Research Article ISSN:xxxx-xxxx
JIIPS

Journal of Innovation and Invention in Pharmacy and Sciences (JIIPS)

Official Publication of Faculty of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore

TRANDOLAPRIL SUBLINGUAL TABLET FORMATION AND EVALUATION

Mhaske Ganesh*,Dr Govind Soni,Lata Kanase, Dr Rakesh k Jatav
Faculty of Pharmacy,Dr A.P.J Abdul Kalam University Indore,
Email ID :-Mhaske.g109@gmail.com

Abstract: The goal of the study was to develop a sublingual tablet containing β-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, trandolaprile 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: Trandolaprile, β-cyclodextrin, Blood Pressure, Bioavailability

1. INTRODUCTION

Oral drug administration refers to the oral delivery of pharmaceutical agents or substances.[1] 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 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.. [1,2]

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

1.2. Function of Oral Mucosa [5,6]

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.

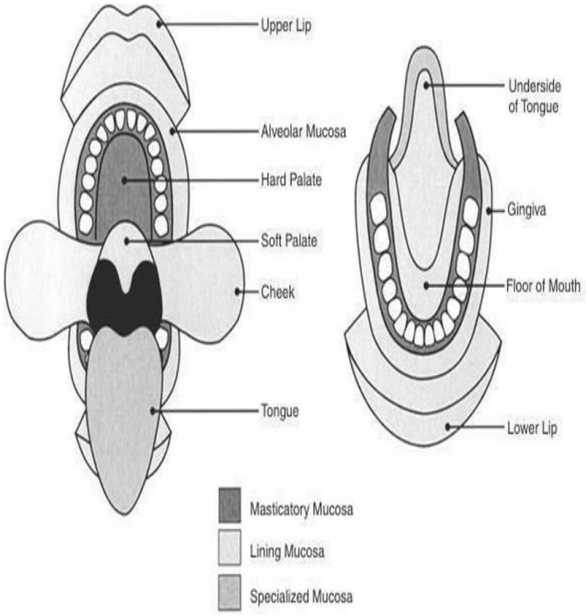


Fig 1.2:- The general anatomy of the oral cavity

1.3 Permeability and Pathophysiology of Oral Mucosa [7,8,9]

Examining normal tissue in animal models aids in understanding the permeability and pathophysiology of the oral mucosa. [10] The 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..[12]

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

Layers	Mean thickness 1 (µm)	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: [11,13]

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.). [14,15]

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.[17] 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. [16,19]

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.[20,21]

TABLE 1.2: Postulated Mechanism For Polymer – Mucosal Adhesive Properties [25,26]

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

		networks.
3	**Electronic**	The electron transport among polymer and mucus generates attractive forces across an electrical double layer.
4	**Wetting**	Evaluates the capacity of the polymer to spread over the biological surface and determine the interfacial tension between them. The tension is proportional to X1/2, where X is the polymer-polymer interaction parameter. Low values of X indicate structural similarity and improved miscibility.
5	**Fracture**	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.[22] 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. [29]

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. 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. [1]

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. [5]

Advantages of Sublingual Tablets: [22]

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.
- 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 tract and hepatic portal system, reducing hepatic first pass metabolism. [24]
- Improves the bioavailability of orally administered drugs by bypassing the GI tract and hepatic portal system, reducing hepatic first pass metabolism.

Disadvantages of Sublingual Tablets: [29]

- Absorption area is lowered considerably.
- Unsuitable for bitter prescription medications.
- Poor patient compliance.
- Eating, drinking, and smoking are not allowed.
- Highly ionic medications are not authorized.
- Why Offering big dosages is not feasible
- .

Limitations of Sublingual Dosage Form [11]

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 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. [15]

TABLE 1.3: Drug Physicochemical Requirements for Sublingual Drug Administration

The drug's physicochemical characteristics	Approved Range
Minimum Dose	< 20 mg
Taste	Not intenselybitter
Stability	Good stabilityin 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	Scientech Pvt. Ltd.
8.	Tablet Punching machine	Pharmaceutical Machinery Works
9.	FTIR	Shimazu
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.	β - cyclodextrin	Alkem Laboratories, Mumbai
9.	Methanol	LOBA CHEMIE PVT. LTD.
10.	Potassium Dihydrogen Phosphate	Merk

2.1 Preformulation studies [23,24]

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 combination of methanolic distilled water and methanolic buffer at a ratio of 1:9. To prepare a stock solution with a concentration of 1000 µg/ml in a volumetric flask.
- **Determination of λ 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 (100µg/ml) and diluted with distilled water and pH 6.8 buffer to create the sub stock solution. To find the maximal absorbance of trandolapril in methanolic distilled water and methanolic pH 6.8 buffer, a dilution of 10 µg/ml was prepared and scanned at 400-200 nm using a UV visible spectrophotometer (Shimadzu 1800, Japan).

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 µg/ml to create the substock solution. At room temperature, the mixture was then stirred for two hours. Distilled water was used to make dilutions of 10–50 µg/ml, which were then compared to a reference solution at 228 nm using a UV spectrophotometer. At different concentrations, the absorbance data was recorded.

- **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 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 µg/ml against a reference solution.

Data on absorbance at different concentrations was noted..

c) Solubility determination: [25]

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 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.

d) Melting point determination: [29]

A capillary tube containing 1mg of Trandolapril medication sample was sealed 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: [27]

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-1.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 [15,18]

a) Preparation of Inclusion Complexes

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

Method: After being weighed individually, β-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.

b) Determination of Solubility: [22]

Inclusion complexes of trandolapril and β-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 full day of room temperature storage, the solution was sufficiently filtered using Whatman's filter paper. After being diluted with phosphate buffer pH 6.8, the sample was examined at 228 nm using a UV-visible spectrophotometer.

c) Percentage Drug Content: [19]

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.:

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

2.3 Preparation of Sublingual Tablet by direct compression method [24]

Inclusion complexes comprising Trandolapril and β-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 β-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 β-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: [21,26,27]

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. 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).
- **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 calculated using the following formula. Weight of blend or powder divided by tapped volume of blend or powder (in millilitres) is the tapped density..
- **Hausner's ratio:** It is a figure that represents a powder's flowability and is 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 θ = Height / 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: [18,21]

- **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 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.
- **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 removed, dusted, and weighed once again. The provided equation was used to calculate the % friability. The maximum weight decrease is limited to 1%.
- 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 removed, dusted, and weighed again. The supplied equation was used to estimate the percentage friability. The maximum weight reduction is no more than 1%.
- ***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, beats were added and the assemblage was placed in phosphate 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 .
- **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. (Wa – Wb) / Wb × 100 is the water absorption ratio,
Where, Wa = weight after water absorption,
Wb = 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

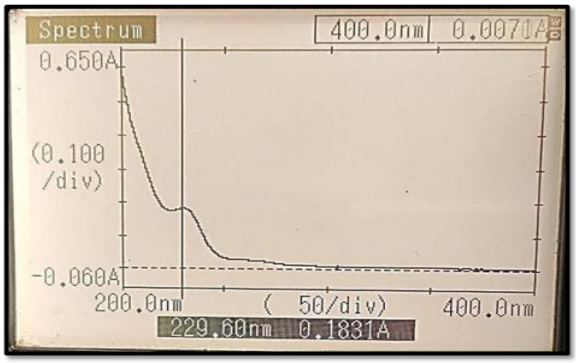
Stability Study: The produced tablets from batch F7 were selected for stability investigations, and the operation was carried out. The pills were kept in a stability chamber at 40±2 ◦C and 75±5% RH for two months. Samples were collected and analyzed for assessment parameters. [22]

3. OUTCOMES AND TALK

3.1 PREFORMULATION STUDIES

3.1.1 Determination of λmax by UV Visible Spectrophotometer:

Using UV spectroscopy, the λ 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: λmax of Trandolapril in methanolic distilled Water.

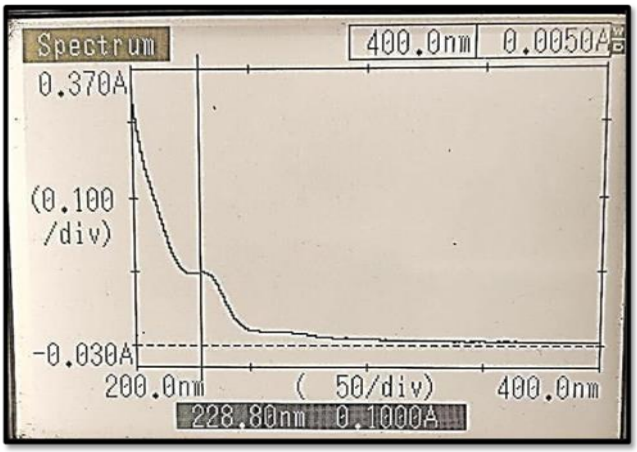


Figure 3.2: λ max of Trandolapril in methanolic phosphate buffer pH 6.8

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 (µg/ml)	Absorbance (Mean±SD)
0	0
10 µg/ml	0.1802 ± 0.001
20 µg/ml	0.3890 ± 0.003
30 µg/ml	0.5053 ± 0.006
40 µg/ml	0.7495 ± 0.002
50 µg/ml	0.8961 ± 0.002

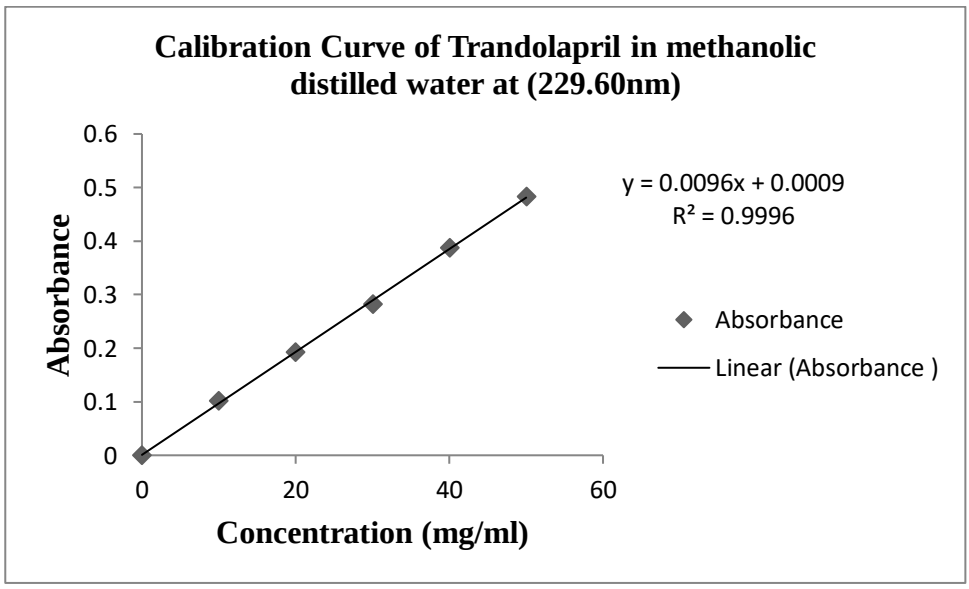


Figure 3.3: Calibration Curve of Trandolapril in methanolic distilled water.

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

Concentration (µg/ml)	Absorbance (Mean±SD)
0	0
10 µg/ml	0.1011 ± 0.001
20 µg/ml	0.19276± 0.004
30 µg/ml	0.2825 ± 0.002
40 µg/ml	0.3866 ± 0.001
50 µg/ml	0.4832 ± 0.01

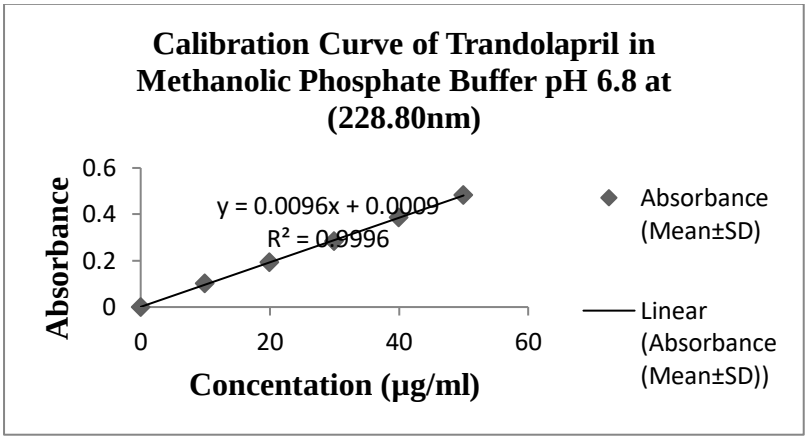


Figure 3.4: Calibration Curve of Trandolapril in Methanolic Phosphate Buffer pH 6.8

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◦c.

Table 3.3: Melting point of Trandolapril:

S. No.	Observed values	Reported value
1.	119◦c	119 to 123◦c
2.	115◦c	
3.	116◦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 β- 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

.

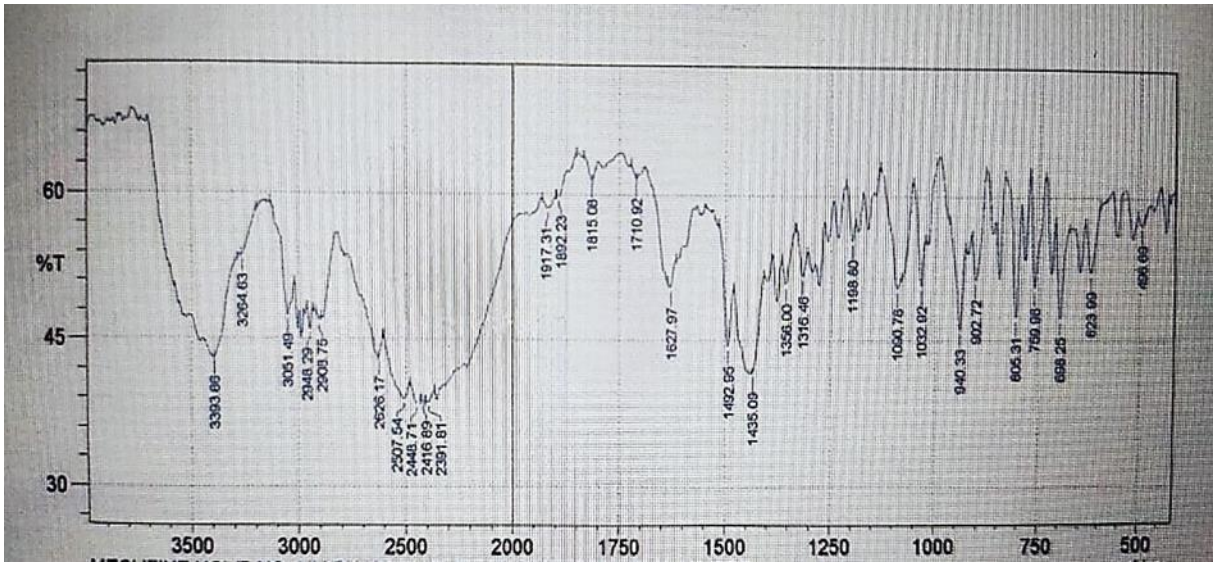


Figure 3.5: FTIR spectrum of Trandolapril

Table 3.5: Data analyzed by FTIR spectra of Trandolapril:

Functional Group	Standard Peak (cm^{-1})	Observed Peak of Drug (cm^{-1})
Phenyl Group	2900 - 2850	2947.28
Methyl CH3	2872	2909.01
C-H, CH3 Derivatives	1372	1356
Chlorophenyl Group	600 – 800	722.01
Disubstituted (Para) Piperazine	800 - 840	807
Diethylenediamine	3300 – 3500	3393.89

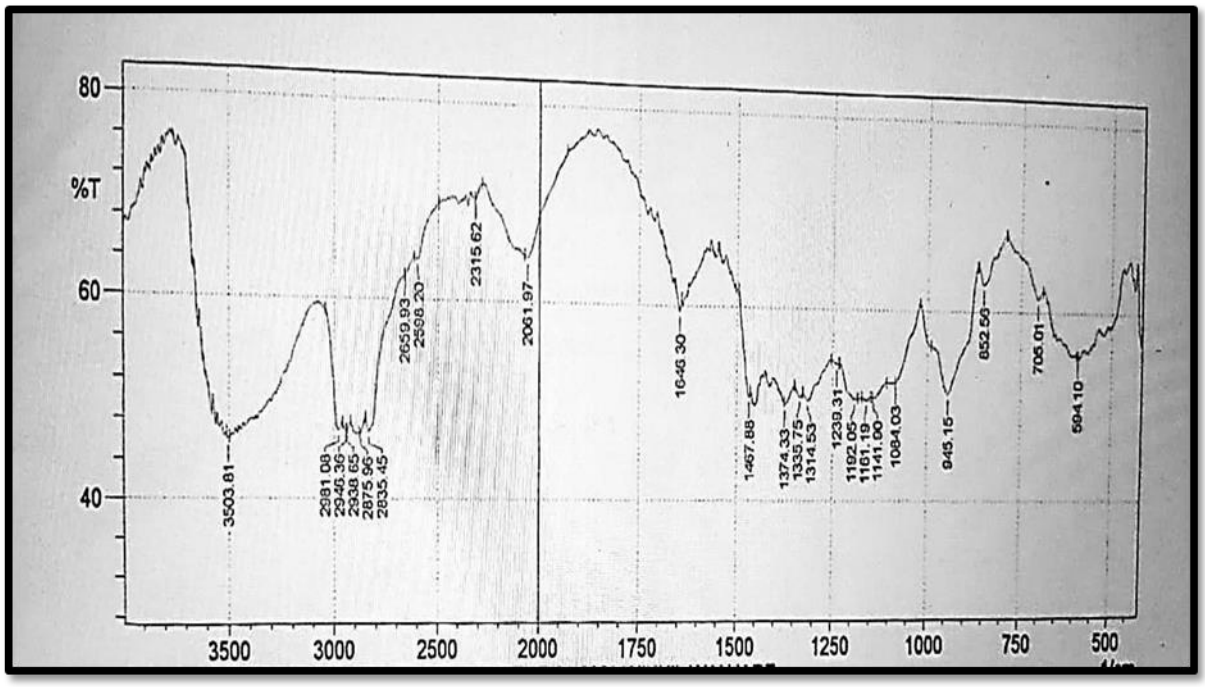


Figure 3.6: FTIR spectrum of Trandolapril + β-cyclodextrin + Magnesium stearate+ Mannitol + Sodium starch glycolate + Cross carmellose sodium + Micro crystalline cellulose+ Talc

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

Functional Group	**Standard Peak (cm^{-1})**	**Observed Peak in physical mixture (cm^{-1})**
Phenyl Group	2900 - 2850	2875.98
Methyl CH_3	2872	2874.01
C-H, 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 Density:

The bulk density of all developed formulations (F1-F9) ranged between 0.48 and 0.574 g/ml, indicating loose powder 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	Bulkdensity (gm/ml) Mean±SD	Tapped density (gm/ml) Mean±SD	Angle of repose (◦) Mean±SD	Carr's Index(%) Mean±SD	Hausner's ratio 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 ± 0.51	14.55 ± 22.79	1.18 ± 0.10
F4	0.45 ± 0.01	0.47± 0.01	29.27 ± 0.19	4.26 ± 8.17	1.05 ± 0.01
F5	0.447 ± 0.05	0.618 ± 0.031	34.12 ± 0.205	27.81 ± 9.53	1.37 ± 0.08
F6	0.475 ± 0.03	0.687 ± 0.04	31.95 ± 0.203	30.42 ± 12.51	1.45 ± 0.12
F7	0.476 ± 0.01	0.46 ± 0.50	29.91 ± 0.402	26.82 ± 6.83	1.37 ± 0.05
F8	0.574 ± 0.01	0.757 ± 0.02	30.46 ± 0.200	27.16 ± 12.77	1.32 ± 0.02
F9	0.557 ± 0.02	0.754 ± 0.009	33.18 ± 0.04	26.34 ± 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 that the mixtures flowed well in all batches.
- **Angle of Repose:** Powders with smooth surfaces had an angle of repose ranging from 29.27◦ to 35.75◦, indicating greater flow.
- **Hausner's Ratio:** The ratio of all developed formulations was between 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 variation and found to be within the acceptable range of ±7.5%.
- **Thickness:** It was discovered to between1.26 and 3.84 mm.

Table 3.8: Post compressional studies**:**

Formulation	**Weight variation (mg) Mean±SD**	**Thickness (mm) Mean±SD**	**Hardness (kg/cm^2) Mean±SD**	**Drug content uniformity (%) Mean±SD**	**Friability (%) Mean±SD**
F1	110.66 ± 0.109	2.4 ± 0.06	2.75 ± 0.10	80.62 ± 0.007	0.57 ± 0.008
F2	99.33 ± 0.057	2.62 ± 0.21	2.66 ± 0.17	95.37 ± 0.003	0.34 ± 0.04
F3	98.8 ± 0.01	3.84 ± 0.09	3.02 ± 0.02	81.87 ± 0.009	0.68 ± 0.04
F4	99.12 ± 0.04	3.72 ± 0.02	3.12 ± 0.01	91.16 ± 0.01	0.26 ± 0.04
F5	97.75 ± 0.20	2.20 ± 0.19	2.6 ± 0.031	85.02 ± 0.09	0.45 ± 0.03
F6	103 ± 0.27	2.21 ± 0.17	1.7 ± 0.19	91.53 ± 0.01	0.39 ± 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/cm2. Additionally, it was shown that all batches' hardness decreases when the 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.
- **Friability:** A Roche Friabilator tester verified that the computed percentage weight loss was within the acceptable limit given in the I.P. The pills were mechanically stable, as indicated by the reduced percentage loss data..
- **Drug Content Uniformity:** The percentage drug content of tablets was determined to be between 80.63% and 99.61%, showing that the drug was uniformly distributed in the tablets.
- **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 binder added to the formulation would decrease, which could shorten the wetting time.
- **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 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	***In vitro* Disintegration test (sec) Mean±SD**	**Wettingtime (sec) Mean±SD**	**Waterabsorption ratio (%) 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 a higher water absorption ratio shortened the tablet absorption time by reducing the wetting and breakdown times
.
- **Dissolution:** Batch F8 showed the maximum drug release of 95.79% within 30 minutes out of all the formulations tested in this investigation.

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

Time [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 ± 5.64	16.86 ± 2.04	33.91 ± 16.14	29.07 ± 8.32	27.05 ± 3.21	21.64 ± 3.69	40.81 ± 8.42	21.38 ± 2.33	32.75 ± 3.02
10 min	41.24 ± 7.34	63.81 ± 4.09	40.15 ± 1.87	63.05 ± 6.30	36.27 ± 10.50	40.47 ± 5.81	60.77 ± 4.72	38.65 ± 1.04	46.52 ± 1.82
15 min	57.61 ± 1.82	78.12 ± 3.44	67.39 ± 2.44	78.17 ± 4.94	51.00 ± 3.26	63.43 ± 8.99	74.34 ± 1.85	68.62 ± 1.16	60.21 ± 1.53
20 min	76.37 ± 6.34	85.21 ± 1.42	76.27 ± 4.91	81.56 ± 2.86	66.38 ± 3.22	74.90 ± 5.05	77.40 ± 11.13	80.81 ± 1.88	76.93 ± 1.44
25 min	85.75 ± 4.34	81.22 ± 8.69	90.79 ± 2.00	87.63 ± 1.99	79.51 ± 7.45	83.64 ± 2.91	89.96 ± 1.38	87.43 ± 2.14	82.18 ± 1.91
30 min	87.28 ± 3.04	92.52 ± 3.31	93.31 ± 0.97	94.35 ± 2.21	93.96 ± 5.02	92.32 ± 3.27	94.89 ± 3.34	95.79 ± 2.06	87.83 ± 1.91

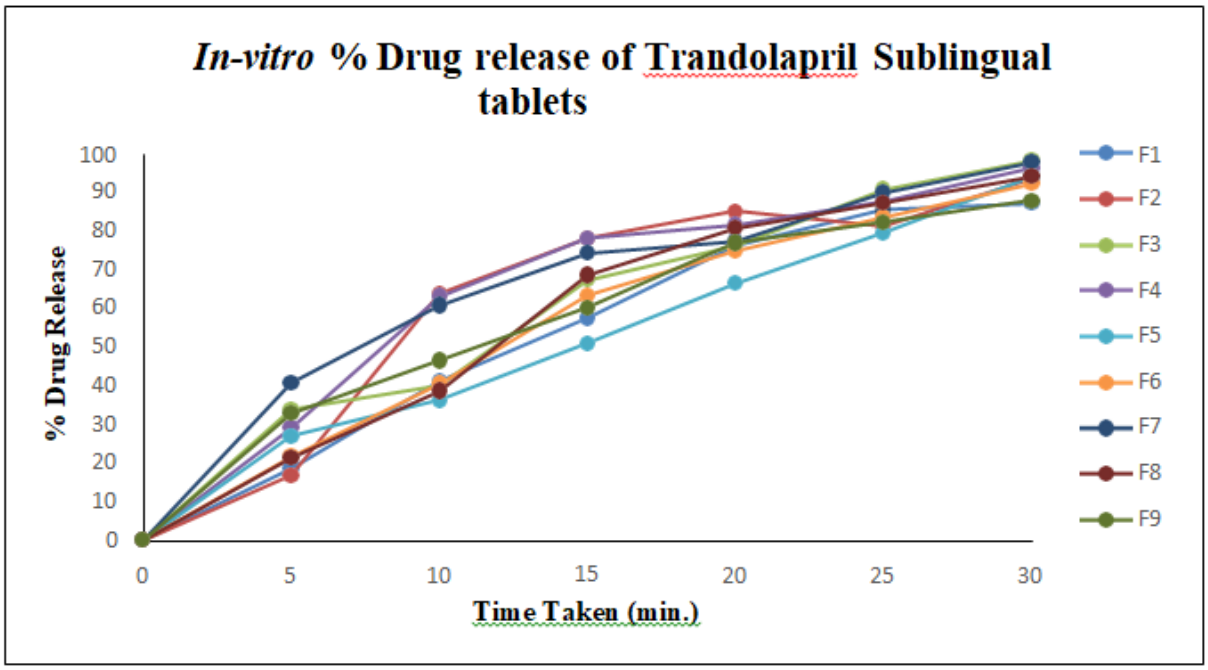


Figure 3.7: In vitro % drug release of sublingual formulation

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 ± 0.15	99.88 ± 0.15	Within limit
2.	Hardness	2.36 ± 0.20	2.37 ± 0.20	Within limit
3.	Drug content	97.89% ± 0.05	96.20% ± 0.05	Within limit
4.	Wetting time	62.32 ± 1.47	69 ± 1.46	Within limit
5.	Water absorption ratio	99.24% ± 0.03	99.24% ± 0.03	Within limit
6.	Disintegration time	59 ± 1.25	65 ± 1.21	Within limit
7.	*In vitro* Drug release	99.15% ± 3.34	98.57% ± 1.01	Within limit

SUMMARY AND CONCLUSION

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

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. Trandolaprile 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.

REFERNCES

1. Mullen KD, Sheikh MY, Bass NM, Poordad FF, Sanyal AJ, and others (2014) For the long-term maintenance of remission from overt hepatic encephalopathy, rifaximin is safe and well tolerated. ClinGastroenterolHepatol 12: 1390-1397.
2. Peppas NA, Buri PA (1985) Surface, interfacial, and molecular aspects of polymer bioadhesion on soft tissues. J Control Release 2:257–275.
3. Hua S. Developments in Nanoparticulate Drug Delivery Methods for Buccal and Sublingual Administration. Front Pharmacol [Online]. 2019; 10.
4. A Novel Method for improving in-vitro dissolution and in-vivo pharmacokinetics of Meclizine hydrochloride.
5. Zahra, S., and Ahmed, T. (2021). Meclizine as a case study: creation and assessment of sublingual tablets for quick treatment from motion sickness.

Pharmaceutical Sciences International Journal, 34(4), 572-579.

6. Crooks PA, Malkawi AH, Al-Ghananeem AM. Ph has an impact on oxycodone hydrochloride's sublingual absorption. Article 23 of AAPS PharmSciTech 2006, 7(1).
7. Chitlange, P.R. and Kilor, V.A., 2020. Formulation, development and evaluation of sublingual antiemetic tablet by melt granulation technique. Int J Pharm Sci Res, 11(8), pp.4039-405.
8. Chowdary, K.P.R., 2013. Recent research on formulation development of BCS class II drugs–A review. International Research Journal of Pharmaceutical and Applied Sciences, 3(1), pp.173- 181.
9. Clarke, J. P. and Thomas, E. A. (2018) 'Sublingual vs oral drug delivery: A comparative review', American Journal of Health-System Pharmacy, 75(6), pp. 336-344. Available at: https://doi.org/10.2146/ajhp170820 (Accessed: 31 December 2024).
10. Collins, L.M., and C. Dawes. The surface area of the adult human mouth and thickness of the salivary film covering the teeth and oral mucosa. 1987;45:2-10..
11. Cox LS, Larenas Linnemann D, Nolte H, Weldon D, Finegold I, Nelson HS. Sublingual immunotherapy: a comprehensive review. J Allergy Clin 2006;117(5):1021–35.
12. Cruchley, A. T., & Bergmeier, L. A. (2018). Structure and Functions of the Oral Mucosa. Oral Mucosa in Health and Disease, 1–18. doi:10.1007/978-3-319-56065-6_1.
13. Tadikonda, R.R., and Daravath, B. (2014). Meclizine Hydrochloride Solid Dispersions: Development and in vitro Characterisation. Adv Drug Del Open Journal, 2, p. 238.
14. Daravath, B., 2021. Surface Solid Dispersion: A Novel Method for improving in-vitro dissolution and in-vivo pharmacokinetics of Meclizine hydrochloride. Research Journal of Pharmacy and Technology, 14(2), pp.685-693.
15. Allen LV. International Journal of Pharmaceutical Technology, 2003, 7:449-450. Rapid dissolving technology: an interview with Lloyd Allen.
16. Amid on GL et al, ―Estimating the fraction dose absorbed from the suspensions of poorly soluble compounds in humans: a mathematical model,‖ Pharm Res., 1993; 10(3): 264-270.
17. A summary of the sublingual method for systemic medication administration. Intraoral Spray Technology.

18. Arther Paul, C. (2009). Developing and Assessing Orodispersible Domperidone Tablets from Specific Solid Dispersions: An Effort to Enhance in Vitro Dissolution, Patient Compliance, and Marketability (Doctoral dissertation, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore).

19. Athavale, A., Athavale, T. and Roberts, D.M., 2020. Antiemetic drugs: what to prescribe and whenAustralian Prescriber, 43(2), p.49.

20. Benn, A.M. and Thomson, W.M., 2014. Saliva: an overview. NZ Dent J, 110(3), pp.92-96.

21. Bentley‘s textbook of pharmaceutics, E.A. Raudind, eighth edition ELBS.

22. Bhardwaj, R. et al. (2023). "Optimization of the production process of sublingual meclizine tablets: Hot-melt extrusion vs. direct compression." AAPS PharmSciTech, 24(5), 2563-2572.

23. Nagrajan RK, Bhati R. A thorough analysis of the oral mucosal medication delivery system. Vol. 3 (1):659-681, IJPSR 2012.

24. IJPSR, 2012; Vol. 3(1): 659-681 ISSN: 0975-8232; Bhati R. and Nagrajan R. K., A DETAILLED REVIEW ON ORAL MUCOSAL DRUG DELIVERY SYSTEM.

25. Nachinolkar, R., and Bhide, P. (2018). Meclizine hydrochloride fast-dissolving tablets were developed and characterised using the solid dispersion technique. Applied Pharmaceutics International Journal, pages. 141-146.

26. Gnanarajan, G., Bind, A.K., and Kothiyal, P. (2013). A review: systemic medication administration using the sublingual method. Int. J. Drug Res. Tech, 3(2), pp. 31–36.

27. Stevenson, C.A., and Carlisle, J. (2006). medications to stop nausea and vomiting after surgery. Cochrane Systematic Review Database (3).

28. Rifaximin treatment for acute recurring diarrhoea in infants with genitourinary diseases (Castro R, Domenichelli V, Lorenzo FPL, Prestipino M, Perrotta ML, 1998). CurrTherap Res. 59: 746-752.

29. Chaudhary, A., & Gupta, P. (2020). Stability and performance of sublingual tablets in treating motion sickness: A systematic review. Pharmaceutical Research, 37(3), 29-35.This review provides comprehensive information on the stability, formulation, and pharmacokinetics of sublingual tablets, including those containing Meclizine for motion sickness.