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Research Article

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Formulation and optimization of sublingual tablet of Ramipril

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ABSTRACT

Tablets are most popular dosage form in India. Sublingual tablets are designed with the aim to provide fastest action. Sublingual route is most popular due to better patient compliance, and unit dose. The sublingual tablets of ramipril are most effective against hypertension and provide rapid onset of action with rapid drug release. The sublingual tablet of ramipril avoids first pass effects of the drug and thus provide complete utilization of the drug. In the present investigation the sublingual tablets of ramipril was prepared by direct compression method. The sublingual tablet SLT9 is found as best tablet, It provide maximum drug release (98.01%)

Key words: Sublingual, Hypertension, SLT, B.P etc.

INTRODUCTION

Blood pressure is the force of our blood against the walls of our blood vessels as our heart pumps blood around our body. If this pressure becomes too high, we are said to have high blood pressure, or hypertension. High blood pressure usually causes no symptoms. That is called a “silent killer.” The top number, or systolic blood pressure, is the pressure when heart is beating. The bottom number, or diastolic blood pressure, is the pressure when heart is resting between beats.

Ramipril is an antihypertensive drug. Ramipril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor class of medications. It is metabolized to ramiprilat in the liver and, to a lesser extent, kidneys. Ramiprilat is a potent, competitive inhibitor of ACE, the enzyme responsible for the conversion of angiotensin I (AT I) to angiotensin II (AT II). AT II regulates blood pressure and is a key component of the renin-angiotensin-aldosterone system (RAAS). Ramipril may be used in the treatment of hypertension, congestive heart failure, nephropathy, and to reduce the rate of death, myocardial infarction and stroke in individuals at high risk of cardiovascular events. In case of hypertension immediate treatment is required so the proposed investigation is totally based to provide the suitable treatment for hypertension. The sublingual tablet of ramipril was prepared by using a number of superdisintegrants which provide rapid release of the drug and make effective therapeutic treatment. Ramipril is basically ACE inhibitor and does not produce any side effect and the bioavailability of ramipril is also increased when it is given in sublingual form. The first pass effect of ramipril is also eliminated and this may provide complete utilization of the drug.[1,2,3]

ANALYSIS OF DRUG

U. V. Analysis

1. Ultraviolet absorption

Ultraviolet spectroscopy analysis of the drug was carried out for wavelength maxima and absorbance determination and calibration of standard curve of the drug. It is performed by preparing various conc. of solution of drug and run the spectroscopy in the range of 200 to 400 nm to obtained the absorbance for their relative concentration.

Preparation of stock solution

10 mg of Ramipril was weighed accurately and dissolved 5ml 0.1N HCL in a 100 ml of volumetric flask and volume was made up to with the Sorenson's buffer pH 6.8. Two ml of this solution was diluted to 10 ml with pH 6.8 Sorenson's buffer to obtain a stock solution of 20ug/ml.

From this stock solution, aliquots of 1ml, 2ml, 3ml, 4ml……10ml were transferred to 10 ml volumetric flasks and volume was made up to 10ml Sorenson's buffer pH 6.8. The absorbances of these solutions were measured at 240 nm against a blank Sorenson's buffer pH 6.8. The calibration curve was plotted between concentration and absorbance.

Table 1: Calibration curve for Ramipril in 0.1 N HCl

Sr. no.	Concentration (µg/ml)	Mean absorbance at 240nm
1	0	0
2	2	0.08
3	4	0.17
4	6	0.24
5	8	0.34
6	10	0.45
7	12	0.52
8	14	0.62
9	16	0.68
10	18	0.74
11	20	0.84
12	22	0.93
13	24	0.98

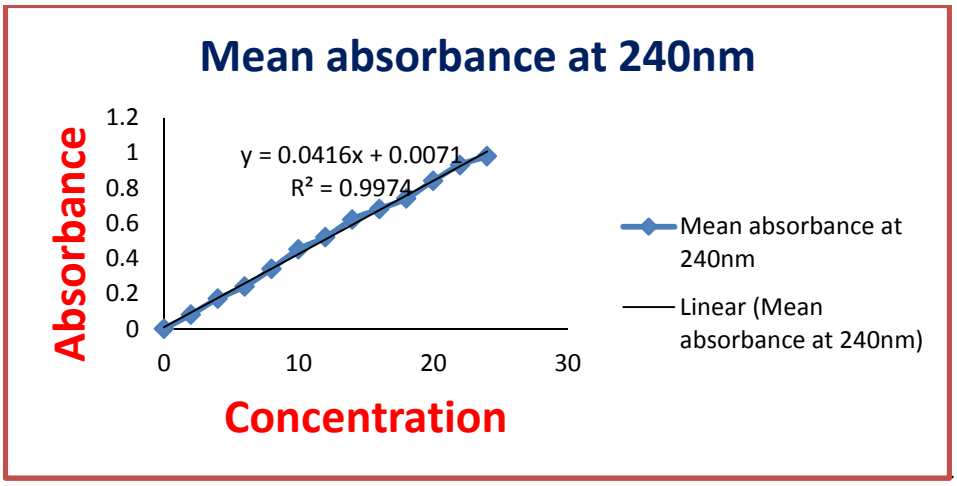

Figure:1 Calibration Curve of Ramipril

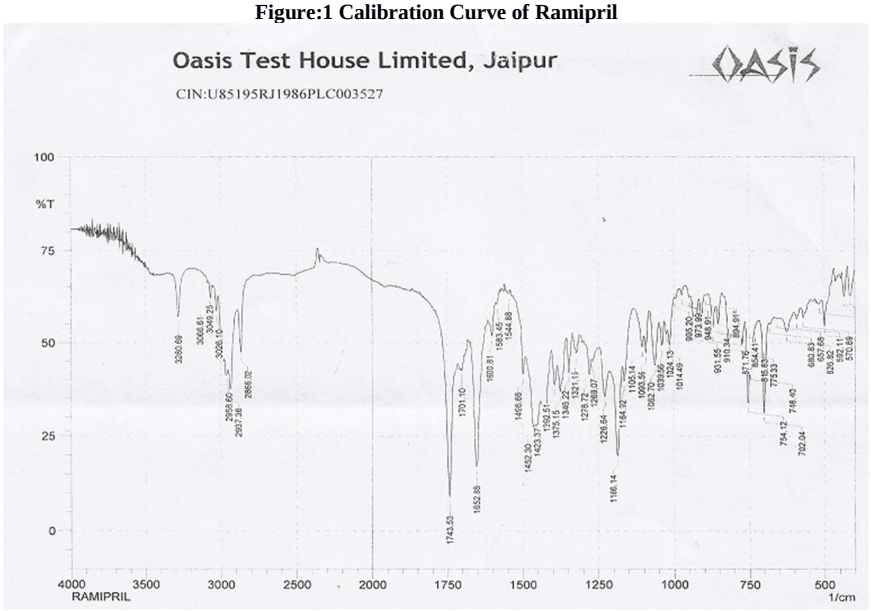

Figure 2: IR Spectra of Pure Ramipril

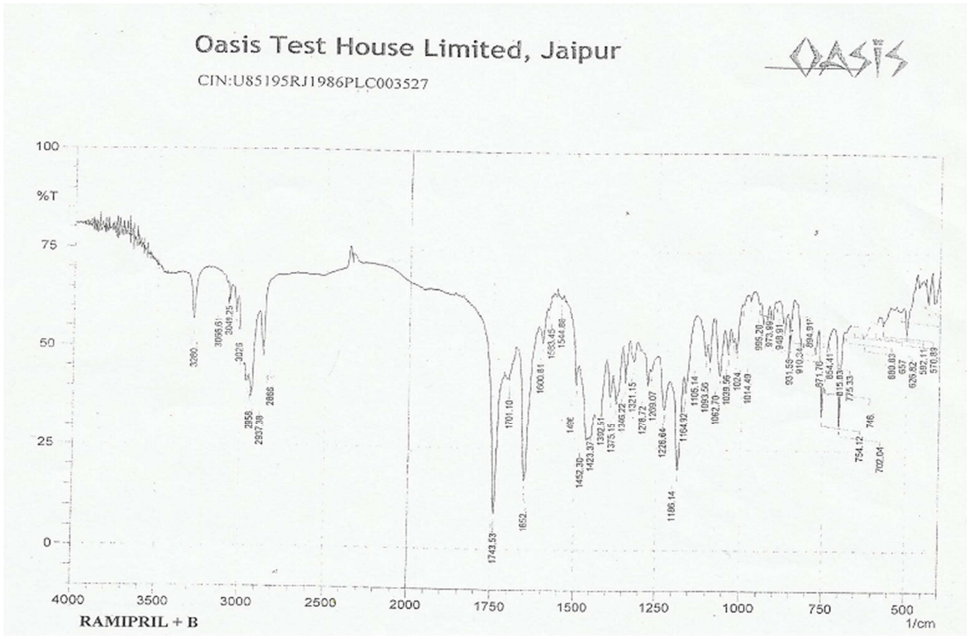

Figure 3: IR Spectra of Ramipril + Sodium Starch Glycolate

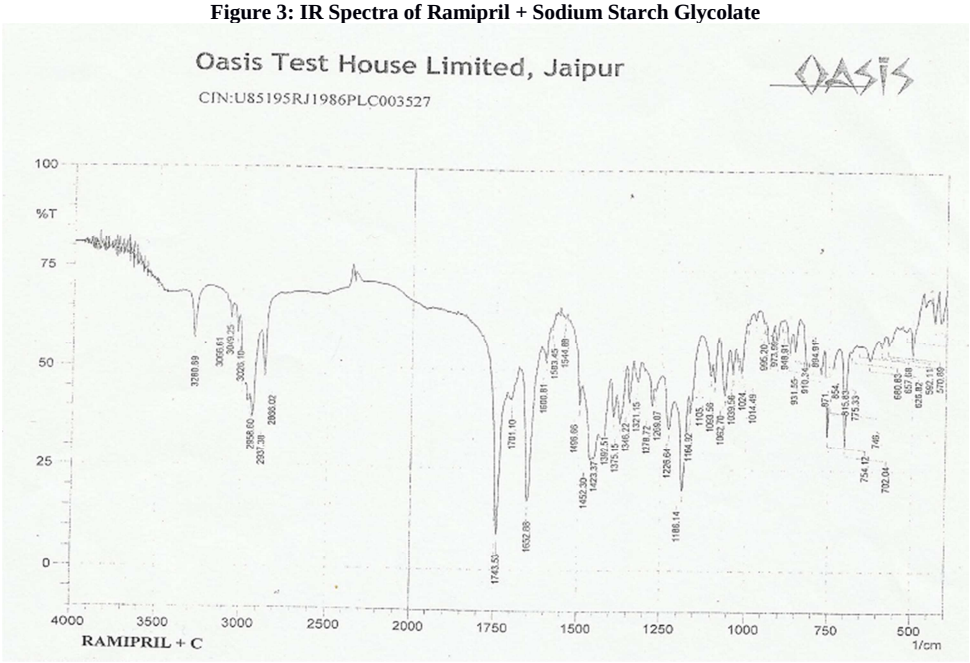

Figure 4: IR Spectra of Ramipril + Cross Carmelose Sodium

FT-IR

The identity of a compound was confirmed by comparison with that of an authentic sample and verification of the presence of functional groups in an unknown molecule was done by IR spectra**.** FT-IR study is used for polymer and Excipient compatibility. The IR spectra obtained was elucidated for important chromophore groups. The IR spectra showed peaks at 3280.69, 2958.60, 2866.02, 1743.53, 1652.88, 1452.30, 1346.22,1321.15 cm^{-1}.

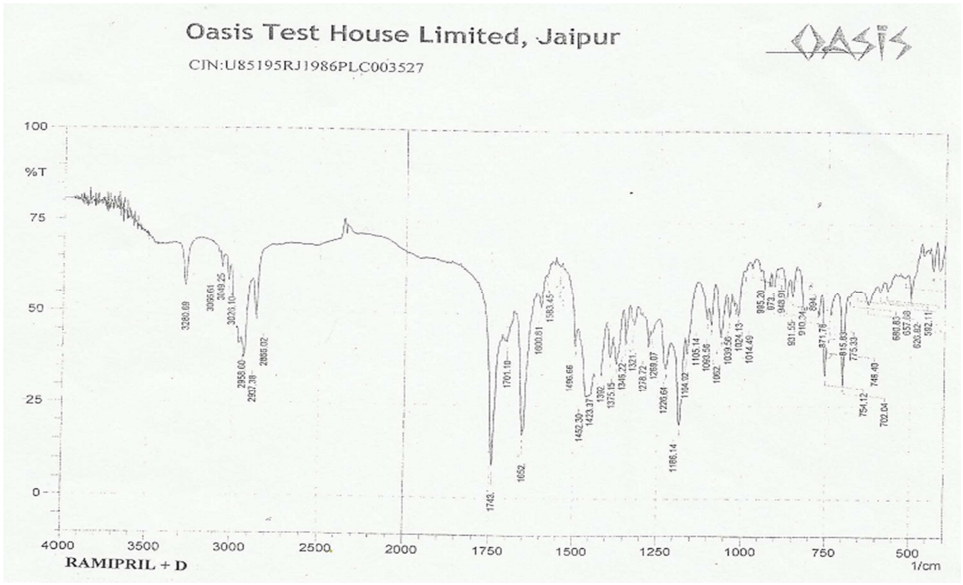

Figure 5: IR Spectra of Ramipril + Crospovidone

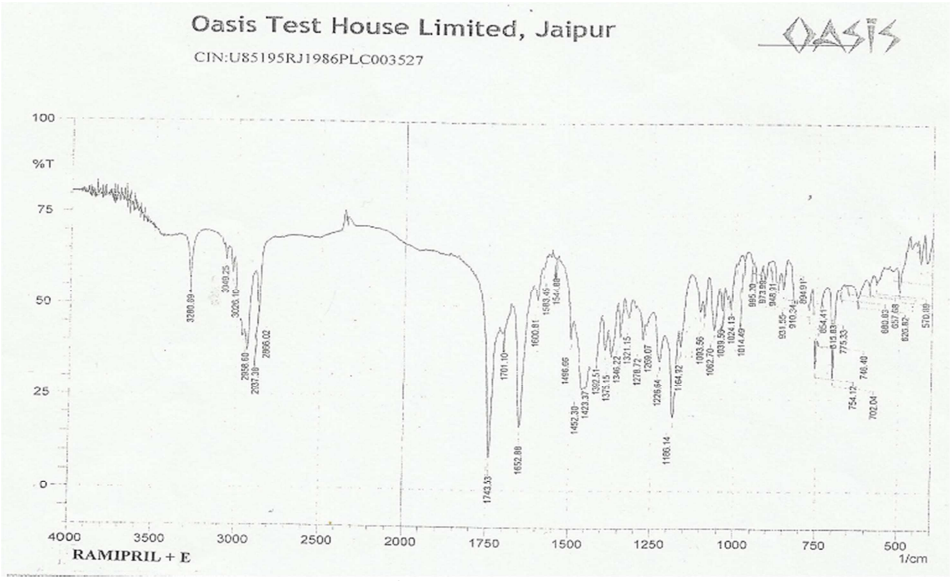

Figure 6: IR Spectra of Ramipril + Micro Crystalline Cellulose

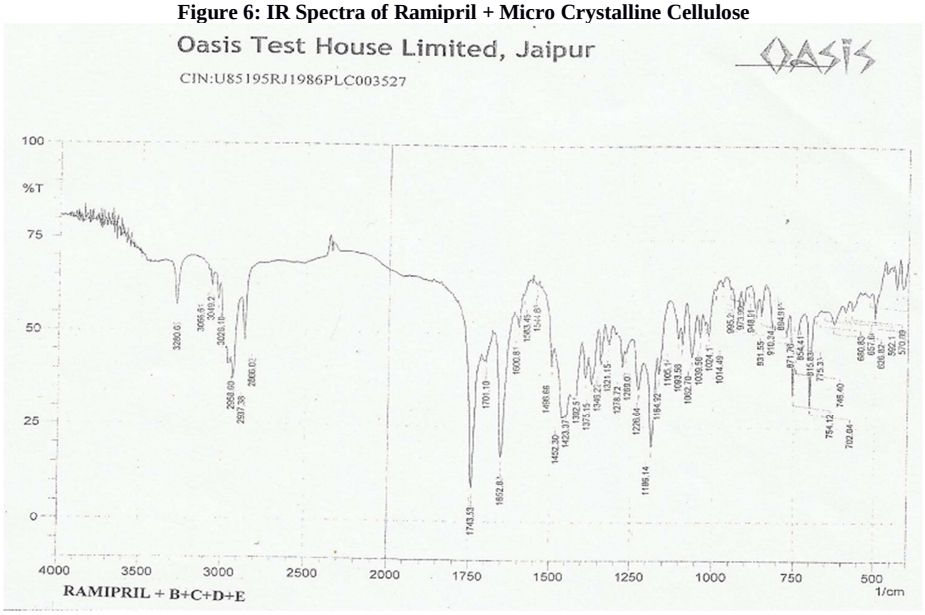

Figure 7: IR Spectra of Ramipril + Sodium Starch Glycolate+ Cross Carmelose Sodium + Crospovidone + Micro Crystalline Cellulose

EXPERIMENTAL SECTION

The drug Ramipril was obtained as a gift sample by Oasis Pharmaceuticals Pvt. Ltd., Jaipur, Sodium Starch Glycolate, Crospovidone, Croscarmellose Sodium and Mannitol was obtained by Signet Chemicals Pvt. Ltd., Mumbai and Microcrystalline Cellulose, Magnesium Stearate and Talc was available in college's practical lab.

Table 2: **Formula for different batches of Ramipril sublingual tablets**

INGREDIENTS	FORMULATIONS								
	SLT1	SLT2	SLT3	SLT4	SLT5	SLT6	SLT7	SLT8	SLT9
Ramipril	20	20	20	20	20	20	20	20	20
Sodium Starch Glycolate	2	3	4	-	-	-	-	-	-
Crospovidone	-	-	-	2	3	4	-	-	-
Croscarmellose sodium	-	-	-	-	-	-	2	3	4
Microcrystalline cellulose	20	30	40	20	30	40	20	30	40
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Mannitol +Sorbitol (Q.S)	103	92	81	103	92	81	103	92	81
Total weight	150	150	150	150	150	150	150	150	150

Preparation of Sublingual Tablets

Nine formulations were prepared which was shown in table. This formula was obtained by using 3 3 full factorial design. Excipients was used in different concentrations to formulates different type of sublingual tablets. The Sublingual tablets of Ramipril were prepared by using direct compression method with the incorporation of weighed amount of drug and superdisintegrants like Microcrystalline cellulose (MCC), Sodium starch glycolate, Croscarmellose Sodium (CCS), and Ramipril equivalent to 150 mg, Mannitol and Microcrystalline Cellulose were mixed thoroughly in glass mortar using a pestle. Superdisintegrants were incorporated in the powder mixture according to each formulation in the tablets and Magnesium stearate and talc was added. The whole mixture was passed through Sieve No. 60 twice. Tablets were prepared by using Shakti Pharmatech 10 station punching machine. The compression force was constant during Punch. The average weight of sublingual tablets was maintained 150mg.

EVALUATION OF TABLETS

Pre compression evaluation

1. Bulk Density

It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$$Db = \frac{M}{Vo}$$

2. Tapped Density

It is the ratio of total mass of powder to the tapped volume of powder. It is calculated by formula [4]

$$Dt = \frac{M}{Vt}$$

3. Angle of Repose

The frictional forces in a loose powder can be measured by the angle of repose ($\boldsymbol{\theta}$). Angle of repose was calculated by formula-

$$\boldsymbol{\theta} = \tan^{-1}\frac{h}{r}$$

4. Carr's Index (I):

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and was calculated by

$$I = \frac{Dt - Db}{Dt}$$

5. Hausner ratio (H):

Hausner ratio is an indirect index of ease of powder flow. It was calculated by the following formula [5]

$$H = \frac{Dt}{Db}$$

Post compression evaluation

1. Tablet thickness and Diameter

Tablet thickness and diameter are important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism.

2. Tablet hardness

The hardness test was done as per standard methods. Randomly selected three tablets of each formulation and hardness was determined by placing each tablet diagonally between two plungers of monsanto hardness tester and applying pressure until the tablet broke down. This reading of scale was noted in Kg/cm^2.

Table 3: Pre compression parameters

Formulation code	Parameters				
	Bulk density (g/cm3)*	Tapped density (g/cm3)*	% Compressibility index	Hausner's ratio	Angle of repose
SLT1	0.304±0.03	0.357±0.08	14.84	1.174	28°52'
SLT2	0.244±0.04	0.279±0.02	12.54	1.143	26°34'
SLT3	0.308±0.02	0.364±0.03	15.38	1.181	31°03'
SLT4	0.255±0.06	0.301±0.05	15.28	1.180	29°32'
SLT5	0.277±0.06	0.312±0.06	11.21	1.126	26°19'
SLT6	0.271±0.08	0.304±0.09	10.81	1.121	22°08'
SLT7	0.285±0.07	0.321±0.05	12.63	1.126	28°37'
SLT8	0.306±0.05	0.344±0.07	11.04	1.124	25°27'
SLT9	0.273±0.08	0.306±0.07	10.60	1.120	19°28'

3. Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure.

A pre weighed tablet was placed in the friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping these tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as [6]

% Friability = loss in weight / Initial weight X 100.

4. Wetting time

The method was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of Sorenson's buffer pH 6.8. A tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and the standard deviation was also determined. [7]

5. Disintegration time

The test was carried out on the 6 tablets using the apparatus specified in I.P.-2010 distilled water at $37^0C \pm 2^0C$ was used as a disintegration media and the time in second taken for complete disinigration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

6. Weight Variation:

Ten tablets were selected randomly from the lot and weighed individually to check for weight variation. IP limit for weight variation in case of tablets weighing up to 250mg is ±7.5%.

Table 4: Characterization of Ramipril sublingual tablets

Formulation	Parameters						
	Diameter (mm)	Thickness (mm)	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Disintegration Time (Sec)	Wetting Time (Sec)
SLT1	6.0	2.5	152.20±0.38	2.6±0.4	0.77±0.13	24±12	12±03
SLT2	6.0	2.5	153.48±0.58	2.7±0.5	0.54±0.24	22±16	14±04
SLT3	6.0	2.5	149.70±0.17	2.4±0.3	0.66±0.18	38±12	17±02
SLT4	6.0	2.5	154.02±1.19	2.8±0.3	0.48±0.22	47±09	11±05
SLT5	6.0	2.5	147.52±1.08	2.4±0.6	0.57±0.37	51±08	16±04
SLT6	6.0	2.5	148.77±0.98	3.0±0.4	0.68±0.22	59±07	15±02
SLT7	6.0	2.5	151.98±0.78	2.8±0.3	0.74±0.12	46±12	18±03
SLT8	6.0	2.5	153.77±0.64	2.9±0.2	0.39±0.23	36±11	13±06
SLT9	6.0	2.5	146.97±0.58	2.5±0.3	0.56±0.22	41±13	11±06

7. Content uniformity

Ten randomly selected tablets were weighed and average weight was calculated, the tablets were powdered in a glass mortar. The weight equivalent to 12.5 mg Ramipril was weighed. The weighed amount was dissolved in 5 ml of methanol in separate volumetric flask using magnetic stirrer, the volume was adjusted to 100 ml with Sorenson's buffer pH 6.8 and the solution was filtered. An aliquot of 1.0 ml from these solution were diluted to 10 ml

Sorenson's buffer pH 6.8 in separate volumetric flasks. The drug content in each formulation was determined spectrophotometrically at 240 nm. [8,9]

Table 5 : Drug Content in the Sublingual tablet of Ramipril

Formulation	Parameters	
	Drug Content (mg per Tablet)	% Drug Content
SLT1	19.498±0.025	97.490
SLT2	19.293±0.049	96.465
SLT3	20.480±0.142	102.40
SLT4	19.412±0.025	97.06
SLT5	19.566±0.041	97.83
SLT6	19.549±0.018	97.745
SLT7	20.532±0.023	102.66
SLT8	19.498±0.011	97.49
SLT9	20.312±0.050	101.56

8. In vitro Drug release profile

In vitro drug release experiments were performed at 37±1°C in six basket dissolution rate apparatus LAB INDIA DS 8000. The data obtained in *in- vitro* Drug release study are tabulated and represented graphically as:

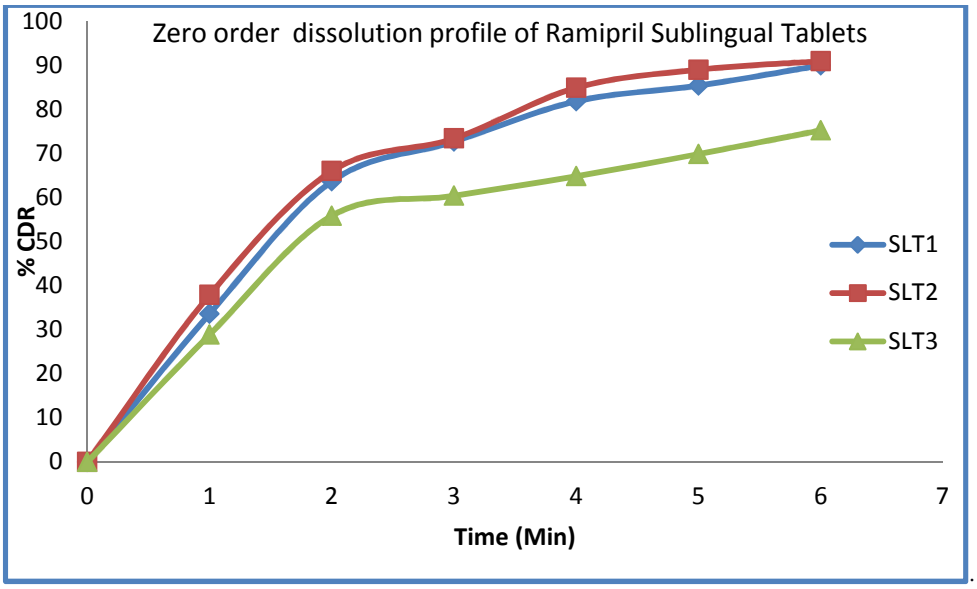

Figure 8: In vitro release curve of Ramipril tablet -Zero Order Release from SLT1 to SLT3

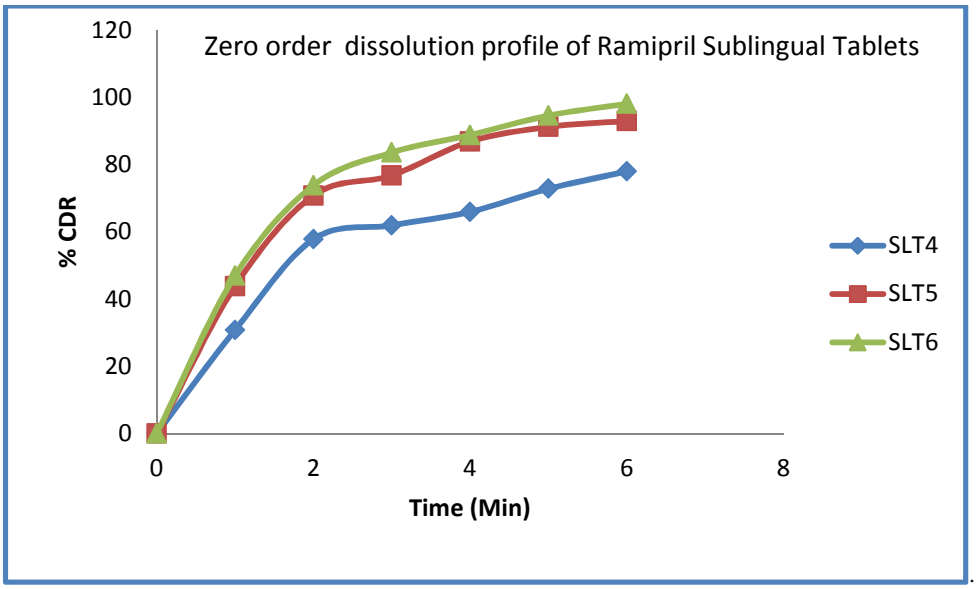

Figure 9: In vitro release curve of Ramipril tablet -Zero Order Release from SLT4 to SLT6

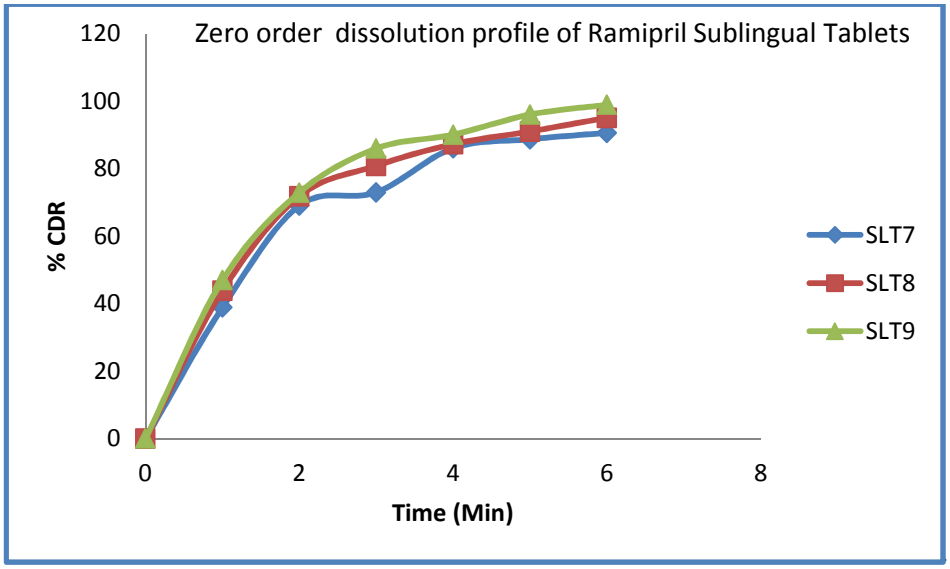

Figure 10: In vitro release curve of Ramipril tablet -Zero Order Release from SLT7 to SLT9.

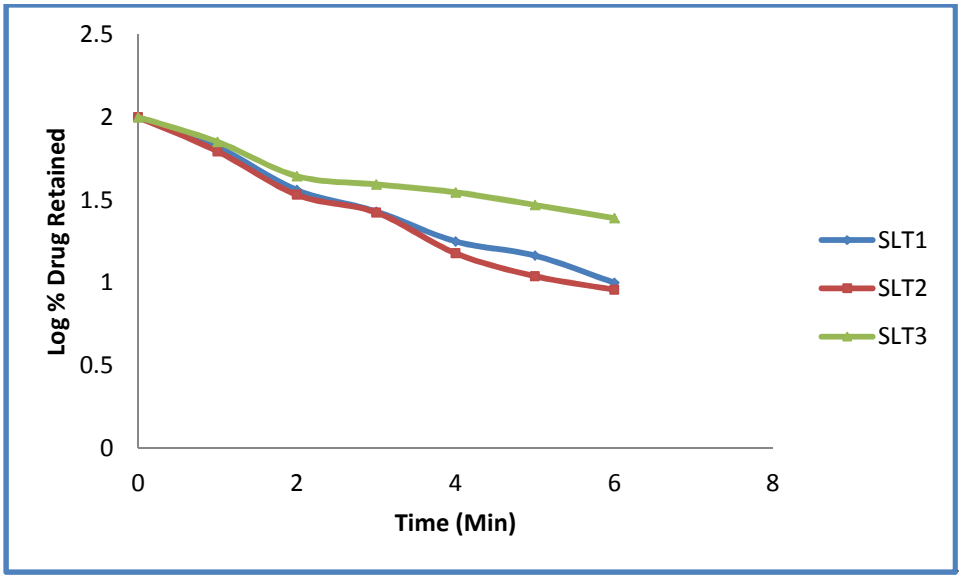

Figure 11: First order dissolution profile of Ramipril Sublingual Tablets from SLT1 to SLT3

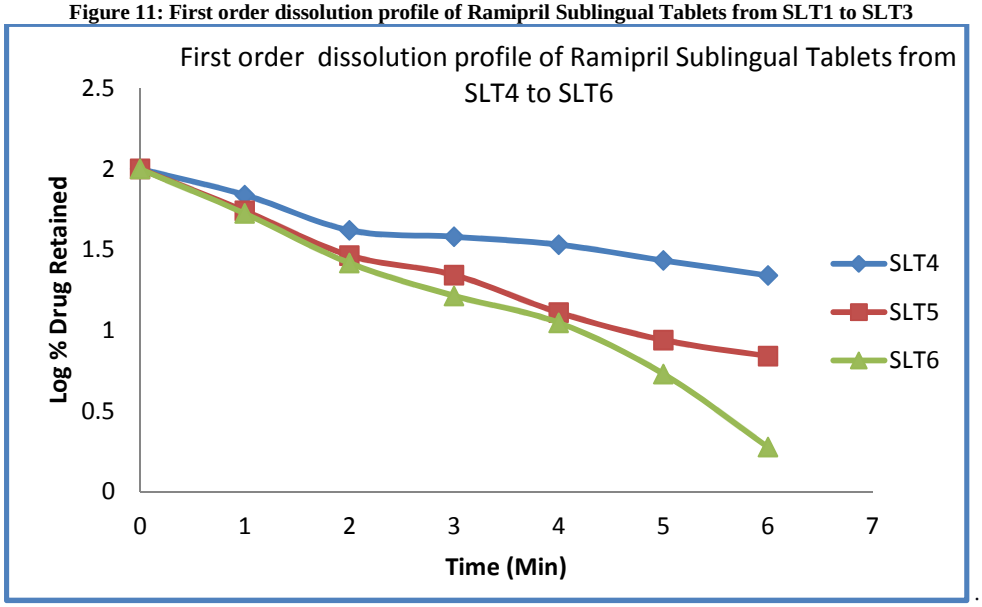

Figure 12: First order dissolution profile of Ramipril Sublingual Tablets From SLT4 to SLT6

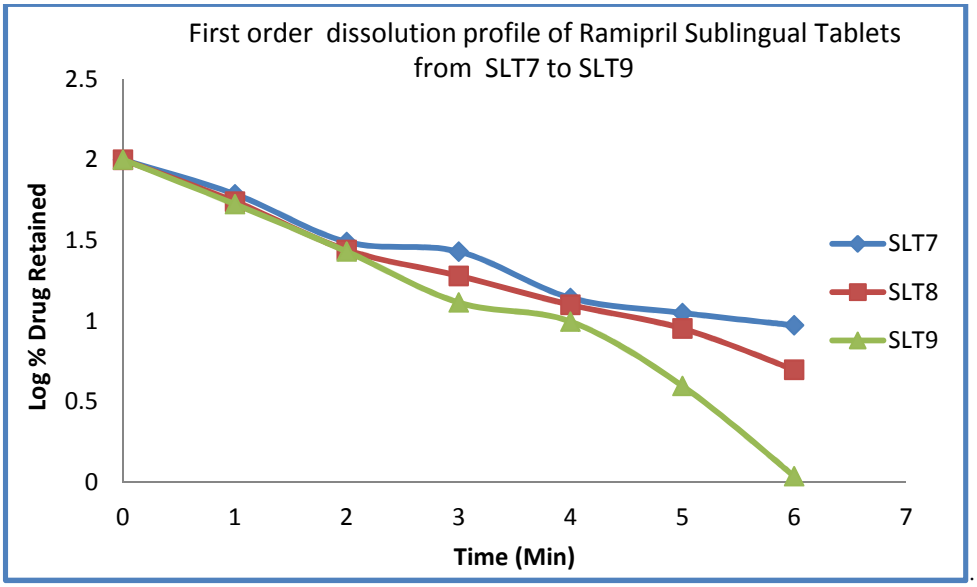

Figure 13: First order dissolution profile of Ramipril Sublingual Tablets from SLT7 to SLT9

Table 6: Zero order dissolution profile of Ramipril Sublingual Tablets

Time in Mins.	% Cumulative Drug Release								
	SLT1	SLT2	SLT3	SLT4	SLT5	SLT6	SLT7	SLT8	SLT9
0	0	0	0	0	0	0	0	0	0
1	33.62	37.90	28.89	30.84	43.88	46.96	38.87	43.85	47.00
2	63.68	66.00	55.89	57.84	70.84	73.85	69.05	71.84	72.90
3	72.69	73.41	60.41	61.96	76.84	83.62	73.00	80.85	86.00
4	81.84	84.92	64.84	65.99	86.90	88.84	86.09	87.28	90.07
5	85.40	89.02	69.88	72.85	91.23	94.62	88.72	91.02	96.04
6	90.00	90.92	75.25	78.00	93.00	97.89	90.60	95.09	98.01

Table 7: Fit of Various Kinetic Models for Sublingual Tablet of Ramipril

Formulation Code	Zero Order R^2	First Order R^2	Higuchi Model R^2	Korsemeyer Model R^2
SLT1	0.845	0.983	0.973	0.952
SLT2	0.833	0.981	0.975	0.961
SLT3	0.825	0.934	0.965	0.919
SLT4	0.827	0.940	0.968	0.922
SLT5	0.799	0.982	0.967	0.980
SLT6	0.792	0.983	0.966	0.970
SLT7	0.812	0.965	0.965	0.950
SLT8	0.794	0.987	0.964	0.965
SLT9	0.796	0.974	0.967	0.981

RESULTS AND DISCUSSION

Pre compression parameters

Parameters	Result observed
Bulk Density	0.244 to 0.308
Tapped Density	0.279 to 0.364
Carr's index	10.60 to 15.38%
Hausner's factor	1.120 to 1.180
Angle of repose	26.03 to 28.52

Post compression parameters

Parameters	Result observed
Average weight	146.97 to 152.02mg
Hardness	2.4 to 3.0 kg/cm^2
Friability	0.39 to 0.74%
Disintegration time	22 to 59 seconds.
Swelling time	11 to 18 seconds
Drug content uniformity	96.465 to 102.40%

CONCLUSION

The sub lingual tablet of Ramipril was successfully prepared by Direct compression method and evaluated, the precompression and post compression parameters of ramipril are found in the acceptable range. The sublingual tablets that was prepared with sodium starch glycolate with microcrystalline cellulose found as best tablet.

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