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Optimization, Formulation and Evaluation of Captopril Sublingual Tablet by Direct Compression Method for the Management of Blood Pressure

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Abstract:

The purpose of this investigation was to formulate, develop and optimize of sublingual drug delivery for antihypertensive drug. Sublingual tablets of Captopril were formulated using mannitol (PVP K-30) as diluents. Sublingual tablet was prepared by direct compression technique as it is a cost-effective method. Sodium saccharin sweetening agent. Magnesium stearate (3% to 4%) as lubricants. Super disintegrants used are cross povidone, croscarmellose sodium, sodium starch glycollate sodium CMC as a disintegrant. The sublingual drug showed acceptable results in all studies such as thickness, strength, disintegration test time, surface pH and drug release are developed. Sublingual tablets of captopril can be successfully prepared by direct Compression method used using selected super disintegrants with Cross povidone 1.5%, 3%, 6%, Croscarmellose 1.5%, 3%, 6% and Sodium starch glycolate 1.5%, 3%, 6%, for the better patient compliance and effective therapy the relative efficiency of these super disintegrants to improve the disintegration and dissolution rate of tablets were found in order. The formulation F3 showed the fastest disintegration time of 43 seconds and drug release 99% in 10 minutes.

Keywords: Sublingual drug delivery, Antihypertensive drug, Captopril, Mannitol.

1. Introduction:

1. Sublingual tablet:

Captopril is a well-known angiotensin-converting enzyme (ACE) inhibitor that plays a crucial role in the management of cardiovascular disorders such as hypertension, congestive heart failure, and myocardial infarction. It works by inhibiting the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, thereby promoting vasodilation and reducing blood pressure. The development of sublingual tablets of captopril represents an important advancement in drug delivery systems, especially for conditions that require rapid onset of action. Sublingual administration involves placing the tablet under the tongue, where it dissolves quickly and allows the drug to be absorbed directly into the systemic circulation through the rich vascular network present in the sublingual mucosa. This route bypasses hepatic first-pass metabolism, thereby improving the bioavailability of the drug and ensuring faster therapeutic action. In emergency conditions such as hypertensive crisis, where immediate reduction in blood pressure is essential, captopril sublingual tablets offer a significant advantage over conventional oral dosage forms.

Additionally, this dosage form improves patient compliance, especially in individuals who have difficulty swallowing tablets. The formulation of sublingual tablets requires careful selection of excipients, particularly super disintegrants, to ensure rapid disintegration and dissolution in the limited volume of saliva present in the oral cavity. Overall, captopril sublingual tablets are an effective and innovative approach in modern pharmaceutics, combining rapid action with improved therapeutic efficiency. (1)

2. Advantages of Sublingual Drug Delivery System:

The sublingual drug delivery system has gained significant importance in recent years due to its unique advantages over traditional oral administration. One of the primary benefits of this route is the rapid onset of action, as the drug is directly absorbed into the bloodstream through the sublingual mucosa, which is highly vascularized. This is particularly beneficial in emergency situations such as hypertensive crisis or angina pectoris, where immediate therapeutic effect is required. Another major advantage is the avoidance of first-pass metabolism in the liver, which can significantly enhance the bioavailability of drugs like captopril that are otherwise extensively metabolized when administered orally. The sublingual route also provides a convenient and non-invasive method of drug administration, improving patient compliance, especially among geriatric and pediatric patients who may have difficulty swallowing conventional tablets. Furthermore, the formulation of sublingual tablets allows for precise dosing and easy administration without the need for water. The small size and fast disintegration properties of these tablets make them highly suitable for on-the-go use. However, the success of this drug delivery system depends on factors such as drug solubility, permeability, and stability in saliva. Despite certain limitations, the sublingual route remains a highly effective and efficient method for delivering drugs that require rapid onset and improved bioavailability. (2)

3. Formulation and Evaluation of Captopril Sublingual Tablets:

The formulation of captopril sublingual tablets involves the careful selection of both active pharmaceutical ingredients and excipients to ensure rapid disintegration, effective drug release, and stability. Super disintegrants such as crospovidone, croscarmellose sodium, and sodium starch glycolate are commonly used to facilitate quick breakdown of the tablet upon contact with saliva. Other excipients like fillers, binders, and lubricants are also included to enhance the physical properties and manufacturability of the tablet. The method of preparation may involve direct compression, which is preferred due to its simplicity and cost-effectiveness. Once formulated, the tablets must undergo a series of evaluation tests to ensure their quality and performance. These tests include weight variation, hardness, friability, disintegration time, wetting time, drug content uniformity, and dissolution studies. Disintegration time is particularly critical for sublingual tablets, as it directly influences the onset of action. The tablets should disintegrate within a few seconds to ensure rapid drug release. Stability studies are also conducted to assess the shelf life and storage conditions of the formulation. Overall, the formulation and evaluation process plays a vital role in ensuring that captopril sublingual tablets meet the required pharmaceutical standards and provide optimal therapeutic benefits. (3)

4. Mechanism of Action of Captopril:

Captopril works by inhibiting the angiotensin-converting enzyme (ACE), which is responsible for converting angiotensin I into angiotensin II, a powerful vasoconstrictor. By blocking this conversion,

captopril reduces the levels of angiotensin II in the body, leading to relaxation of blood vessels and decreased blood pressure. It also reduces aldosterone secretion, which decreases sodium and water retention, further lowering blood pressure. This mechanism helps in improving blood flow and reducing the workload on the heart. In sublingual form, this action occurs more rapidly because the drug directly enters systemic circulation without first-pass metabolism. This makes it highly effective in emergency conditions like hypertensive crises. Additionally, captopril increases bradykinin levels, which contributes to vasodilation but may also cause side effects such as dry cough. Overall, its mechanism is highly beneficial in managing cardiovascular conditions quickly and effectively. [4]

5. Indications and Uses of Captopril Sublingual Tablets:

Captopril sublingual tablets are mainly used in the treatment of hypertension, especially in emergency situations where rapid reduction of blood pressure is required. They are also used in the management of congestive heart failure and left ventricular dysfunction after myocardial infarction. The sublingual route is particularly useful when patients are unable to swallow oral tablets or when a fast therapeutic effect is needed. It may also be used in certain kidney disorders such as diabetic nephropathy to reduce proteinuria and protect renal function. Due to its quick onset, it is commonly used in hospital settings for immediate blood pressure control. However, its use should be carefully monitored by healthcare professionals to avoid excessive hypotension. The versatility of captopril makes it an important drug in cardiovascular therapy. [5]

6.Pharmacokinetics of Captopril:

The pharmacokinetics of captopril involve absorption, distribution, metabolism, and excretion processes. When administered sublingually, captopril is rapidly absorbed through the oral mucosa, leading to faster onset of action compared to oral tablets. The bioavailability is improved as it bypasses first-pass metabolism in the liver. Captopril is moderately bound to plasma proteins and is widely distributed in body tissues. It undergoes partial metabolism in the liver to inactive metabolites. The drug is primarily excreted through the kidneys, and its elimination half-life is relatively short, requiring multiple doses for sustained effect. Factors such as age, renal function, and disease conditions can influence its pharmacokinetics. Proper dose adjustment is necessary in patients with renal impairment to avoid drug accumulation and toxicity. [6]

7. Side Effects of Captopril:

Captopril, like other ACE inhibitors, may cause several side effects. The most common side effect is a persistent dry cough due to increased bradykinin levels. Other side effects include dizziness, hypotension, headache, and fatigue. Some patients may experience taste disturbances or a metallic taste, especially with sublingual administration. Serious adverse effects include angioedema, hyperkalemia, and renal impairment. Skin rashes and allergic reactions may also occur in some individuals. Long-term use requires monitoring of kidney function and electrolyte levels. Although most side effects are mild and manageable, careful supervision is necessary to ensure patient safety. Despite these effects, captopril remains widely used due to its effectiveness in treating hypertension and heart-related conditions. [7]

8. Stability and Storage Conditions:

Captopril is chemically unstable and sensitive to environmental factors such as moisture, heat, and oxygen. Therefore, special care must be taken during formulation and storage of sublingual tablets. The tablets should be stored in airtight containers, preferably with desiccants to prevent moisture absorption. Exposure to air can lead to oxidation, reducing the drug's potency. Proper packaging materials like aluminum foil strips are commonly used to enhance stability. Temperature control is also important, as high temperatures can accelerate degradation. Stability studies are conducted to determine shelf life and suitable storage conditions. Maintaining proper storage ensures that the drug remains effective and safe for use throughout its intended shelf life. [8]

9. Evaluation Parameters of Sublingual Tablets:

Evaluation of captopril sublingual tablets involves several quality control tests to ensure safety and efficacy. These include physical tests such as hardness, friability, and weight variation to check tablet strength and uniformity. Disintegration time is a critical parameter, as sublingual tablets must dissolve quickly in the mouth. Dissolution studies are performed to assess drug release rate. Content uniformity ensures that each tablet contains the correct amount of drug. Additional tests like wetting time and in-vitro dispersion time are also conducted. Stability testing is performed under different environmental conditions. These evaluation parameters help ensure that the final product meets pharmacopoeial standards and provides the desired therapeutic effect. [9]

2. Material and Methods:

Materials:

Captopril was obtained from Dham Tec Pharma & Consultants, Mumbai. Crospovidone, Croscarmellose sodium, Sodium starch glycolate were purchased from Sun Pharma, Mumbai. PVP K-30, Mannitol, Saccharin sodium, Magnesium stearate, were purchased from Madras Pharmaceutical, Mumbai. Tale was purchased from orchid Pharmaceutical, Chennai.

Methods:

Captopril sublingual tablets were prepared by the direct compression method as per the standardized procedure.

Table 6.1: List of materials and their suppliers

S.NO	MATERIALS	MANUFACTURING INDUSTRY
1	Captopril	Dhamtec pharma amp consultants,

2	Sodium starch glycollate	Sun pharma, Mumbai.
3	Crospovidone	Sun pharma, Mumbai.
4	Croscarmellose sodium	Sun pharma, Mumbai.
5	Magnesium stearate	Madras pharmaceutical, Mumbai.
6	PvP K 30	Madras pharmaceutical, Mumbai.
7	Saccharin sodium	Madras pharmaceutical, Mumbai.
8	Mannitol	Madras pharmaceutical, Mumbai.
9	Talc	Orchid pharmaceutical, Chennai.

Preparation Of Stock Solution With Ph 6.8 Phosphate Buffer:

A standard stock solution of Captopril (1 mg/mL) was prepared by dissolving accurately weighed 100 mg of the drug in a 100 mL volumetric flask using phosphate buffer (pH 6.8), and the volume was made

up to the mark with the same buffer to obtain a concentration of 1000 µg /mL (Stock 1). From this stock solution, 1 mL was further diluted to 100 mL with phosphate buffer (pH 6.8) to get a working standard solution of 10 µg/ml. The resulting solution was scanned in the UV range of 200–400 nm using phosphate buffer (pH 6.8) as a blank in a Shimadzu UV-1700 spectrophotometer. The wavelength of maximum absorption (λ_{max}) was found to be 217 nm.

λ_{max}:

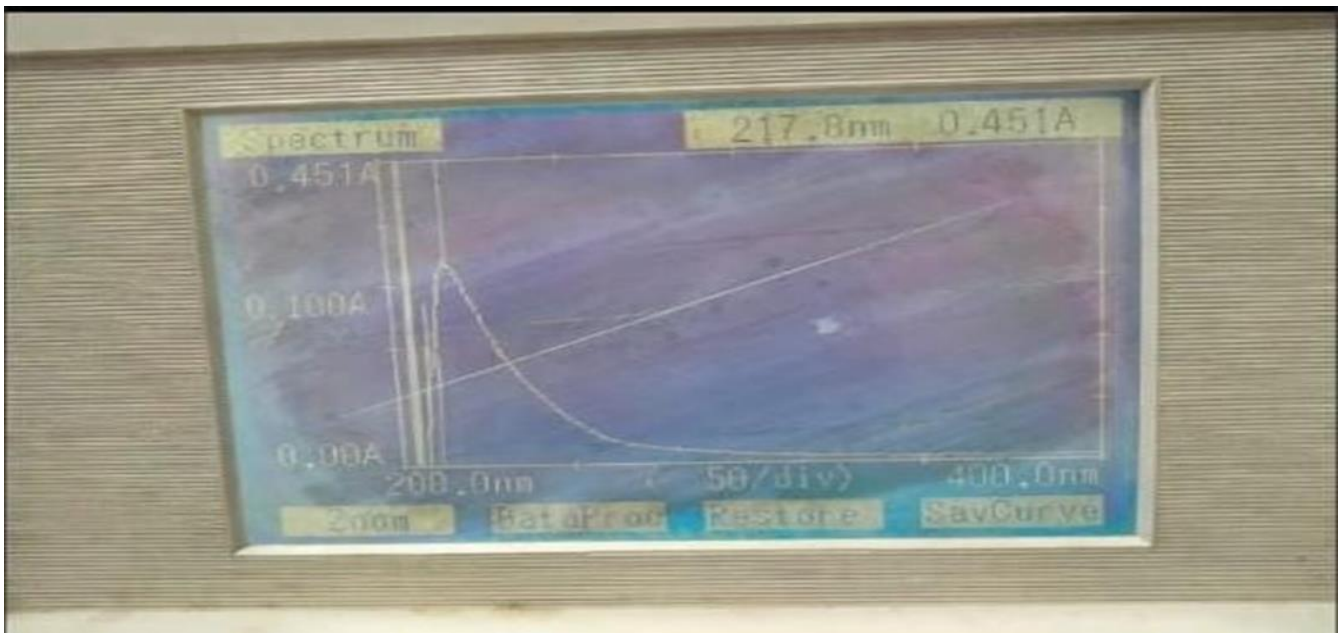
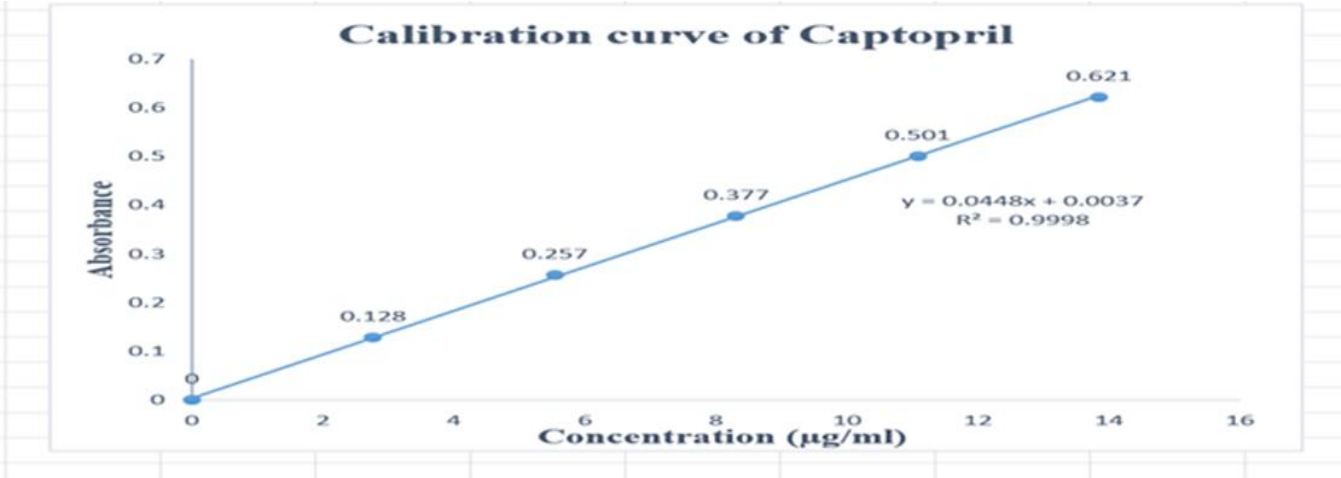


Figure 1: UV-Visible spectrum of Captopril ($\lambda_{max\ of}$=217 nm).

Preparation of Calibration Curve:

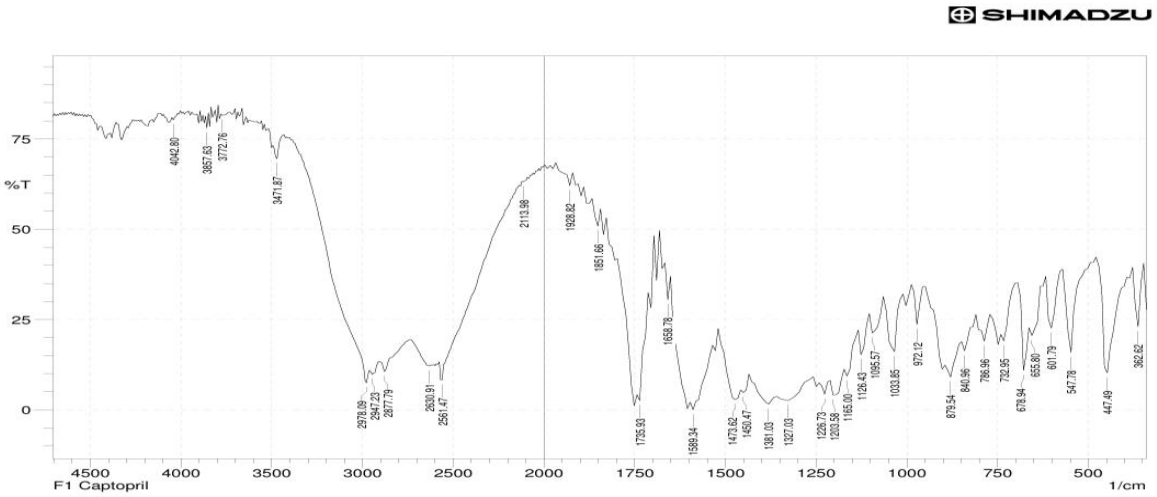
Aliquots of 2 mL, 4 mL, 6 mL, 8 mL, and 10 mL from the stock solution were transferred into a series of 10 mL volumetric flasks. The volume was adjusted up to the mark with phosphate buffer (pH 6.8) to obtain final concentrations of 2, 4, 6, 8, and 10 µg/mL, respectively. The absorbance of each resulting solution was measured at 217 nm (λ_{max}) using a UV-Visible spectrophotometer. All measurements were performed in triplicate (n=3). A standard calibration curve was plotted between concentration and absorbance, from which the regression equation and the coefficient of determination (R^2) were calculated.



Graph 1: Calibration curve of captopril.

Ftir Studies:

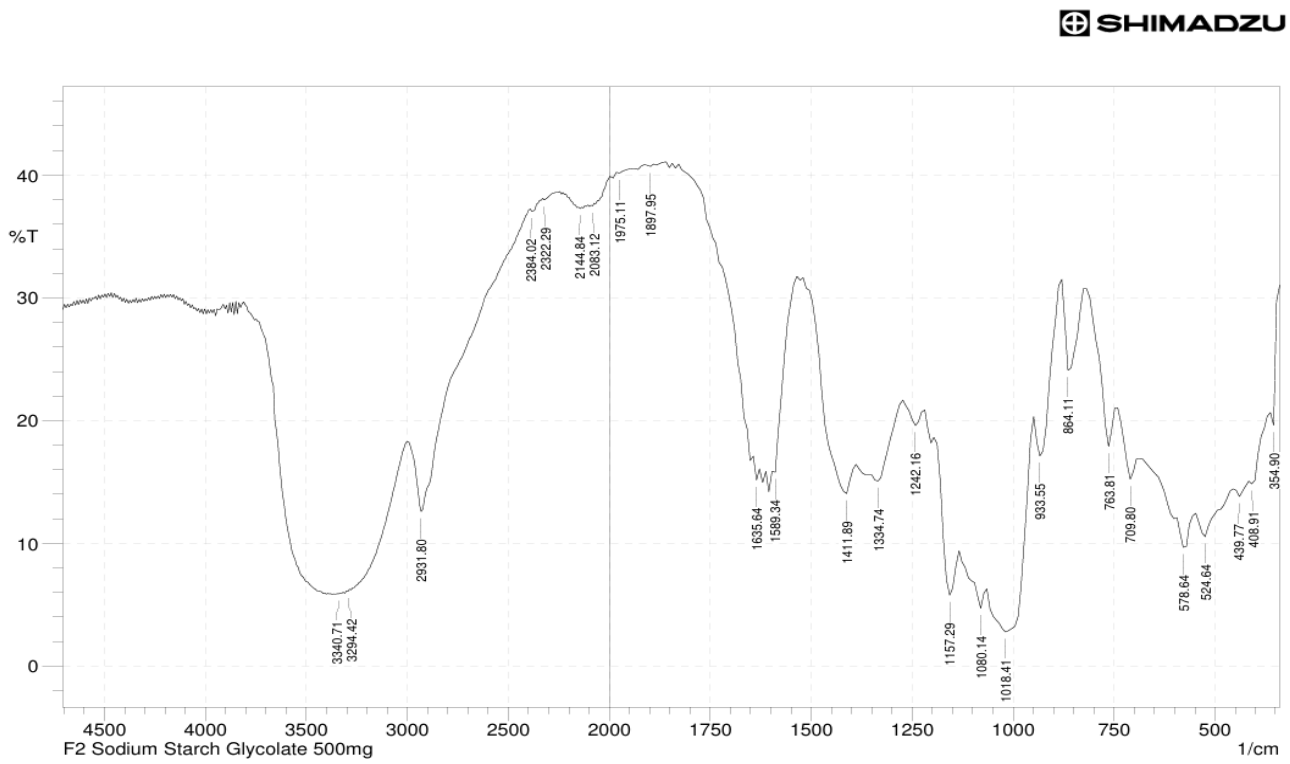
The IR absorption spectra of the captopril drug and with different super disintegrants, were taken in the range of 4000-450 cm^{-1} using KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powdered and dried potassium bromide. These quantities are usually sufficient to give a disc of 10-15 mm diameter and pellet of suitable intensity by a hydraulic press. The scans were evaluated for presence of principal peaks of drug, shifting and masking of super disintegrants. Drug peaks were evaluated for any significant shifts or changes due to the presence of super disintegrants.



Graph 2: FTIR spectrum of Captopril.

Characteristic frequencies (Interpretation) in IR spectrum of captopril.

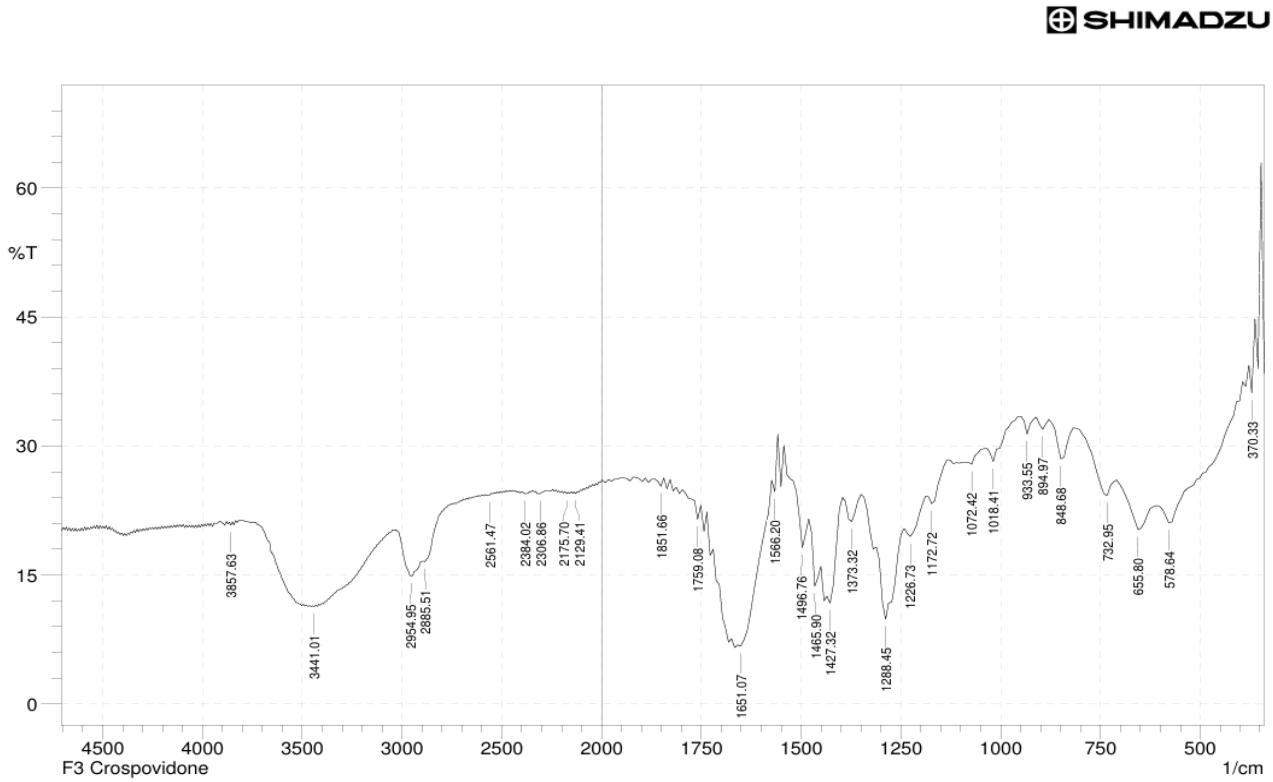
Wave no.(cm^{-1})	Inference
2978.09	SH
1658.78	C=O
3471.87	O-H
1327.03	C-N
3471.87	N-H
1381.03	$-CH_3$
1450.47	$-CH_2$



Graph 3: FTIR spectrum of Sodium starch glycolate.

Wave number	Functional group
1080.14	C-O
1635.64	C=O
3294.42	O-H
933.55	C-C
1157.29	C-O-C

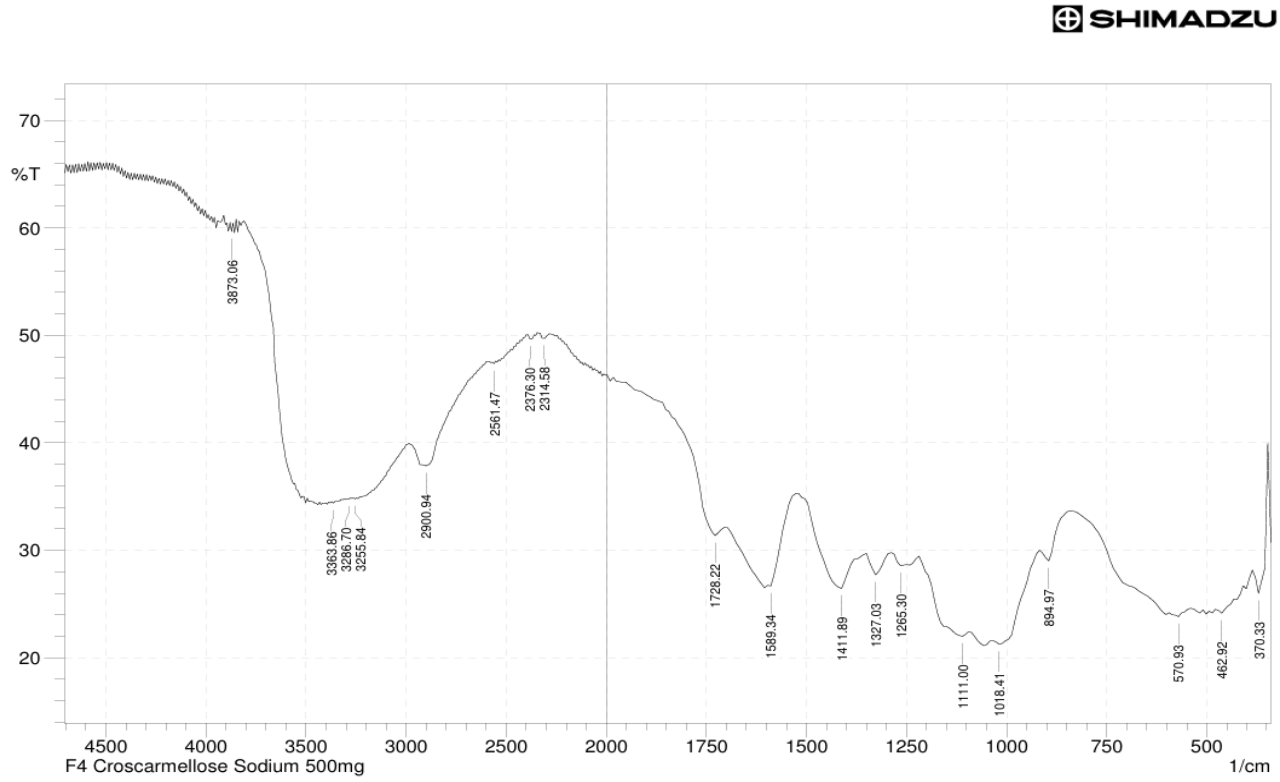
2931.80	C-H



Graph 4: FTIR spectrum of Crospovidone.

Wavenumber	Functional group
1651.07	C=O
1288.45	C-N
2954.95	C-H
848.68	C-C

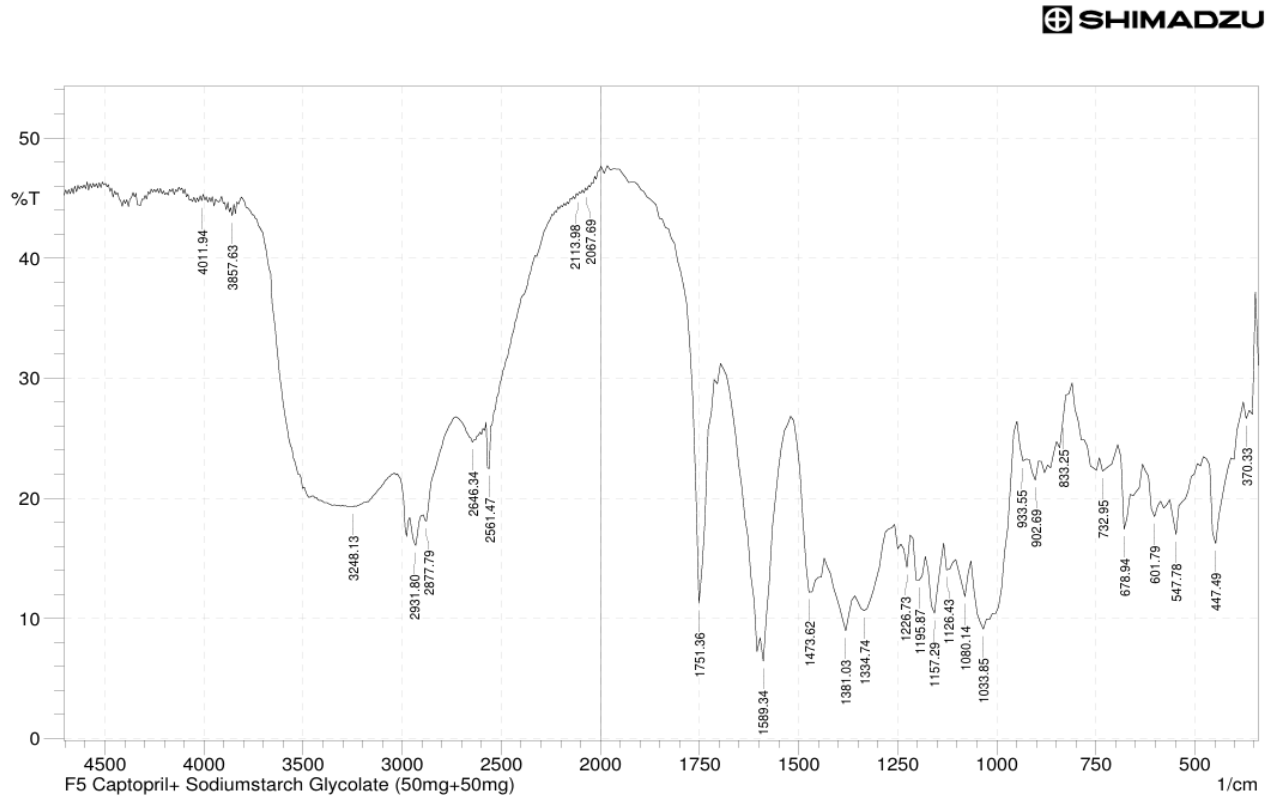
3441.01	O-H



Graph 5: FTIR spectrum of Croscarmellose Sodium.

Wave number	Functional group
1728.22	C=O
1018.41	C-O
3363.86	OH
2900.94	C-H
1111.00	C-O-C

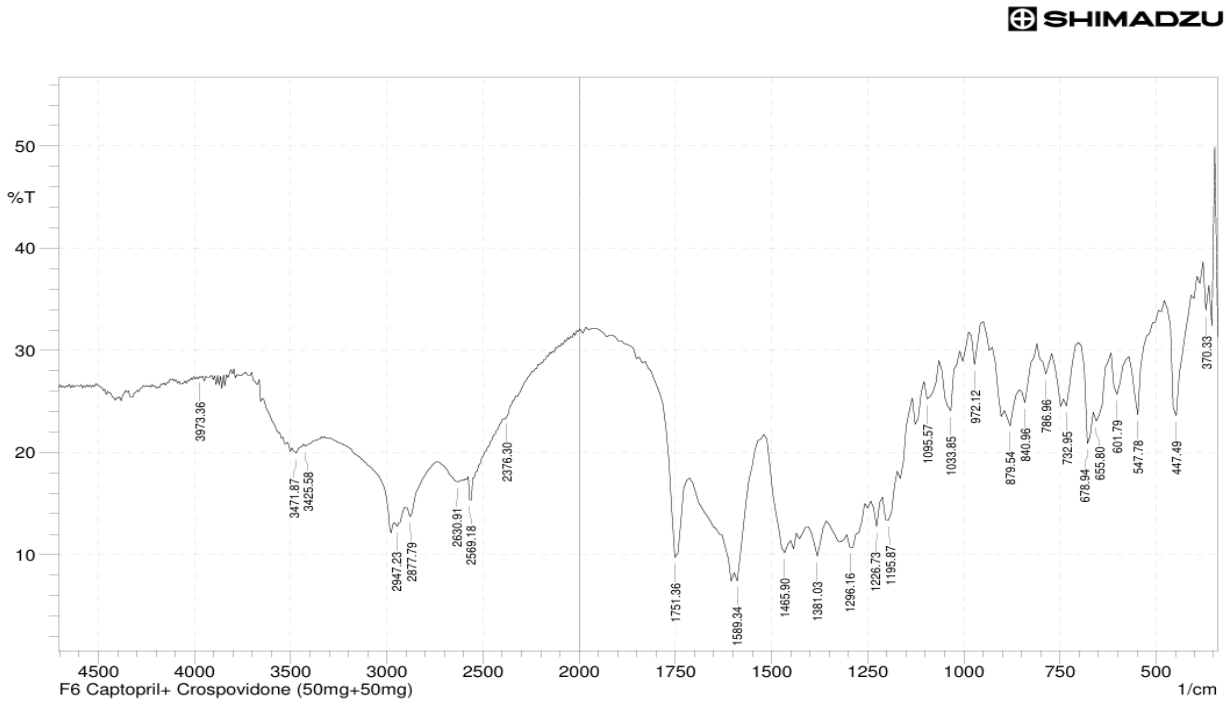
894.97	C-C



Graph 6: FTIR spectrum of Captopril +Sodium starch glycolate.

Wavenumber	Functional group
1751.36	C=O
2561.47	SH
3248.13	O-H
1334.74	C-N
1381.03	CH_3
902.69	C-C
2931.80	C-H

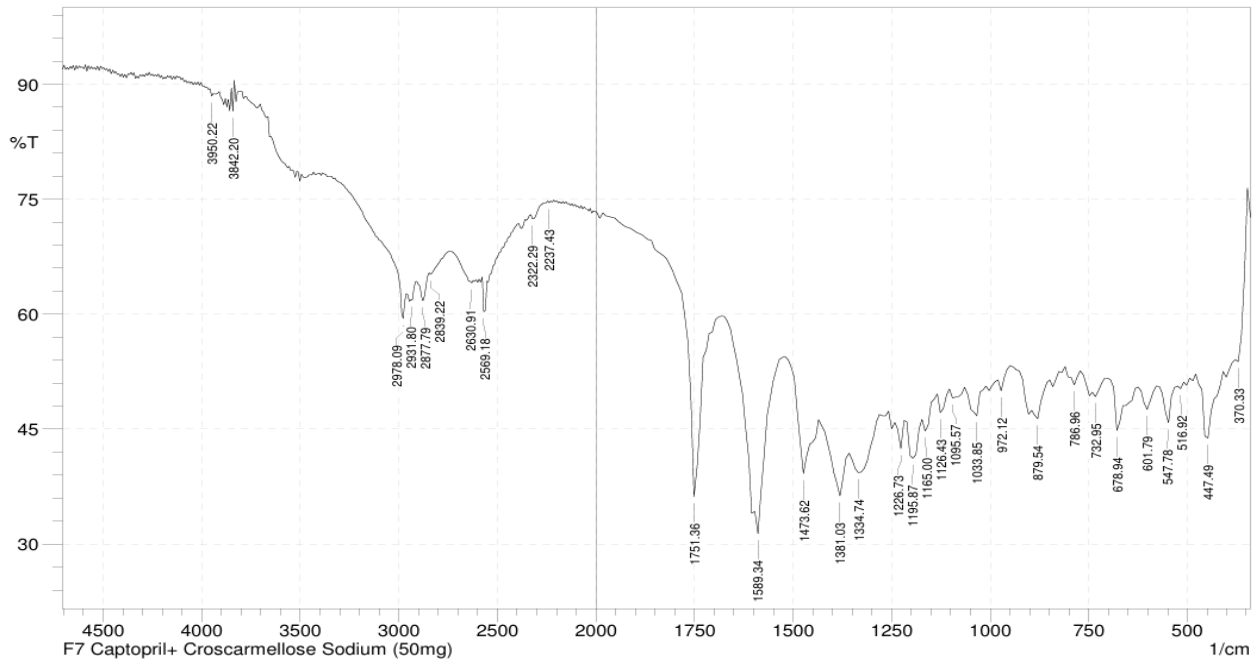
1157.29	C-O-C
3248.13	N-H



Graph 7: FTIR spectrum of Captopril+Crospovidone.

Wavenumber	Functional group
1751.36	C=O
3471.87	O-H
1296.16	C-N
3471.87	N-H
2877.79	C-H

878.94	C-C
1381.03	CH_3



Graph 8: FTIR spectrum of Captopril+Croscarmellose Sodium.

Wavenumber	Functional group
1751.36	C=O
2569.18	O-H
1334.74	C-N
3842.20	N-H
1195.87	C-O
879.54	C-C

2978.09	C-H
1165.00	C-O-C
1381.03	CH_3

Table2: Evaluation of powder blends of captopril

Formulation code	Bulk density (g/mL)	Tapped density(g/mL)	Angle of repose (Ɵ)	Carr's index (%)	Hausner' ratio
F1	0.50±0.0053	0.606±0.0058	21.8±0.9	17.5±0.9	1.21±0.012
F2	0.49±0.0058	0.598±0.006	23.9±1.1	18.1±1.1	1.22±0.006
F3	0.48±0.0053	0.598±0.0058	26.6±1.2	18.6±1.1	1.23±0.006
F4	0.51±0.0058	0.610±0.0058	23.5±0.12	16.4±0.12	1.20±0.005
F5	0.50±0.0058	0.608±0.0012	33.7±1.2	17.5±0.90	1.21±0.012
F6	0.48±0.000	0.560±0.010	35.5±1.2	10.7±0.72	1.12±0.008
F7	0.50±0.0058	0.530±0.0058	37.6±1.2	9.4±0.12	1.10±0.0058
F8	0.44±0.0058	0.506±0.0058	22.6±1.2	12±0.12	1.14±0.006
F9	0.58±0.006	0.606±0.0012	22.6±1.1	17.5±0.9	1.21±0.012

All vales are expressed as mean±SE, n=3

1. Angle of Repose:

The Angle of repose of various powder mixed blends, prepared with different super disintegrants, was measured by funnel method. Angle of repose was found in the range 21.8±0.9-37.6±1.2. The good flow ability of powder blend was also evidence with angle of repose.

2. Bulk density:

The bulk density of various powder mixed blends prepared with different super disintegrants was measured by graduated cylinder. The bulk density was found in the range0.44±0.0058-0.58±0.006 g/mL.

3. Tapped Density:

The Tapped density of various powder mixed blends prepared with different super disintegrants was measured by using measuring cylinder. The tapped density was found in the range0.506±0.0058-0.610±0.0058g/mL values indicate good packing characteristics and the powder was not bulky.

4. Compressibility Index:

The Compressibility index of various powder mixed blends, prepared with different super disintegrants, using bulk density and tapped density data, compressibility index was calculated. It was found in the range9.4±0.12- 18.6±1.1. This indicates good flow properties.

5. Hausner's ratio:

The Hausner's ratio of various powder mixed blends, prepared with different super disintegrants, it is calculated by using bulk density and tapped density data. It was found in the range of 1.10±0.0058-1.23±0.006 reveals good flow properties (<1.25).

Table3: Formulated Composition of different Batches of sublingual tablet

s.no.	Ingredients(mg/tab)	Formulation code								
		F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9(mg)
1	Captopril	25	25	25	25	25	25	25	25	25
2	Crospovidone	3	6	9	_	_	_	_	_	_
3	Croscarmellose sodium	_	_	_	3	6	9	_	_	_
4	Sodium starch glycolate	_	_	_	_	_	_	3	6	9
5	Mannitol	67	64	61	67	64	61	67	64	61
6	Magnesium stearate	1	1	1	1	1	1	1	1	1
7	Pvp k30	2	2	2	2	2	2	2	2	2
8	Saccharin sodium	1	1	1	1	1	1	1	1	1
9	Talc	1	1	1	1	1	1	1	1	1

10	Total	100	100	100	100	100	100	100	100	100

3. RESULT AND DISCUSSION:

Table4: Evaluation of captopril tablets.

Formulation code	Dimension		Hardness(kg/cm^2)	Friability (%)	Drug content(%W/W)	Weight variation
	Thickness (mm)	Diameter(mm)				
F1	2.60±0.02	7.36±0.03	2.26±0.04	0.79±0.01	95.44±0.52	102±1.2
F2	2.50±0.03	7.26±0.02	2.36±0.03	0.8±0.02	102.79±0.65	101±0.8
F3	2.70±0.04	7.26±0.02	2.26±0.05	0.9±0.01	96.91±0.48	103±1.5
F4	2.60±0.02	7.25±0.03	2.35±0.02	0.9±0.02	99.12±0.72	102±1.1
F5	2.70±0.03	7.24±0.04	2.40±0.04	0.8±0.01	101.52±0.55	98±0.9
F6	2.60±0.02	7.26±0.02	2.40±0.04	0.9±0.02	103.52±0.82	97±1.3
F7	2.50±0.04	7.36±0.03	2.40±0.05	0.8±0.01	98.68±0.44	97±0.7
F8	2.70±0.04	7.26±0.02	2.26±0.02	0.9±0.02	101.03±0.58	104±1.4
F9	2.60±0.03	7.46±0.03	2.36±0.04	0.9±0.01	102.06±0.61	102±0.9

1. Dimension (Thickness and Diameter):

Tablets were evaluated by using Vernier caliper. Excessive variation in the tablet thickness and diameter can result in problems with packaging as well as consumer acceptance. There were no marked variations in the thickness and diameter of tablets within each formulation indicating uniform die fill throughout the compression process.

The size (diameter) of the tablets of all formulations was found to be2.50±0.03-2.70±0.04 mm and thickness of the tablets was found in the range7.24±0.04-7.46±0.03 mm.

2. Weight variation:

Tablets were prepared using direct compression technique. Since the material was free flowing, tablets were obtained of uniform weight due to uniform die fill. Tablets were obtained in the range with acceptable weight variations as per Pharmacopoeia specifications, less than 7.5.

3. Hardness:

Tablets were evaluated by using Monsanto Hardness tester. Hardness of the tablets was in the range 2.26±0.02- 2.40±0.05 Uniform hardness was obtained due to equal compression force. The obtained hardness range showed good mechanical strength with an ability to withstand physical and mechanical stress conditions.

4. Friability:

Tablets were evaluated by using Roche Friabilator and friability of tablets was observed in acceptable range. 0.79±0.01-0.9±0.02 %) This indicated a good mechanical resistance of the prepared mouth dissolving tablets.

5. Drug content of captopril.

Tablets were evaluated by using assay method. The drug content was obtained in the acceptable limit. The drug content was found in the range 95.44±0.52-103.52±0.82%w/w. (e.g. 99-101% w/w). The found range was within the specified limit as per Indian Pharmacopoeia 2007.

4. Invitro Disintegration Time:

Disintegration times for sublingual tablets were determined using USP tablet disintegration apparatus with saline phosphate buffer of pH 6.8 as medium. Maintained the medium temp at 37±2ºC. The time in seconds taken **or** complete disintegration of the tablets with no palatable mass remaining in the apparatus was recorded.

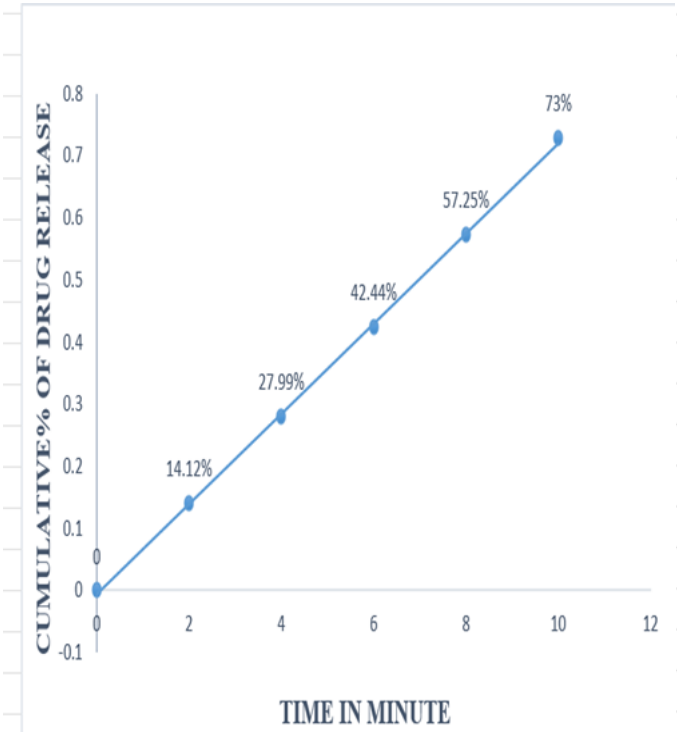
Table 5: Wetting time and water absorption ratio of Captopril sublingual tablets.

Formulation Code	Wetting Time (Sec)	Water Absorption Ratio (%)
F1	28±1.52	72.45±2.10
F2	24±1.00	80.32±1.85
F3	12±1.41	118.50±2.66
F4	35±2.08	68.10±3.20
F5	27±1.73	82.44±2.96
F6	21±1.15	90.66±1.41
F7	25±2.00	78.24±2.02
F8	18±1.41	104.80±3.10
F9	14±1.00	73.56±4.25

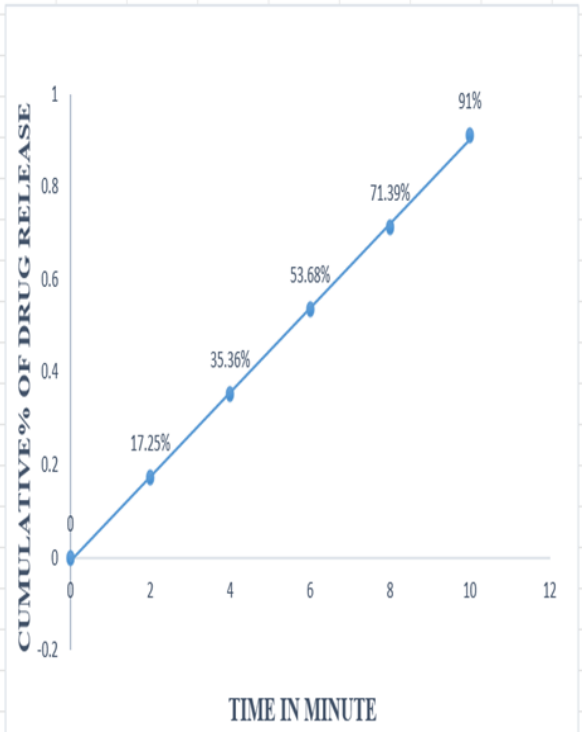
NOTE: Each value represents Mean standard Deviation (n=3).

IN VITRO DISSOLUTION STUDIES:

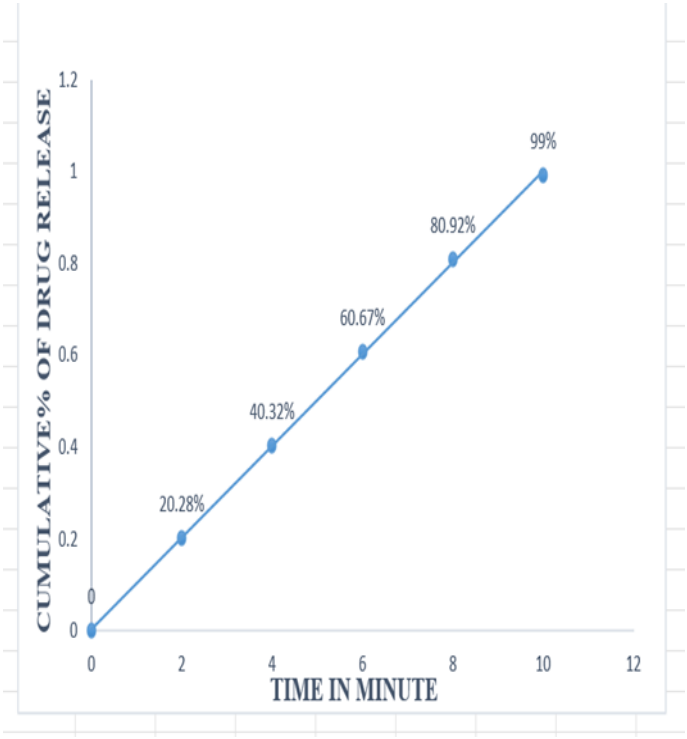
Dissolution of the tablet of each batch was carried out using USP XXIII dissolution type II apparatus (ELECTRO LAB) using paddles at 50 rpm. As per the official recommendation of IP 900 ml of 6.8 pH phosphate buffer was used as the dissolution medium and the temperature of the medium was set at 37 ± 0.5ºC. 5 ml of sample was withdrawn at predetermined time interval of 2, 4, 6, 8 and 10 min. The same volume of fresh medium was replaced. The withdrawn samples were analyzed by an UV spectrophotometer at 217 nm using buffer solution as blank solution.



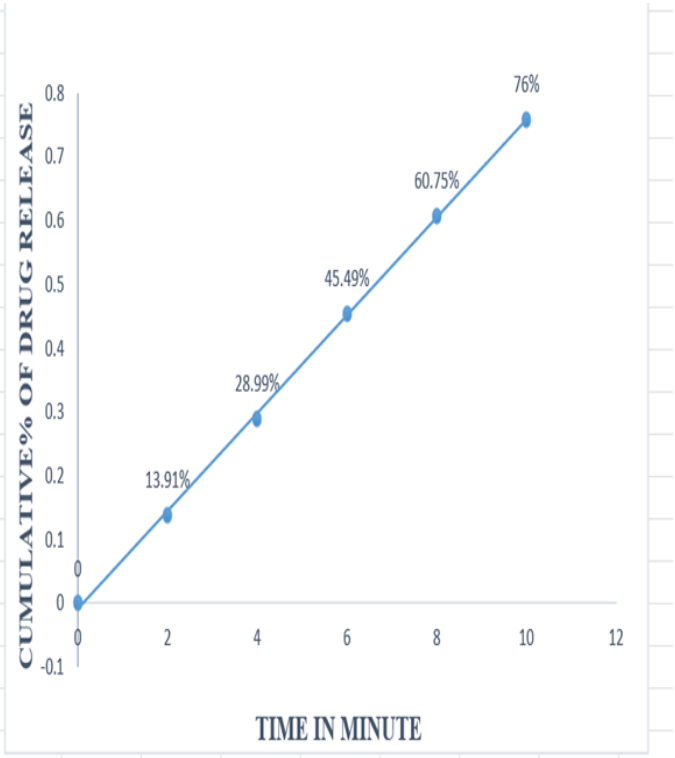
Graph 9: Dissolution profile of Formulation F1.



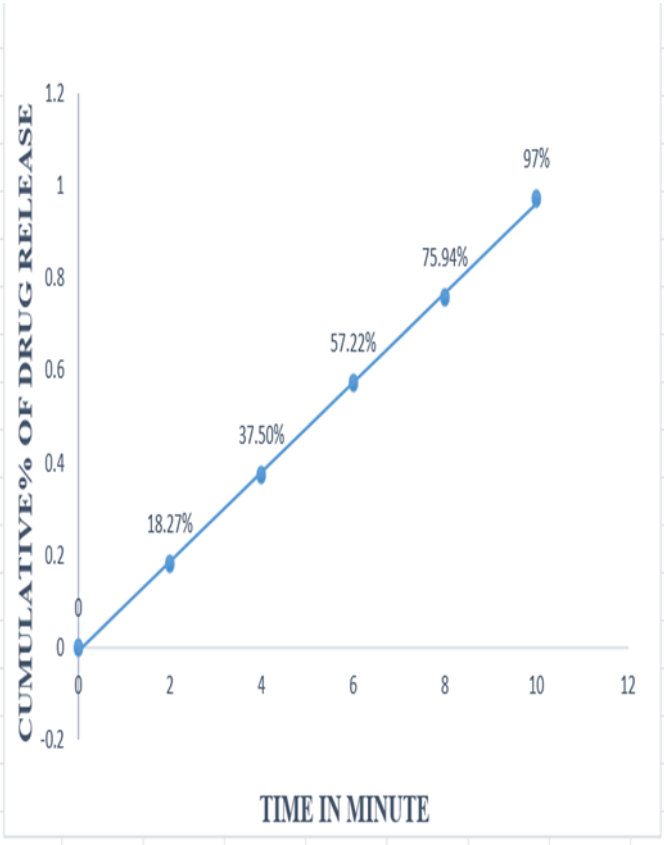
Graph 10: Dissolution profile Formulation F2.



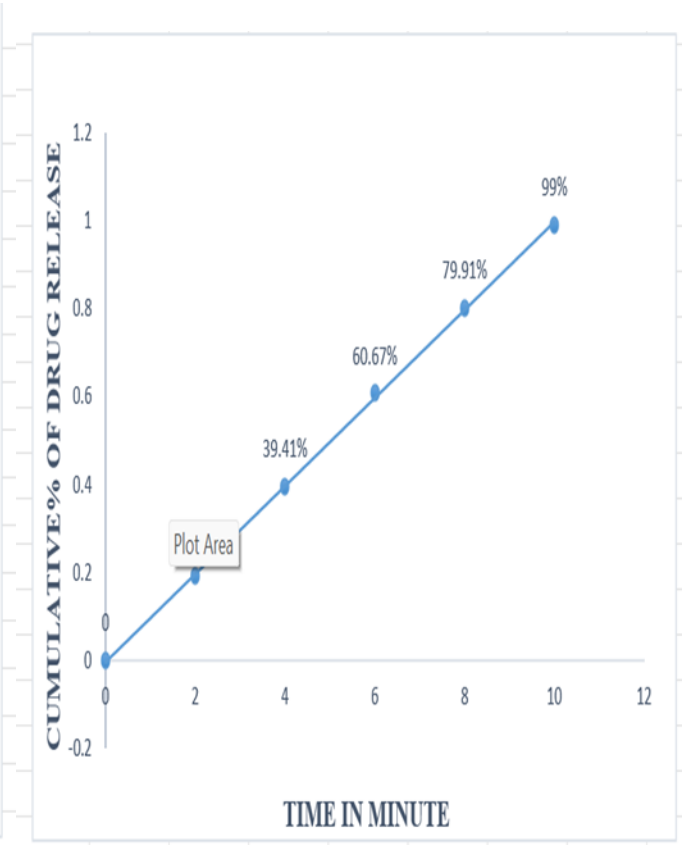
Graph 11: Dissolution profile of Formulation F3.



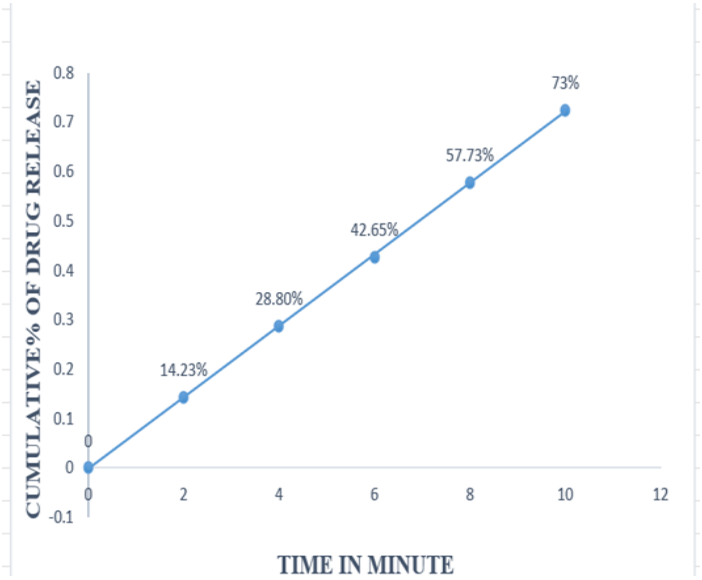
Graph 12: Dissolution profile of Formulation F4.



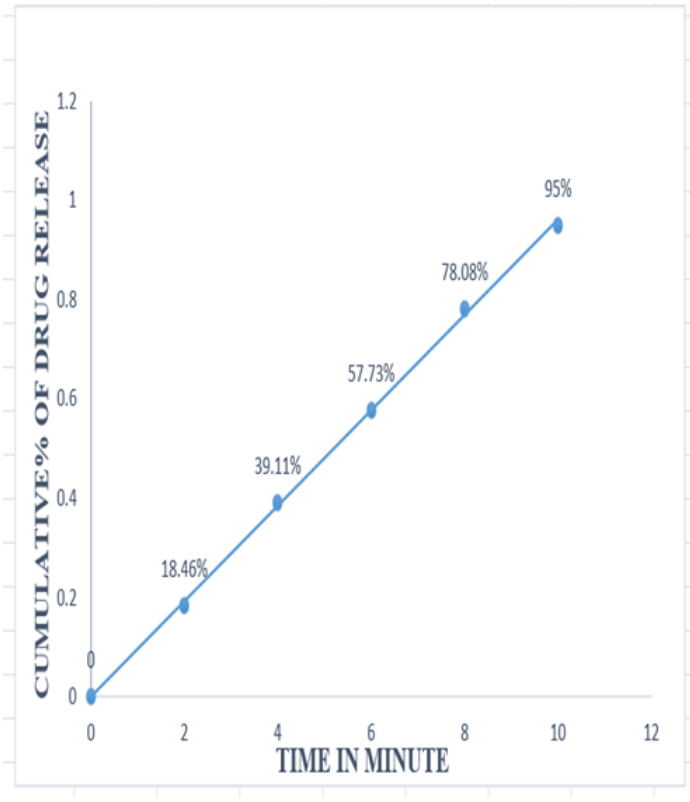
Graph 13: Dissolution profile of Formulation F5.



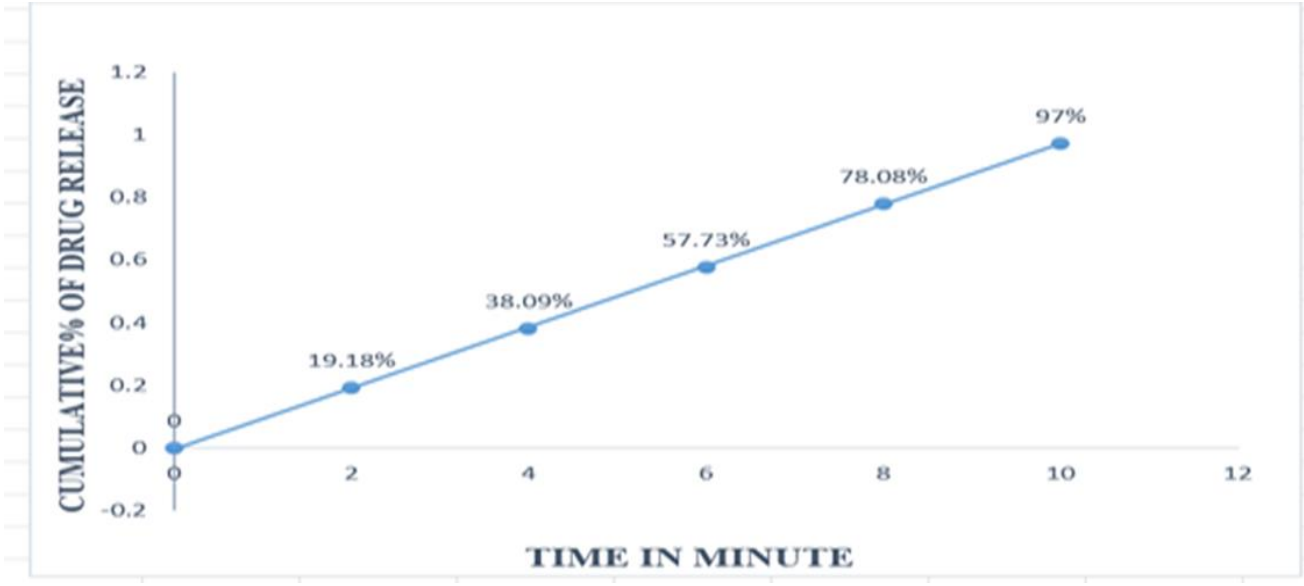
Graph 14: Dissolution profile of Formulation F6.



Graph 15: Dissolution profile of Formulation F7.



Graph 16: Dissolution profile of Formulation F8.



Graph 17: Dissolution profile of Formulation F9.

5. Conclusion:

The present study successfully formulated and evaluated sublingual tablets of captopril with the aim of achieving rapid onset of action and improved patient compliance. Various formulations were prepared using suitable super disintegrants, and all the preformulation and post-compression parameters were found

to be within acceptable limits. The optimized formulation exhibited satisfactory hardness, minimal friability, and rapid disintegration time, which are essential for sublingual drug delivery.

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This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement:

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration:

This research does not involve any clinical trials.

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Not applicable.

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