, including a plentiful blood supply, quick action, improved bioavailability, fewer initial pass and sustenance effects, more patient consistency, and easier self-solution.

<sup>1</sup>

The tablet should dissolve in saliva, and patients should avoid eating, drinking, smoking, and speaking after placing it under the tongue. Bland excipients are used to prevent salivary stimulation. Tablets are tiny, flat, and must dissolve quickly for immediate drug absorption.<sup>5</sup>

- Increased bioavailability
- Fewer adverse effects.
- Helps treat nausea, vomiting, migraines, and schizophrenia.
- Tablets do not require water for ingestion.
- Long-lasting medication delivery.

- Making drug administration easy.
- The sublingual region is more porous than the buccal area.
- Improves the bioavailability of orally administered drugs by bypassing the GI

**Disadvantages of Sublingual Tablets:** <sup>29</sup>

- Absorption area is lowered considerably.
- Unsuitable for bitter prescription medications.
- Poor patient compliance.
- .

**Limitations of Sublingual Dosage Form** <sup>11</sup>

- 1. Limited drug selection:** Certain medications may not be suited for sublingual administration. The medicine must be efficacious, soluble, and stable in the mucosal barrier. Poorly flavored medications may not be an acceptable option.
- 2. Mucosal Irritation:** Prolonged usage of high-concentration prescription

tract and hepatic portal system, reducing hepatic first pass metabolism. <sup>24</sup>

- Improves the bioavailability of orally administered drugs by bypassing the GI tract and hepatic portal system, reducing hepatic first pass metabolism.
- Eating, drinking, and smoking are not allowed.
- Highly ionic medications are not authorized.
- Why Offering big dosages is not feasible

medications in sublingual tablets may irritate or harm the mouth's mucosa.

- 3. Taste:** Some drugs may have an unpleasant taste, which might reduce patient compliance. Masking the flavor might be challenging.
- 4. Restricted Dosage Forms:** Because the size of the pill may be uncomfortable or difficult to place beneath the tongue, sublingual tablets might not be advised for larger quantities. <sup>15</sup>

**TABLE 1.3: Drug Physicochemical Requirements for Sublingual Drug Administration**

| The drug's physicochemical characteristics | Approved Range                     |
|--------------------------------------------|------------------------------------|
| Minimum Dose                               | < 20 mg                            |
| Taste                                      | Not intensely bitter               |
| Stability                                  | Good stability in water or saliva  |
| Molecular weight                           | Moderate to small (163.3-400g/mol) |

|               |                                            |
|---------------|--------------------------------------------|
| pKa value     | < 10 for basic drugs; > 2 for acidic drugs |
| Log p         | 1.6 to 3.5                                 |
| Lipophilicity | Lipophilic                                 |

## 2. MATERIAL AND METHOD:

**Table – 2.1:** List of Instruments:

| S. No. | INSTRUMENTS                    | MANUFACTURE                    |
|--------|--------------------------------|--------------------------------|
| 1.     | Weighing balance               | Shimadzu ELB800                |
| 2.     | UV – Visible Spectrophotometer | Shimadzu UV – 1800, Japan      |
| 3.     | Magnetic stirrer               | Remi 1 MLH                     |
| 4.     | Bath Sonicator                 | Life care (2K1100908)          |
| 5.     | Dissolution apparatus          | Electro lab, Mumbai            |
| 6.     | Stability chamber              | Electro lab, Mumbai            |
| 7.     | Roche friabilator              | Sciencetech Pvt. Ltd.          |
| 8.     | Tablet Punching machine        | Pharmaceutical Machinery Works |
| 9.     | FTIR                           | Shimadzu                       |
| 10.    | Bulk density apparatus         | Escio International            |
| 11.    | Hardness tester                | Monsanto Labs Pvt. Ltd.        |
| 12.    | Vernier caliper                | P. K. Scientific               |
| 13.    | Melting point apparatus        | Remi Pvt. Ltd.                 |

**Table – 2.2:** List of Chemicals:

| S. No. | CHEMICALS                  | SOURCE                                      |
|--------|----------------------------|---------------------------------------------|
| 1.     | Drug (Trandolapril)        | Jiyan Chemicals and Pharmaceutical, Gujarat |
| 2.     | Mannitol                   | LOBA CHEMIE PVT. LTD.                       |
| 3.     | Cross Carmello's Sodium    | LOBA CHEMIE PVT. LTD.                       |
| 4.     | Microcrystalline Cellulose | LOBA CHEMIE PVT. LTD.                       |
| 5.     | Sodium Starch Glycolate    | LOBA CHEMIE PVT. LTD.                       |
| 6.     | Magnesium Stearate         | LOBA CHEMIE PVT. LTD.                       |
| 7.     | Talc                       | LOBA CHEMIE PVT. LTD.                       |

|     |                                |                            |
|-----|--------------------------------|----------------------------|
| 8.  | $\beta$ - cyclodextrin         | Alkem Laboratories, Mumbai |
| 9.  | Methanol                       | LOBA CHEMIE PVT. LTD.      |
| 10. | Potassium Dihydrogen Phosphate | Merk                       |

## 2.1 Preformulation studies<sup>23,24</sup>

### a) Preparation of standard stock solution of drug in methanolic distilled water and methanolic phosphate buffer pH 6.8 (1:9 ratio):

- In a 50ml volumetric flask, 50mg of Trandolapril was dissolved in a
- **Determination of  $\lambda$  max in methanolic distilled water and methanolic buffer pH 6.8:** A 10 ml volumetric flask was filled with 1 ml of the standard solution (100 $\mu$ g/ml) and diluted with distilled water and pH 6.8 buffer to create the sub stock solution. To find the maximal

### b) Trandolapril calibration curve preparation in methanolic distilled water:

In the Two millilitres of the standard solution were diluted in 20 millilitres of distilled water at a concentration of 100  $\mu$ g/ml to create the substock solution. At room temperature, the mixture was then

- **Creating a trandolapril calibration curve in a pH 6.8 methanolic phosphate buffer:** The substock solution was prepared by dissolving 2 millilitres of the standard solution in 20 millilitres of phosphate buffer pH 6.8 at a concentration of 100 microgrammes

combination of methanolic distilled water and methanolic buffer at a ratio of 1:9. To prepare a stock solution with a concentration of 1000  $\mu$ g/ml in a volumetric flask.

absorbance of trandolapril in methanolic distilled water and methanolic pH 6.8 buffer, a dilution of 10  $\mu$ g/ml was prepared and scanned at 400-200 nm using a UV visible spectrophotometer (Shimadzu 1800, Japan).

stirred for two hours. Distilled water was used to make dilutions of 10–50  $\mu$ g/ml, which were then compared to a reference solution at 228 nm using a UV spectrophotometer. At different concentrations, the absorbance data was recorded.

per millilitre. After that, the mixture was stirred for two hours at room temperature. A UV spectrophotometer set to 228 nm was used to measure dilutions containing phosphate buffer pH 6.8 at concentrations ranging from 10 to 50  $\mu$ g/ml against a reference solution.

Data on absorbance at different

**c) Solubility determination:** <sup>25</sup>

Take five millilitre glass vials filled with phosphate buffer pH 6.8 and distilled water. Add more medication and sonicate at room temperature for two hours. After that, place the samples on a magnetic stirrer for 48

**d) Melting point determination:** <sup>29</sup>

A capillary tube containing 1mg of Trandolapril medication sample was sealed

concentrations was noted..

hours and set away for 24 hours. The solution was then filtered and tested for solubility using UV visible spectroscopy at 229.60 nm and 228 nm, with the procedure repeated three times to ensure precise results.

on one end and placed in a melting point equipment. The temperature was measured when the medication began to melt.

**e) Drug-excipients interaction study:** <sup>27</sup>

An FTIR spectrophotometer (Shimadzu) was used to get the drug's FTIR spectra. Organic, polymeric, and inorganic compounds can be found using Fourier Transform infrared spectroscopy (FTIR), also referred to as FTIR spectroscopy. A hydraulic press was used to compress the materials into pellets, which were subsequently formed into discs. The final signal at the detector indicates a spectrum

ranging from 4000 to 400 cm<sup>-1</sup>. FTIR analysis is used to:

- Identify and characterize unknown samples of materials.
- Identify contaminants and impurities in the sample.
- Identify additives extracted from polymeric matrix.
- Identify oxidation and decomposition during failure analysis studies.

**2.2 Sublingual tablet formulation and assessment using the kneading method**  
<sup>15,18</sup>

**a) Preparation of Inclusion Complexes**

Trandolapril inclusion complexes were prepared by kneading in  $\beta$ -cyclodextrin at three different dosage ratios (1:1, 1:2, and 1:3).

**b) Determination of Solubility:** <sup>22</sup>

**Method:** After being weighed individually,  $\beta$ -cyclodextrin and trandolapril were triturated for an hour in a mortar and pestle. After that, they were mixed in a polybag for fifteen minutes before going through sieve number sixty. The drug content and yield of this powdered bulk were further examined.

Inclusion complexes of trandolapril and  $\beta$ -cyclodextrin were made at different ratios (1:1, 1:2, and 1:3) and dissolved in 5 millilitres of pH 6.8 phosphate buffer in vials. For 48 hours, the mixture was agitated at room temperature. After a

**c) Percentage Drug Content:**<sup>19</sup>

A 10 ml phosphate buffer pH 6.8 solution was used to dissolve inclusion complexes containing 25 mg of trandolapril after they had been precisely weighed. Filter paper was used to filter the solutions, which were then diluted appropriately. The following formula is used to estimate the drug content at 228

nm using a UV-visible spectrophotometer. After being diluted with phosphate buffer pH 6.8, the sample was examined at 228 nm

using a UV-visible spectrophotometer.:

$$\% \text{ Drug content} = \frac{\text{Actual weight of drug in solid dispersion}}{\text{Calculated theoretical weight of drug in solid dispersion}} \times 100$$

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Calculated theoretical weight of drug in solid dispersion

**2.3 Preparation of Sublingual Tablet by direct compression method**<sup>24</sup>

Inclusion complexes comprising Trandolapril and  $\beta$ -cyclodextrin in a 1:1 ratio were shown to be more efficient than other ratios. So this ratio was utilized to make sublingual pills. The sublingual tablet was manufactured using a direct compression process, combining additional excipients with the medication and  $\beta$ -cyclodextrin ratio and passing through filter

number 60. After triturating the mixture for the proper duration, it was mixed in a polybag for 15 minutes. The combined powder was tested for precompressional properties such as bulk density, tapered density, and so on. Furthermore, the tablet was formed using a tablet punching machine, and the resulting tablets were assessed for several post-granulation characteristics.

**Table 2.3:** Formula Table for Sublingual tablet of Meclizine Hydrochloride:

| Ingredient (mg)                                    | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|----------------------------------------------------|----|----|----|----|----|----|----|----|----|
| Drug and $\beta$ -cyclodextrin complex (1:1 ratio) | 8  | 8  | 8  | 8  | 8  | 8  | 8  | 8  | 8  |
| Microcrystalline cellulose                         | 20 | 23 | 20 | 23 | 20 | 23 | 20 | 23 | 20 |

|                         |     |     |     |     |     |     |     |     |     |
|-------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Crosscarmellose sodium  | 15  | 20  | 15  | 20  | 15  | 20  | 15  | 20  | 15  |
| Sodium starch Glycolate | 20  | 15  | 20  | 15  | 20  | 15  | 20  | 15  | 20  |
| Mannitol                | 25  | 20  | 25  | 20  | 25  | 20  | 25  | 20  | 25  |
| Talc                    | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   | 6   |
| Magnesium stearate      | 8   | 8   | 6   | 8   | 6   | 8   | 6   | 8   | 6   |
| Total(mg)               | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

## 2.4 Evaluation Studies: <sup>21,26,27</sup>

### 2.4.1 Precompression Study:

- **Bulk Density:** The entire amount of powder was precisely weighed and passed through sieve #60 before being transferred to the measurement cylinder.
- **Tapped Density:** A 10 ml measuring cylinder was filled with precisely measured powder and set on the tapping apparatus. After 100 cycles of tapping, the reading was obtained. and
- **Hausner's ratio:** It is a figure that represents a powder's flowability and is

Value is measured by the volume occupied by powder without any tapping on the cylinder, as shown in the formula below:

Bulk density = Weight of blend or powder / Bulk volume of blend or powder (in ml).

calculated using the following formula. Weight of blend or powder divided by tapped volume of blend or powder (in millilitres) is the tapped density..

calculated using formulas: Hausner's ratio = Tapped / Bulk density.

**Table 2.4:** Hausner's ratio acceptance criteria:

| Flow Character | Hausner's Ratio |
|----------------|-----------------|
| Excellent      | 1.00 – 1.11     |
| Good           | 1.12 – 1.18     |
| Fair           | 1.19 – 1.25     |
| Passable       | 1.26 – 1.34     |
| Poor           | 1.35 – 1.45     |
| Very Poor      | 1.45 – 1.59     |

- **Carr's index:** The compressibility index is also called Carr's index.

Carr's Index (%) = [(Tapped Density of powder – Bulk density of powder)] / Tapped Density

**Table 2.5:** Carr's index acceptable criteria:

| Flow Property | Carr's Index |
|---------------|--------------|
| Excellent     | 5 – 15       |
| Good          | 12 – 16      |
| Passable      | 18 – 25      |
| Poor          | 26 – 31      |
| Very Poor     | 32 – 37      |

- **Angle of repose:** A weighed amount of powder was allowed to pass through the funnel after it was placed on the burner stand.  $\tan \theta = \text{Height} / \text{radius}$  was used to determine the pile's height (h) and radius (r).

**Table 2.6:** Acceptance criterion for angle of repose:

| Nature of Flow | Angle of Repose |
|----------------|-----------------|
| Excellent      | <25             |
| Good           | 25 – 30         |
| Passable       | 30 – 40         |
| Very Poor      | >40             |

#### 2.4.2 Post compression Study: <sup>18,21</sup>

- **Weight variation:** Twenty pills were chosen from each formulation and weighed individually before the average weight was calculated, according to I.P. From the overall weight, the average weight of a single pill was determined..

**Table 2.7:** Weight variation acceptance criteria:

| Tablet weight on average (mg) | Maximum permitted % of difference |
|-------------------------------|-----------------------------------|
| 80 mg or less                 | ± 10                              |
| 80 mg to 250 mg               | ± 7.5                             |
| More than 250 mg              | ± 5                               |

- **Thickness:** Each tablet's diameter was measured with a Vernier Calliper. The tablet was simply placed between the jaws of a vernier calliper, and the displayed reading was recorded after the scale arm was slid to press the tablet against the stationary arm.

- **Hardness:** Tablet hardness was measured using the Monsanto hardness tester. The scale jaw moved in the direction of the fixed jaw, pushing it till
- **Friability:** Using a Roche friabilator, ten tablets from each formulation were swallowed, rotated at 25 rpm for four minutes, and then dropped at a height of six inches with each revolution. After 100 revolutions, the tablets were
- Friability = (initial weight of tablets – final weight of tablets) / (initial weight of tablets) × 100
- **Drug Content:** Using a Roche friabilator, the ten tablets from each formulation were spun at 25 rpm for four minutes before being dropped from a height of six inches in each revolution. After 100 revolutions, the pills were
- **In vitro Disintegration Study:** Using a disintegration equipment, four tablets from each formulation were dissolved in 600 cc of phosphate buffer with a pH of 6.8. After that, beads were added and the assemblage was placed in phosphate .
- **Wetting time and the ratio of water absorption:** After being folded twice, a piece of tissue paper was put in a petri dish with six millilitres of water. The tablet was taken out and weighed once more after soaking.

it broke, while the tablet was placed between two jaws. For every batch, the pressure at which the tablet breaks is noted and repeated three times.

removed, dusted, and weighed once again. The provided equation was used to calculate the % friability. The maximum weight decrease is limited to 1%.

removed, dusted, and weighed again. The supplied equation was used to estimate the percentage friability. The maximum weight reduction is no more than 1%.

buffer pH 6.8 at 37±0.5°C. In order to break down pills, the device started moving up and down in buffer, and the amount of time it took for the tablets to dissolve in solution was noted

$(W_a - W_b) / W_b \times 100$  is the water absorption ratio,

Where,  $W_a$  = weight after water absorption,

$W_b$  = weight before water absorption

- **Studies on In vitro Dissolution:** A United States Pharmacopoeia (USP) dissolving testing device (paddle technique) was used to measure the in vitro drug release rate of meclizine hydrochloride sublingual tablets. A 900 mL jar of phosphate buffer with a pH of 6.8 was used for the dissolving test. At intervals of five, ten, fifteen, twenty,

twenty-five, and thirty minutes, a five-millilitre sample of the solution was taken from the dissolving apparatus. New dissolutions were used in place of the samples. A UV spectrophotometer was used to analyse the samples after they had been filtered via filter paper, and the percentage of medication release was calculated.

## 2.5

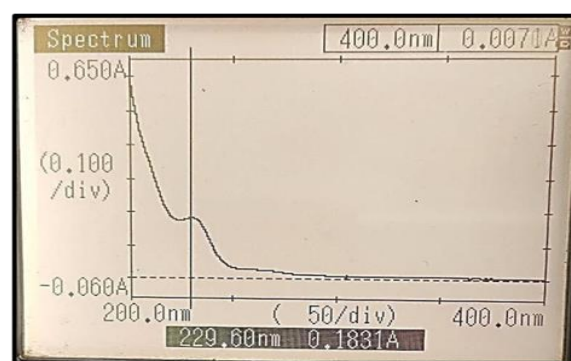
**Stability Study:** The produced tablets from batch F7 were selected for stability investigations, and the operation was carried out. The pills were kept in a stability chamber at  $40 \pm 2$  °C and  $75 \pm 5\%$  RH for two months. Samples were collected and analyzed for assessment parameters. <sup>22</sup>

## 3. OUTCOMES AND TALK

### 3.1 PREFORMULATION STUDIES

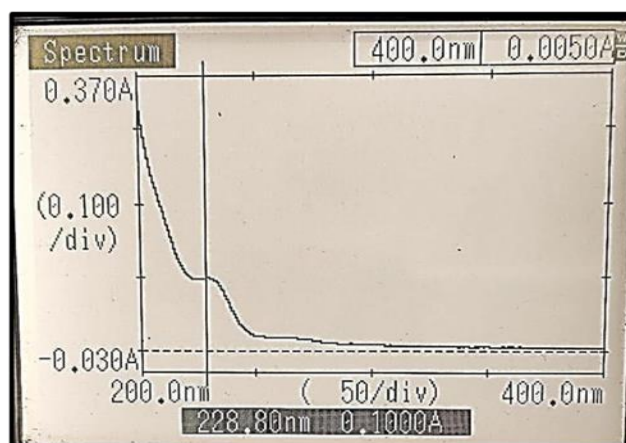
#### 3.1.1 Determination of $\lambda_{\text{max}}$ by UV Visible Spectrophotometer:

Using UV spectroscopy, the  $\lambda_{\text{max}}$  of trandolapril was determined to be 229.60 nm



in methanolic distilled water and 228.80 nm in methanolic phosphate buffer pH 6.8.

**Figure 3.1:**  $\lambda_{\text{max}}$  of Trandolapril in methanolic distilled Water.



**Figure 3.2:**  $\lambda$  max of Trandolapril in methanolic phosphate buffer pH 6.8

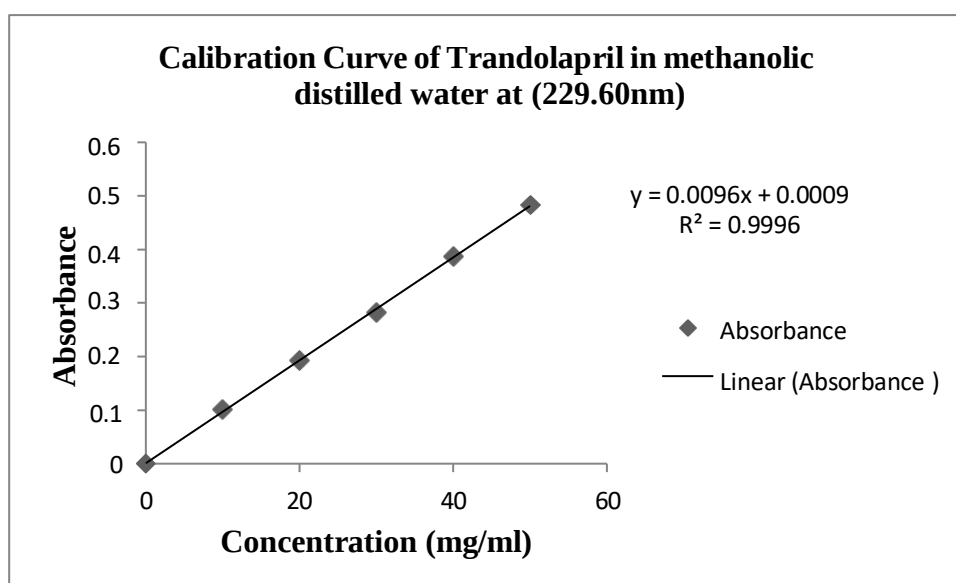
### 3.1.2 Preparation of calibration curve of drug (Trandolapril):

- Calibration curve of Trandolapril in methanolic Distilled water:**

Below are the prepared calibration curves:

**Table 3.1:** Absorbance observed of Trandolapril in methanolic distilled water:

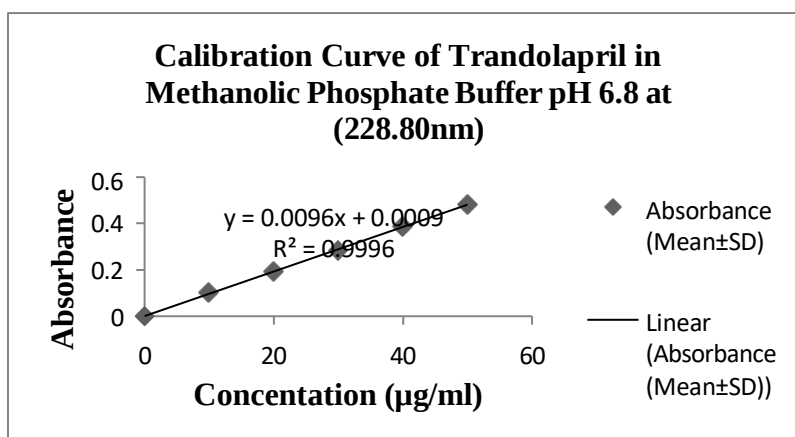
| Concentration ( $\mu\text{g/ml}$ ) | Absorbance (Mean $\pm$ SD) |
|------------------------------------|----------------------------|
| 0                                  | 0                          |
| 10 $\mu\text{g/ml}$                | 0.1802 $\pm$ 0.001         |
| 20 $\mu\text{g/ml}$                | 0.3890 $\pm$ 0.003         |
| 30 $\mu\text{g/ml}$                | 0.5053 $\pm$ 0.006         |
| 40 $\mu\text{g/ml}$                | 0.7495 $\pm$ 0.002         |
| 50 $\mu\text{g/ml}$                | 0.8961 $\pm$ 0.002         |



**Figure 3.3:** Calibration Curve of Trandolapril in methanolic distilled water.

**Table 3.2:** Absorbance observed of Trandolapril in methanolic phosphate buffer pH 6.8:

| Concentration ( $\mu\text{g/ml}$ ) | Absorbance (Mean $\pm$ SD) |
|------------------------------------|----------------------------|
| 0                                  | 0                          |
| 10 $\mu\text{g/ml}$                | 0.1011 $\pm$ 0.001         |
| 20 $\mu\text{g/ml}$                | 0.19276 $\pm$ 0.004        |
| 30 $\mu\text{g/ml}$                | 0.2825 $\pm$ 0.002         |
| 40 $\mu\text{g/ml}$                | 0.3866 $\pm$ 0.001         |
| 50 $\mu\text{g/ml}$                | 0.4832 $\pm$ 0.01          |

**Figure 3.4:** Calibration Curve of Trandolapril in Methanolic Phosphate Buffer pH 6.8

### 3.1.3 Melting Point of Drug:

The melting point of drug was determined by capillary method and melting point of Trandolapril was found in range of 119-123 $^{\circ}\text{C}$ .

**Table 3.3:** Melting point of Trandolapril:

| S. No. | Observed values        | Reported value                |
|--------|------------------------|-------------------------------|
| 1.     | 119 $^{\circ}\text{C}$ | 119 to 123 $^{\circ}\text{C}$ |
| 2.     | 115 $^{\circ}\text{C}$ |                               |
| 3.     | 116 $^{\circ}\text{C}$ |                               |

### 3.1.4 Solubility determination of Trandolapril:

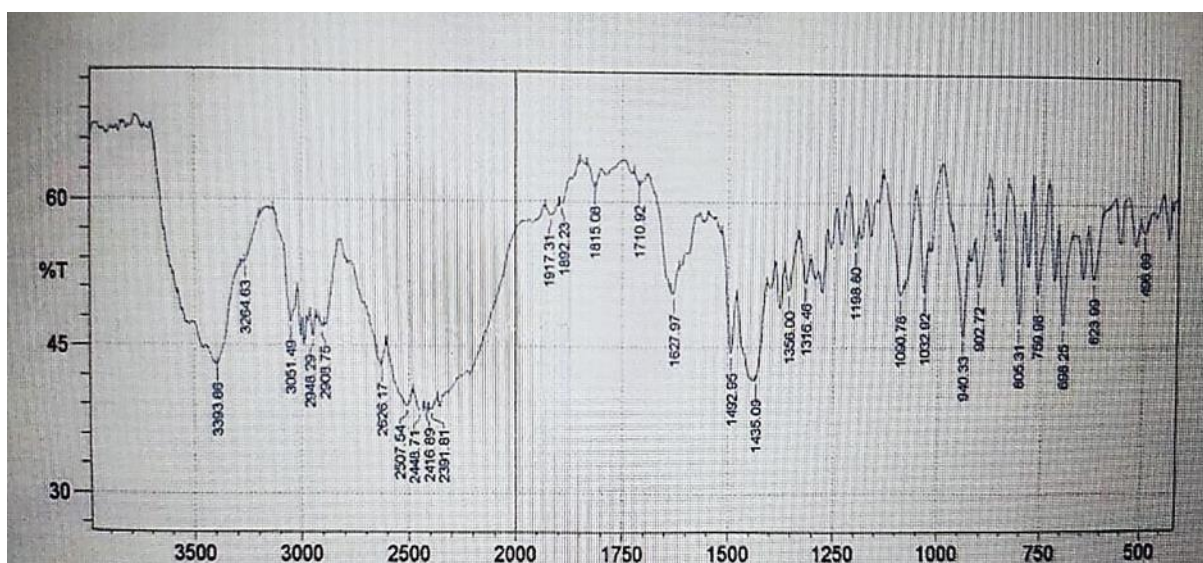
**Table 3.4:** Solubility of Trandolapril and inclusion complexes in different solvent:

| S. No. | Name of Solvents | Solubility (mg/ml) | Ratio of Drug and $\beta$ - cyclodextrin Inclusion |
|--------|------------------|--------------------|----------------------------------------------------|
|        |                  |                    |                                                    |

|    |                         | n=3            | complexes (mg/ml) |              |              |
|----|-------------------------|----------------|-------------------|--------------|--------------|
|    |                         |                | 1:1               | 1:2          | 1:3          |
| 1. | Distilled water         | 0.0253 mg/ml   | 3.8042 mg/ml      | 3.5201 mg/ml | 1.6092 mg/ml |
| 2. | Phosphate Buffer pH 6.8 | 0.016902 mg/ml | 7.79615 mg/ml     | 4.1072 mg/ml | 3.0602 mg/ml |

### 3.1.5 Drug and Excipients Interaction Study:

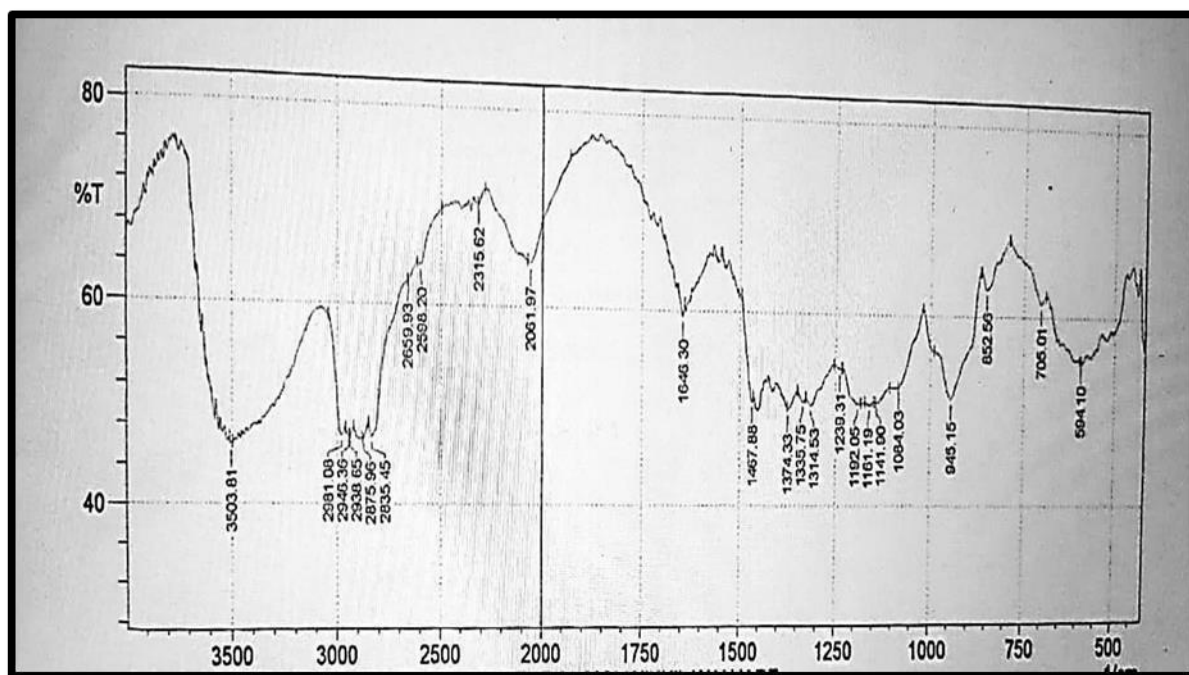
This was done to ensure drug-excipient compatibility. FTIR graphs are shown below. It has been shown to be compatible with a variety of excipients used in dosage forms



**Figure 3.5:** FTIR spectrum of Trandolapril

**Table 3.5:** Data analyzed by FTIR spectra of Trandolapril:

| Functional Group                 | Standard Peak (cm <sup>-1</sup> ) | Observed Peak of Drug (cm <sup>-1</sup> ) |
|----------------------------------|-----------------------------------|-------------------------------------------|
| Phenyl Group                     | 2900 - 2850                       | 2947.28                                   |
| Methyl CH <sub>3</sub>           | 2872                              | 2909.01                                   |
| C-H, CH <sub>3</sub> Derivatives | 1372                              | 1356                                      |
| Chlorophenyl Group               | 600 – 800                         | 722.01                                    |
| Disubstituted (Para) Piperazine  | 800 - 840                         | 807                                       |
| Diethylenediamine                | 3300 – 3500                       | 3393.89                                   |



**Figure 3.6:** FTIR spectrum of Trandolapril +  $\beta$ -cyclodextrin + Magnesium stearate+ Mannitol + Sodium starch glycolate + Cross carmellose sodium + Micro crystalline cellulose+ Talc

**Table 3.6:** Data analyzed by FTIR spectra of Trandolapril +  $\beta$ -cyclodextrin + Magnesium stearate+ Mannitol + Sodium starch glycolate + Cross carmellose sodium + Microcrystalline cellulose+ Talc.

| Functional Group                | Standard Peak ( $\text{cm}^{-1}$ ) | Observed Peak in physical mixture ( $\text{cm}^{-1}$ ) |
|---------------------------------|------------------------------------|--------------------------------------------------------|
| Phenyl Group                    | 2900 - 2850                        | 2875.98                                                |
| Methyl $\text{CH}_3$            | 2872                               | 2874.01                                                |
| C-H, $\text{CH}_3$ Derivatives  | 1372                               | 1335.75                                                |
| Chlorophenyl Group              | 600 – 800                          | 772                                                    |
| Disubstituted (Para) Piperazine | 800 - 840                          | 853.02                                                 |
| Diethylenediamine Group         | 3300 – 3500                        | 3505.01                                                |

### 3.2 Formulation and Evaluation of Sublingual Tablet containing Trandolapril:

A powder blend for the manufacture of sublingual pharmaceuticals containing varying amounts of super disintegrate and other excipients was created with a 1:1 dose

ratio, yielding the best results for drug content homogeneity and in vitro disintegrating test. Sublingual tablets were manufactured using the direct compression

method with a tablet punching machine and tested for pre and after compression properties.

### 3.2.1 Precompressional evaluation parameters:

#### Bulk

The bulk density of all developed formulations (F1-F9) ranged between 0.48 and 0.574 g/ml, indicating loose powder

#### Density:

packing. Carr's index and Hausner's ratio, which are used to measure flow ability, were then created using these numbers.

**Table 3.7:** Evaluation of Precompressional studies:

| Formulation | Bulk density<br>(gm/ml)<br>Mean±SD | Tapped<br>density<br>(gm/ml)<br>Mean±SD | Angle of<br>repose (°)<br>Mean±SD | Carr's<br>Index (%)<br>Mean±SD | Hausner's<br>ratio<br>Mean±SD |
|-------------|------------------------------------|-----------------------------------------|-----------------------------------|--------------------------------|-------------------------------|
| F1          | 0.48 ± 0.01                        | 0.57 ± 0.01                             | 29.82 ± 0.3                       | 15.79 ± 0.52                   | 1.18 ± 0.09                   |
| F2          | 0.456 ± 0.05                       | 0.724 ± 0.12                            | 35.48 ± 0.9                       | 35.47 ± 25.3                   | 1.62 ± 0.29                   |
| F3          | 0.506 ± 0.05                       | 0.58 ± 0.03                             | 33.74 ±<br>0.51                   | 14.55 ±<br>22.79               | 1.18 ± 0.10                   |
| F4          | 0.45 ± 0.01                        | 0.47 ± 0.01                             | 29.27 ±<br>0.19                   | 4.26 ± 8.17                    | 1.05 ± 0.01                   |
| F5          | 0.447 ± 0.05                       | 0.618 ±<br>0.031                        | 34.12 ±<br>0.205                  | 27.81 ± 9.53                   | 1.37 ± 0.08                   |
| F6          | 0.475 ± 0.03                       | 0.687 ± 0.04                            | 31.95 ±<br>0.203                  | 30.42 ±<br>12.51               | 1.45 ± 0.12                   |
| F7          | 0.476 ± 0.01                       | 0.46 ± 0.50                             | 29.91 ±<br>0.402                  | 26.82 ± 6.83                   | 1.37 ± 0.05                   |
| F8          | 0.574 ± 0.01                       | 0.757 ± 0.02                            | 30.46 ±<br>0.200                  | 27.16 ±<br>12.77               | 1.32 ± 0.02                   |
| F9          | 0.557 ± 0.02                       | 0.754 ±<br>0.009                        | 33.18 ±<br>0.04                   | 26.34 ±<br>5.32                | 1.34 ± 0.04                   |

#### • Tapped

#### Density:

The bulk density of all developed

formulations (F1-F9) ranged between

0.46 and 0.573 g/ml, indicating loose powder packaging. The results were

then used to calculate Carr's index and Hausner's ratio to estimate flowability

- **Carr's Index:** The compressibility index of all prepared batches ranged between 4.26% to 35.49%, indicating
- **Angle of Repose:** Powders with smooth surfaces had an angle of repose ranging
- **Hausner's Ratio:** The ratio of all developed formulations was between

that the mixtures flowed well in all batches.

from 29.27° to 35.75°, indicating greater flow.

1.16 and 1.38, indicating adequate flow ability.

### 3.2.2 Post compressional evaluation parameters of sublingual tablet:

- **Weight Variation:** Every manufactured sublingual tablet was checked for weight
- **Thickness:** It was discovered to

variation and found to be within the acceptable range of  $\pm 7.5\%$ .

between 1.26 and 3.84 mm.

**Table 3.8:** Post compressional studies:

| Formulation | Weight variation (mg) Mean $\pm$ SD | Thickness (mm) Mean $\pm$ SD | Hardness (kg/cm <sup>2</sup> ) Mean $\pm$ SD | Drug content uniformity (%) Mean $\pm$ SD | Friability (%) Mean $\pm$ SD |
|-------------|-------------------------------------|------------------------------|----------------------------------------------|-------------------------------------------|------------------------------|
| F1          | 110.66 $\pm$ 0.109                  | 2.4 $\pm$ 0.06               | 2.75 $\pm$ 0.10                              | 80.62 $\pm$ 0.007                         | 0.57 $\pm$ 0.008             |
| F2          | 99.33 $\pm$ 0.057                   | 2.62 $\pm$ 0.21              | 2.66 $\pm$ 0.17                              | 95.37 $\pm$ 0.003                         | 0.34 $\pm$ 0.04              |
| F3          | 98.8 $\pm$ 0.01                     | 3.84 $\pm$ 0.09              | 3.02 $\pm$ 0.02                              | 81.87 $\pm$ 0.009                         | 0.68 $\pm$ 0.04              |
| F4          | 99.12 $\pm$ 0.04                    | 3.72 $\pm$ 0.02              | 3.12 $\pm$ 0.01                              | 91.16 $\pm$ 0.01                          | 0.26 $\pm$ 0.04              |
| F5          | 97.75 $\pm$ 0.20                    | 2.20 $\pm$ 0.19              | 2.6 $\pm$ 0.031                              | 85.02 $\pm$ 0.09                          | 0.45 $\pm$ 0.03              |
| F6          | 103 $\pm$ 0.27                      | 2.21 $\pm$ 0.17              | 1.7 $\pm$ 0.19                               | 91.53 $\pm$ 0.01                          | 0.39 $\pm$ 0.05              |

|    |               |             |              |               |              |
|----|---------------|-------------|--------------|---------------|--------------|
| F7 | 100.31 ± 0.15 | 1.87 ± 0.23 | 2.37 ± 0.206 | 99.62 ± 0.005 | 0.17 ± 0.01  |
| F8 | 100.8 ± 0.12  | 1.25 ± 0.24 | 3.38 ± 0.26  | 98.72 ± 0.004 | 0.41 ± 0.03  |
| F9 | 99.43 ± 0.07  | 1.96 ± 0.02 | 2.71 ± 0.10  | 96.83 ± 0.01  | 0.57 ± 0.036 |

- **Hardness:** Every pill had a hardness between 1.7 and 3.39 kg/cm<sup>2</sup>. Additionally, it was shown that all batches' hardness decreases when the
- **Friability:** A Roche Friabilator tester verified that the computed percentage weight loss was within the acceptable
- **Drug Content Uniformity:** The percentage drug content of tablets was determined to be between 80.63% and
- **Wetting time:** The table below makes it clear that as the absorption ratio drops, the concentration of the super disintegrant will rise and the amount of
- **The ratio of water absorption:** For batches F1 through F8, it ranged from 59.61% to 98.24%. Reducing the binder concentration and increasing the super

amount of binder is reduced. The lower the hardness, the shorter the wetting time, which has an impact on the dissolution studies of sublingual tablets. limit given in the I.P. The pills were mechanically stable, as indicated by the reduced percentage loss data..

99.61%, showing that the drug was uniformly distributed in the tablets.

binder added to the formulation would decrease, which could shorten the wetting time.

disintegrant concentration in the formulation resulted in the highest water content..

**Table 3.9:** Below are the results of the in vitro disintegration test, wetting time, and water absorption ratio:

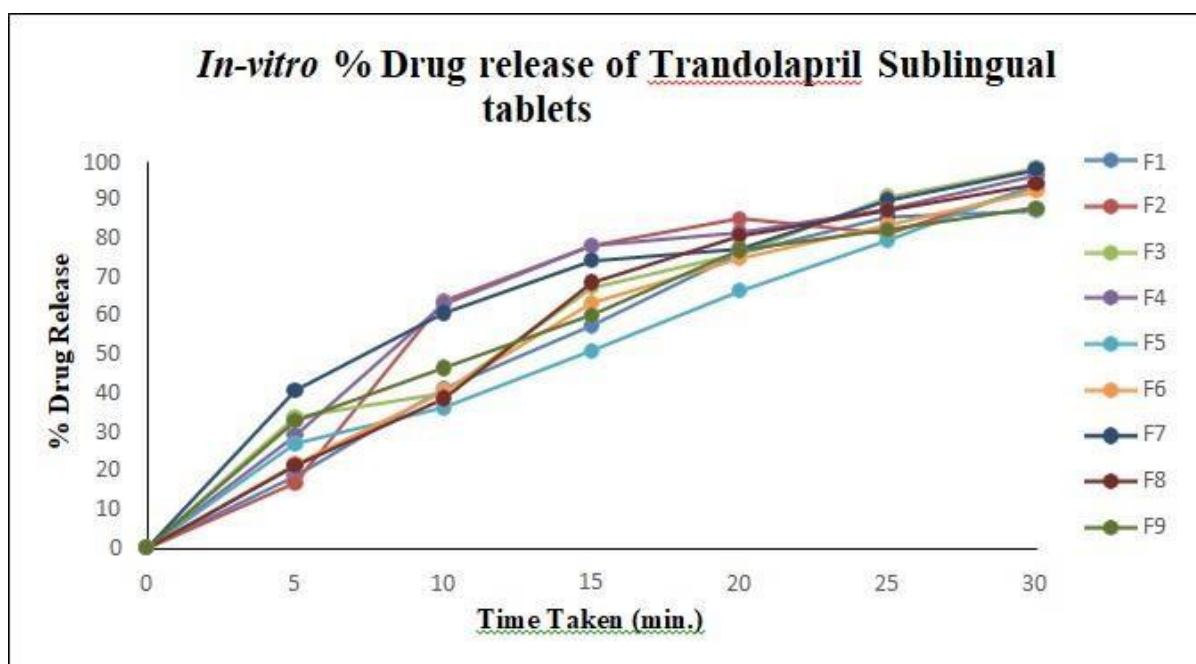
| Formulation | <i>In vitro</i> Disintegration test (sec)<br>Mean±SD | Wettingtime(sec)<br>Mean±SD | Waterabsorption ratio (%)<br>Mean±SD |
|-------------|------------------------------------------------------|-----------------------------|--------------------------------------|
| F1          | 90 ± 2.79                                            | 84 ± 0.68                   | 81.61 ± 0.29                         |
| F2          | 97.90 ± 1.01                                         | 89 ± 1.35                   | 78.32 ± 0.05                         |
| F3          | 90 ± 3.15                                            | 82.08 ± 0.46                | 75 ± 0.16                            |

|    |              |              |               |
|----|--------------|--------------|---------------|
| F4 | 89.34 ± 1.91 | 76 ± 2.72    | 64.62 ± 0.06  |
| F5 | 90 ± 3.17    | 67.32 ± 2.44 | 91.28 ± 0.06  |
| F6 | 99.32 ± 0.97 | 99.98 ± 2.52 | 62.57 ± 0.031 |
| F7 | 59.61 ± 1.25 | 62.34 ± 1.47 | 99.22 ± 0.003 |
| F8 | 67.65 ± 0.86 | 90 ± 3.17    | 97.63 ± 0.009 |
| F9 | 89.67 ± 1.00 | 78.34 ± 1.17 | 97.54 ± 0.012 |

- **Disintegration Study:** It was shown that the tablet absorption time by reducing a higher water absorption ratio shortened the wetting and breakdown times.
- **Dissolution:** Batch F8 showed the 30 minutes out of all the formulations maximum drug release of 95.79% within tested in this investigation.

**Table: 3.10 Below are the results of the in vitro disintegration test, wetting time, and water absorption ratio.**

| Time<br>[min.] | Below are the results of the in vitro disintegration test, wetting time, and water absorption ratio. |                 |                  |                 |                  |                 |                  |                 |                 |
|----------------|------------------------------------------------------------------------------------------------------|-----------------|------------------|-----------------|------------------|-----------------|------------------|-----------------|-----------------|
|                | F1                                                                                                   | F2              | F3               | F4              | F5               | F6              | F7               | F8              | F9              |
| 5 min          | 18.65<br>± 5.64                                                                                      | 16.86<br>± 2.04 | 33.91 ±<br>16.14 | 29.07 ±<br>8.32 | 27.05 ±<br>3.21  | 21.64 ±<br>3.69 | 40.81 ±<br>8.42  | 21.38<br>± 2.33 | 32.75 ±<br>3.02 |
| 10 min         | 41.24<br>± 7.34                                                                                      | 63.81<br>± 4.09 | 40.15 ±<br>1.87  | 63.05 ±<br>6.30 | 36.27 ±<br>10.50 | 40.47 ±<br>5.81 | 60.77 ±<br>4.72  | 38.65<br>± 1.04 | 46.52 ±<br>1.82 |
| 15 min         | 57.61<br>± 1.82                                                                                      | 78.12<br>± 3.44 | 67.39 ±<br>2.44  | 78.17 ±<br>4.94 | 51.00 ±<br>3.26  | 63.43 ±<br>8.99 | 74.34 ±<br>1.85  | 68.62<br>± 1.16 | 60.21 ±<br>1.53 |
| 20 min         | 76.37<br>± 6.34                                                                                      | 85.21<br>± 1.42 | 76.27 ±<br>4.91  | 81.56 ±<br>2.86 | 66.38 ±<br>3.22  | 74.90 ±<br>5.05 | 77.40 ±<br>11.13 | 80.81<br>± 1.88 | 76.93 ±<br>1.44 |
| 25 min         | 85.75<br>± 4.34                                                                                      | 81.22<br>± 8.69 | 90.79 ±<br>2.00  | 87.63 ±<br>1.99 | 79.51 ±<br>7.45  | 83.64 ±<br>2.91 | 89.96 ±<br>1.38  | 87.43<br>± 2.14 | 82.18 ±<br>1.91 |
| 30 min         | 87.28<br>± 3.04                                                                                      | 92.52<br>± 3.31 | 93.31 ±<br>0.97  | 94.35 ±<br>2.21 | 93.96 ±<br>5.02  | 92.32 ±<br>3.27 | 94.89 ±<br>3.34  | 95.79<br>± 2.06 | 87.83 ±<br>1.91 |



**Figure 3.7:** In vitro % drug release of sublingual formulation

### 3 Stability studies

As indicated in the table below, drug assays and in vitro dissolution tests were used to assess the stability of the F8 formulation following two months of storage. A

substantial difference between before and after storage was found by statistical analysis ( $P < 0.08$ ). The reported trials are listed below, and the tablets were evaluated within two months.

**Table 3.11:** Stability studies of F8 formulation:

| S. No. | Parameter                    | Before storage     | After 2 months     | Inference    |
|--------|------------------------------|--------------------|--------------------|--------------|
| 1.     | Weight variation             | $100.34 \pm 0.15$  | $99.88 \pm 0.15$   | Within limit |
| 2.     | Hardness                     | $2.36 \pm 0.20$    | $2.37 \pm 0.20$    | Within limit |
| 3.     | Drug content                 | $97.89\% \pm 0.05$ | $96.20\% \pm 0.05$ | Within limit |
| 4.     | Wetting time                 | $62.32 \pm 1.47$   | $69 \pm 1.46$      | Within limit |
| 5.     | Water absorption ratio       | $99.24\% \pm 0.03$ | $99.24\% \pm 0.03$ | Within limit |
| 6.     | Disintegration time          | $59 \pm 1.25$      | $65 \pm 1.21$      | Within limit |
| 7.     | <i>In vitro</i> Drug release | $99.15\% \pm 3.34$ | $98.57\% \pm 1.01$ | Within limit |

### SUMMARY AND CONCLUSION

In this research, the aim was to develop a sublingual tablet using Trandolapril and  $\beta$ -

cyclodextrin in a 1:1 dosage ratio. The tablet was created by combining the two components through kneading. The calibration curve for 10-50 µg/ml showed a regression value of 0.997 in methanolic phosphate buffer, pH 6.8. Trandolapril sublingual tablets dissolve better with lower β-cyclodextrin concentrations, according to formulation data.

Inclusion complexes using β-cyclodextrin in a 1:1 ratio of drug and solubility enhancer demonstrated superior water solubility, drug content, and dissolution rates. Therefore, the goal of the current study is to use direct compression technology to create a sublingual tablet of trandolapril. Additionally, the purpose of creating this dosage form is to address drug solubility problems utilizing the inclusion complex technique and to provide a rapid onset of action, which is helpful in the treatment of disorders like hypertension.

The direct compression method was used to generate this formulation, and it was examined for evaluation parameters both before and after compression. All batches' powdered blends were assessed for bulk and tapped density, Carr's and Hausner's ratios, and angle of repose prior to compression. Thickness, hardness, weight variation, friability, disintegration time, wetting time, water absorption ratio, and medication content uniformity were all assessed for sublingual tablets. All batches had friability of less than 1%, while thickness and hardness were confirmed to be within acceptable bounds. Trandolapril sublingual tablets are an efficient blood pressure treatment with better patient compliance, according to research on the F8 formulation's low wetting time and water absorption ratio. Before it is put on the market, more clinical trials are required.

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