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FORMULATION AND EVALUATION OF SUBLINGUAL TABLET OF VALSARTAN

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Abstract: Valsartan is the drug of choice in hypertension and congestive cardiac failure. Its bioavailability is very low about 23-25%. Present investigation was undertaken to formulate sublingual tablet of Valsartan to overcome the first pass metabolism and provide rapid onset of action.The solid dispersion of Valsartan prepared with different carriers like β-cyclodextrin, poloxamer 407, PEG 6000, PEG 4000, poloxamer 188 and PVP K-30. The proportion of drug and carrier was selected 1:1 due to dose limitation of drug and solubility study was performed to select the carrier, for Beta-cyclodextrin molar ratio (1:1) was slelcted. The prepared solid dispersion was utilized for the formulation of sublingual tablet by direct compression. Different superdisintegrants like Cross carmellose sodium, Cross povidone, and Sodium starch glycolate were introduced and optimized. Tablets were evaluated for weight variation, thickness, friability, content uniformity, hardness, disintegration time, wetting time, *in-vitro* drug release and *ex-vivo* permeation study. Stability study of optimized formulation was performed as per ICH guideline. The optimized formulation (batch F6) containing Drug-Beta cyclodextrin complex (1:1) and cross carmellose sodium (5%) showed greater drug dissolution and satisfactory *in vitro* disintegration time (19 sec). Stability study of optimized formulation showed that optimized formulation was stable at accelerated environment condition.

Keywords: Sublingual tablet, Valsartan, Phase solubility study, Beta-cyclodextrin, Crosscarmellose sodium

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INTRODUCTION

Valsartan is an angiotensin-receptor blocker (ARB) that may be used to treat a variety of cardiac conditions including hypertension, diabetic nephropathy and heart failure. Valsartan lowers blood pressure by antagonizing the renin-angiotensin-aldosterone system (RAAS). [1] Valsartan is poorly soluble and the aqueous solubility is reported to be less than 1mg/ml. It is BCS class-II drug. Valsartan undergoes extensive hepatic first pass metabolism leading to poor bioavailability of 23-25%. Peak plasma concentration of valsartan achieve at 2-4 hours after an oral dose.[2][3] A rapid onset of action is required to provide fast relief in the treatment of cardiac failure. Therefore, it is necessary to enhance the aqueous solubility and dissolution rate of valsartan to obtain a faster onset of action and improve its overall oral bioavailability bypassing first pass hepatic metabolism.

So, sublingual route gives the better alternative and more reliable in the terms of....

- Avoidance of first pass effect
- Provide fast dissolution and disintegration in oral cavity without need of water
- Onset of action
- Improved patient compliance

Sublingual administration of the drug means placement of the drug 'under the tongue' and drug reaches directly in to the blood stream through the ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and braciocephalic vein and then drained into systemic circulation. [4]

Sublingual route provides systemic delivery of drugs through the mucosal membranes lining the floor of the mouth to the systemic circulation. Systemic drug delivery provide immediate onset of pharmacological effect through the sublingual route. [5]

Drugs having short delivery and infrequent dosing regimen could be delivered successfully through sublingual route because of high permeability and rich blood supply, the sublingual route produces a rapid onset of action. [6]

Advantages of Sublingual Tablet.... [4] [7] [8]

- Drug is directly entered into systemic circulation so there is no loss of drug by first pass effect.

- Higher bioavailability and onset of action compare to oral route.
- Rapid absorption due to high vascularization beneath the tongue.
- Reduce the side effect due to low dose and high efficacy.
- Provide fast dissolution or disintegration in oral cavity without water or chewing action.
- Convenience in administration of drug and accurate dosing as compared to liquid formulations.
- Relatively large contact surface area provides rapid and extensive absorption
- Water is not required for swallowing the dosage form, which is convenient feature for patients who are traveling and do not have immediate access to water.
- It provides advantages of liquid formulations in the form of solid dosage form.
- Ease of administration to patients who refuse to swallow a tablet, such as pediatric, geriatric patients and psychiatric patients.
- Due to rapidity in action these sublingual dosage forms are widely used in emergency conditions e.g. asthma, angina.
- pH in the mouth is relatively neutral so drug will be more stable.
- Less variability in therapeutic effect, more predictable pharmacokinetics
- Optimal effect achieved with less drugs, less side effects
- Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.
- Flexible formulation options
- Improved patient compliance.

MATERIAL AND METHOD:

Valsartan was obtained as a gift sample from Alembic Pharmaceutcals ltd., Baroda, india. Beta-cyclodextrin was procured from Alembic Pharmaceutcals ltd., Baroda, india. Cross PVP, Sodium starch glycolate, Croscarmellose sodium were supplied by Yarrow chem., Mumbai, India. All other materials used were of pharmaceutical or analytical grade.

Differential Scanning Calorimetry (DSC) Study

Differential Scanning Calorimeter study of Valsartan and solid dispersions of Valsartan+ Beta-cyclodextrin was carried out using Shimadzu DSC-60 (Shimadzu, Kyoto, Japan) instrument.

FTIR Spectrophotometric Study

Fourier transform infrared (FTIR) technique was used to study the physical and chemical interaction between drug and excipients used. The infrared spectrum of the native valsartan and mixture of Valsartan and excipients were recorded in the range of 4000-400 cm^{-1} using KBr mixing method on FTIR instrument (FTIR-8400S, Shimadzu, Kyoto, Japan).

Phase Solubility Study [9]

The physical mixtures of drug (50mg) and carrier as per specified table 4.3 and 4.4 ratio was added to vial containing 10 ml of phosphate buffer 6.8 pH and subjected to shaking on a rotary shaker for 24 hours at 37°C. Then the flasks were removed and content was filtered by 0.45μm whatman filter paper and analyzed for the drug content after appropriate dilution with phosphate buffer and compared with pure drug solubility.

Table 1: Physical mixture of drug with carrier

Sr. No.	Carrier	Drug:carrier
1.	Poloxamer 407	1:1
2.	PEG 4000	1:1
3.	PEG 6000	1:1
4.	Beta-cyclodextrin	1:0.38
5.	Poloxamer 188	1:1
6.	PVP K 30	1:1

Table 2: Solid dispersion of drug with carrier

Sr. No.	Carrier	Drug:carrier
1.	Poloxamer 407	1:1
2.	PEG 4000	1:1
3.	PEG 6000	1:1
4.	Beta-cyclodextrin	1:0.38
5.	Poloxamer 188	1:1
6.	PVP K 30	1:1

Phase solubility study of solid dispersions was performed and solubility was calculated.

Dissolution Studies of Solid Dispersion [10] [11]

Drug release tests were carried out using a dissolution tester. Test samples containing 40 mg of valsartan or dose equivalent solid dispersion placed in a USP dissolution apparatus II containing 300 ml of phosphate buffer pH 6.8 at 37 °C at 50 rpm. Samples were withdrawn at predetermined time intervals with replacement of distilled water. Results are shown in Table 8 and Figure 5.

Selection of Super-disintegrant in Tablet Formulation

Preparation of Sublingual Tablets by Direct Compression Method

Sublingual tablets of valsartan were prepared by direct compression. All the ingredients were passed through # 80 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 150 mg by direct compression method using 8 mm flat punches on a Rotary Tablet Compression Machine (Rimek 10 station minipress). For optimization of super disintegrant different types of disintegrants were selected like sodium starch glycolate, crospovidone, crosscarmalose sodium and in concentration range 3%. Composition of batches F1 to F3 shown in Table 3.

Table 3: Composition of batches F1 to F3

Ingredients	Quantity per tablet (mg)		
	F1	**F2**	**F3**
Drug+ β-cyclodextrin	80	80	80
Sodium starch glycolate	4.5	--	--
CCS	--	4.5	--
Cross povidone	--	--	4.5
MCC	59.5	59.5	59.5
Aspartame	1.5	1.5	1.5
Aerosil	1.5	1.5	1.5
Talc	3.0	3.0	3.0
Total weight	150	150	150

Drug-Excipient Compatibility Study by FTIR

Fourier transform infrared (FTIR) technique was used to study the physical and chemical interaction between drug and excipients used. The infrared spectrum of the native Nitrendipine

and mixture of Nitrendipine and excipients were recorded in the range of 4000-400 cm-1 using KBr mixing method on FTIR instrument (FTIR-8400S, Shimadzu, Kyoto, Japan). Results are shown in table 13, figure 9 and figure 10.

Optimization of Concentration of Superdisintegrant in Tablet Formulation

Sublingual tablets of valsartan were prepared by direct compression. All the ingredients were passed through # 80 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 150 mg by direct compression method using 8 mm flat punches on a Rotary Tablet Compression Machine (Rimek 10 station minipress). For selection of concentration of super disintegrant cross carmellose sodium in 1%, 3% and 5% were taken. Composition of batches F4 to F6 is shown in Table 4.

Table 4: Formula for different concentration of superdisintegrant

Ingredients	Quantity per tablet (mg)		
	F4	**F5**	**F6**
Drug+ Beta-cyclodextrin	80	80	80
Cross carmellose sodium	1.5	4.5	7.5
Mirocrystalline cellulose	62.5	59.5	56.5
Aspartame	1.5	1.5	1.5
Aerosil	1.5	1.5	1.5
Talc	3.0	3.0	3.0
Total weight	150	150	150

Evaluation of Batches (F1 to F6)

Batches F1 to F6 were evaluated for Hardness, Wetting time, *In-vitro* disintegration test, % Assay, % Friability, Uniformity of weight , *In-vitro* drug release study. Results are shown in Table 10-12 and Table 14-16. Figure 8 and 11.

***Ex-vivo* Permeation Study**

Ex-vivo permeation study of sublingual tablet of drug (without solid dispersion) and optimized solid dispersion were carried out.

Preparation of Sublingual Tablets for *Ex-vivo* Permeation Study

Sublingual tablets of batch F6 (optimized formulation of solid dispersion) were taken for *Ex-Vivo* permeation study as per formula give in Table 4.

Sublingual tablets of drug alone were prepared by following formula:

Table 5: Formula for sublingual tablet of dug (without solid dispersion)

Ingredient	Quantity per tablet (mg)
Valsartan	40
CCS	7.5 (5%)
MCC	96.5
Aspartame	1.5
Aerosil 200	1.5
Talc	3.0
Total Weight	150

Sublingual mucosa was used to check the permeation of drug through the mucosa using Franz diffusion cell at 37 ± 0.5 ^{0}C. Fresh goat sublingual mucosa was mounted between the donor and receptor compartments. The sublingual tablet was placed with the core facing the mucosa, and the compartments were clamped together. The donor compartment was filled with 2 ml of phosphate buffer pH 6.8. The receptor compartment (72 ml capacity) was filled with phosphate buffer pH 6.8 and the hydrodynamics in the compartment was maintained by stirring with a magnetic bead at uniform slow speed. Five milliliter samples were withdrawn at predetermined time intervals (5, 10, 15, 20, 25 and 30) and analyzed for drug content by UV/Vis double beam spectrophotometer at 250 nm. Results are shown in Table 17 and Figure 12.

Short Term Stability Studies of the Optimized Formulation (F6)

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. To assess the drug and formulation stability, stability studies were done according to ICH guidelines Q1C. The stability studies were carried out on the optimized formulations as per ICH guidelines Q1C. The optimized formulation sealed in aluminum packaging and kept in humidity chamber maintained 40 ± 2 °C / 75 ± 5 %RH for 1 month. The optimized formulation sealed in aluminum foil was also kept at room temperature and humidity condition. At the end of studies, samples were analyzed for the % drug release and drug content. Results of this experiment has been shown in Table 18,19 and Figure 13.

RESULTS AND DISCUSSION:

Differential Scanning Calorimetry (DSC) study

Valsartan is a white substance and its melting point under nitrogen is reported to be 104-107 °C by DSC. The thermogram of drug was characterized by melting endotherm at 102.10°C as

shown in Figure 2. Thus the DSC thermogram of the drug was found to be in agreement to the specifications.

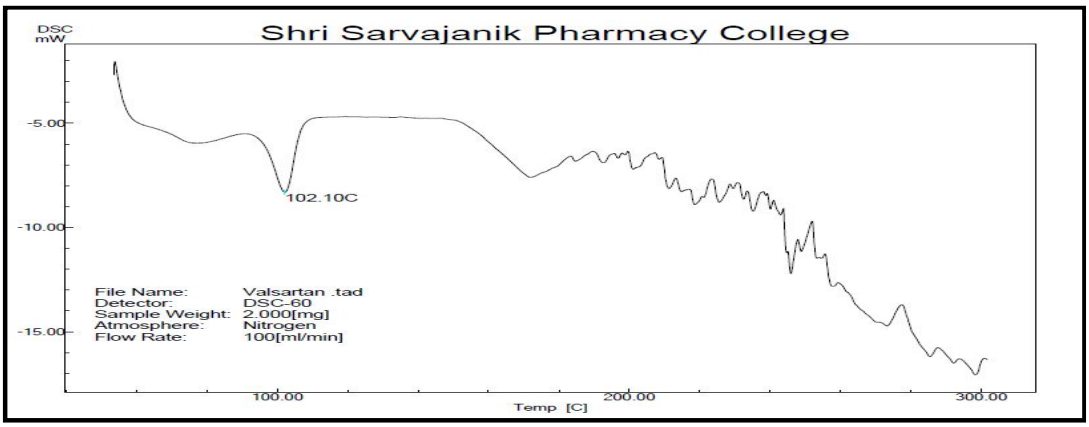

Figure 1: DSC spectrum of Valsartan

FTIR Spectrophotometric Study

The FTIR spectra of valsartan showed a characteristic peaks of valsartan appeared at 1130-1210cm-1(N-H stretching), 1550-1640 cm-1 (N-H bending), 1670-1820 cm-1 (C=O stretching), 1080-1360 cm-1 (C-N stretching), 3000-3010 cm-1(Methyl bond).

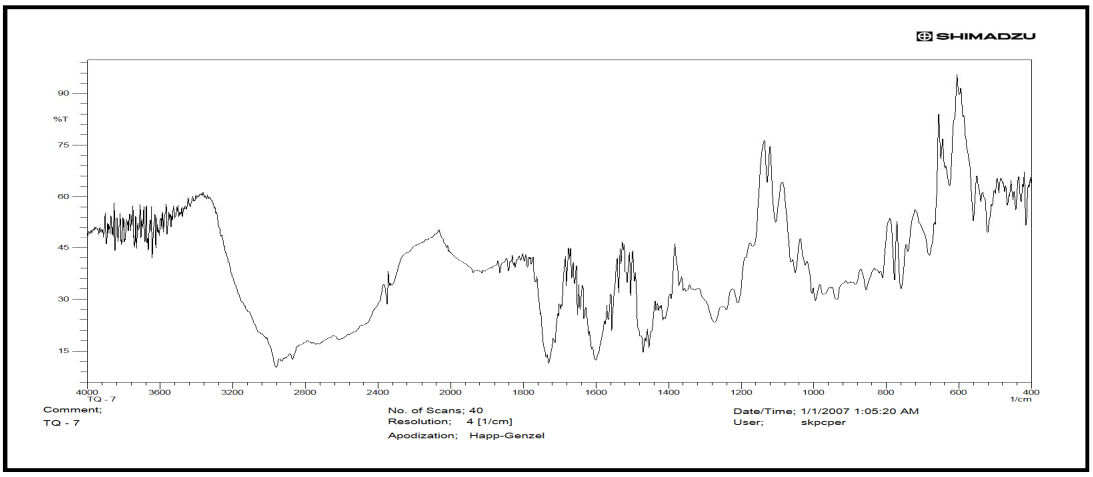

Figure 2: FTIR spectrum of Valsartan

Table 6: Phase solubility data of physical mixture of drug with carrier

Sr. No.	Polymer	Drug:carrier	Absorbance	Solubility (mg/ml)
1.	Poloxamer -407	1:1	0.309	1.74
2.	PEG-4000	1:1	0.176	0.964
3.	PEG-6000	1:1	0.354	1.98
4.	β-cyclodextrin	1:0.38	0.426	2.43
5.	Poloxamer -188	1:1	0.165	0.912
6.	PVP-K 30	1:1	0.324	1.83

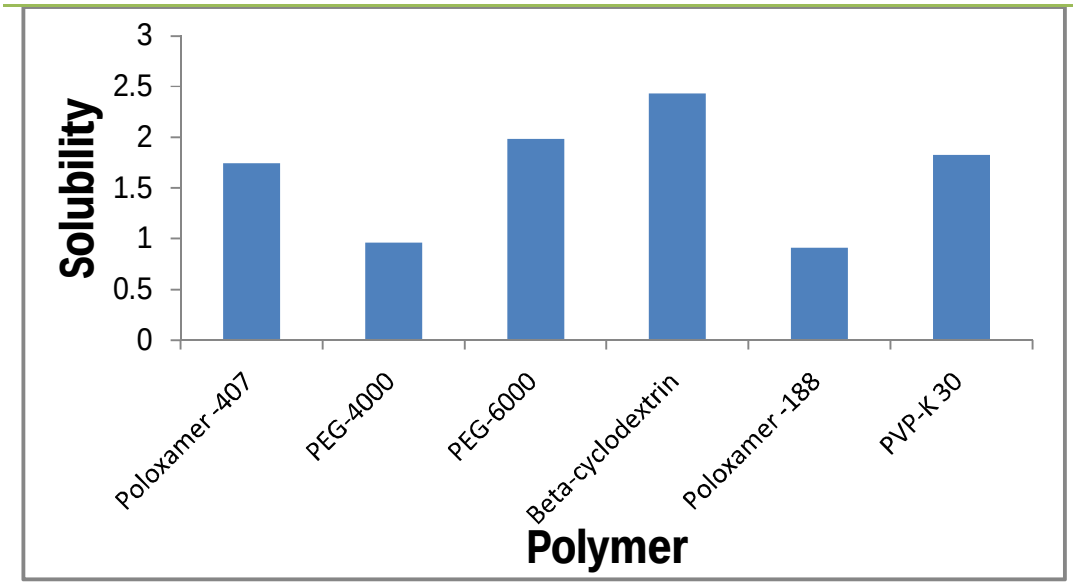

Figure 3: Comparison of solubility of physical mixture

1:1 ratio of drug and carrier was taken for all polymer as it was dose limitation and in above physical mixture beta-cyclodextrin shown highest improvement in the solubility of valsartan drug. So for formulation solid dispersion is prepared using beta-cyclodextrin.

Table 7: Phase solubility data of solid dispersion of drug with carrier

Sr. No.	Polymer	Drug:carrier	Absorbance	Solubility (mg/ml)
1.	Poloxamer -407	1:1	0.792	4.58
2.	PEG-4000	1:1	0.680	3.92
3.	PEG-6000	1:1	0.783	4.53
4.	β-cyclodextrin	1:0.38	0.863	5.02
5.	Poloxamer -188	1:1	0.688	3.85
6.	PVP-K 30	1:1	0.829	4.80

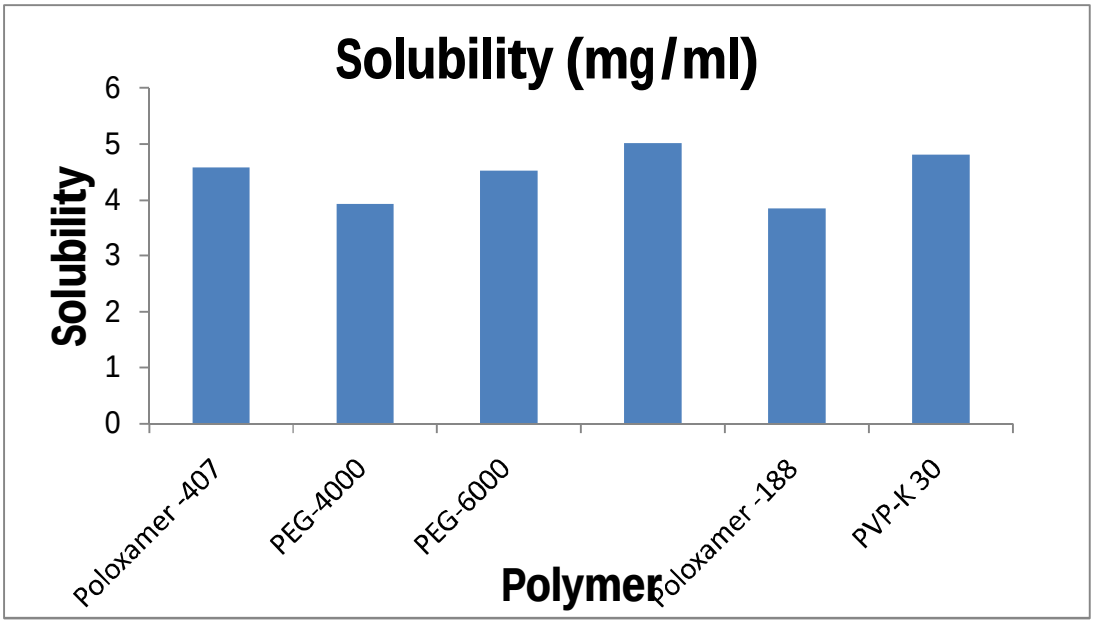

Figure 4: Comparison of solubility of solid dispersion

From the solubility data of solid dispersion, beta-cyclodextrin shown highest improvement in the solubility of valsartan drug. So beta-cyclodextrin is the optimized carrier for the improvement in the solubility of drug. For this *in-vitro* drug release comparison was made between physical mixture and solid dispersion of beta-cyclodextrin.

Dissolution Studies of Solid Dispersion

Drug release tests were carried out using valsartan-beta cyclodextrin solid dispersion and physical mixture. Test samples containing 40 mg of valsartan or dose equivalent solid dispersion placed in a USP dissolution apparatus II containing 300 ml of phosphate buffer pH 6.8 at 37 °C (paddle method at 50 rpm). It is observed that the Solid dispersion (SD) released 87.32 % drug in 15 min while physical mixture (PM) shown total 63.22% drug release. There is much significance difference between SD and PM. So, valsartan-beta cyclodextrin solid dispersion was optimized. Results are shown in Table 8.

Table 8: *In-Vitro* dissolution study of PM and SD of β-cd in Phosphate buffer pH 6.8

Sr. No.	Time (min)	%CPR (PM)	%CPR (SD)
1.	0	0	0
2.	5	32.40	62.08
3.	10	47.56	76.16
4.	15	63.22	87.32
5.	20	68.76	97.42
6.	25	75.17	98.06
7.	30	89.08	98.34

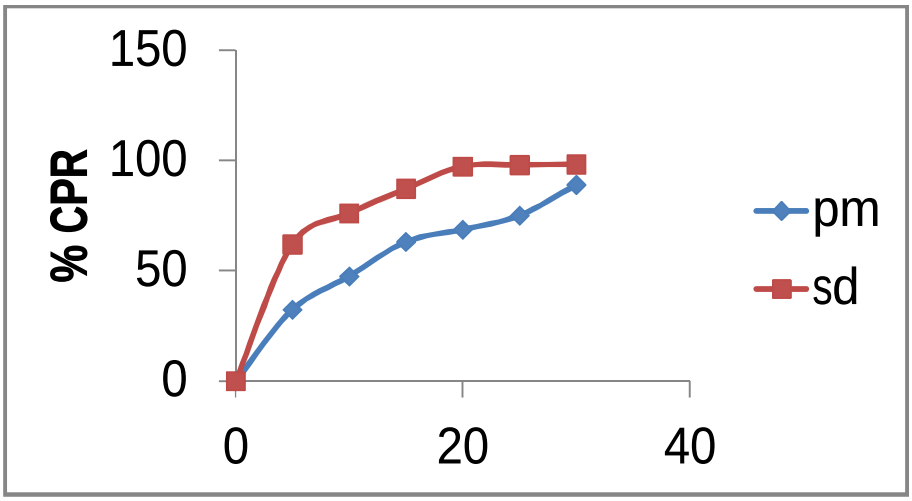

Figure 5: *In-vitro* dissolution comparision of PM and SD

PM: physical mixture

SD: solid dispersion

Evaluation of Solid Dispersion by Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimeter study of solid dispersion of valsartan and beta- cyclodextrin was carried out using Shimadzu DSC-60 (Shimadzu, Kyoto, Japan), The results are show in figure 5. 9 and 5.10 respectively.

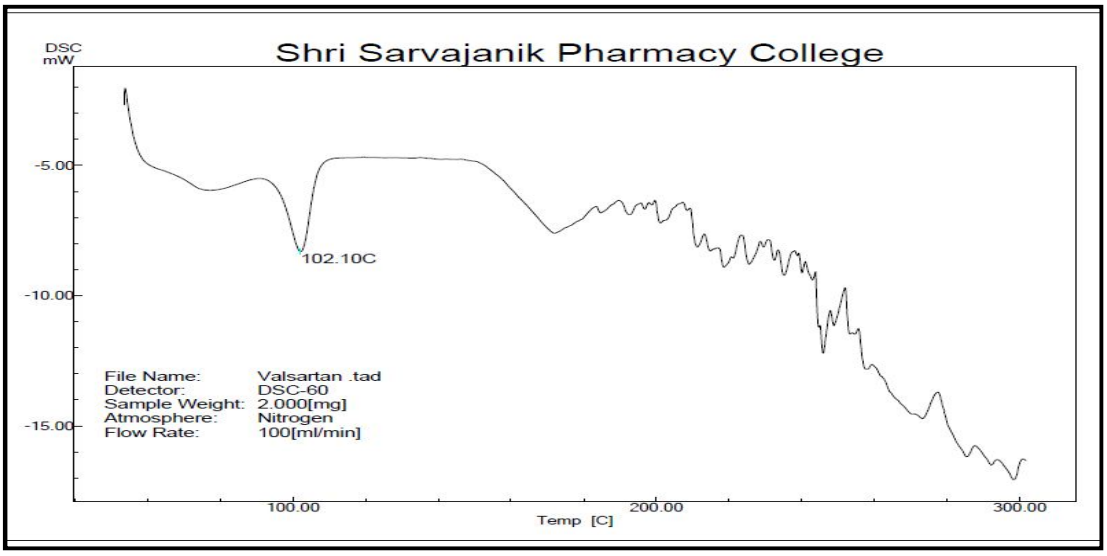

Figure 6: DSC spectrum of valsartan

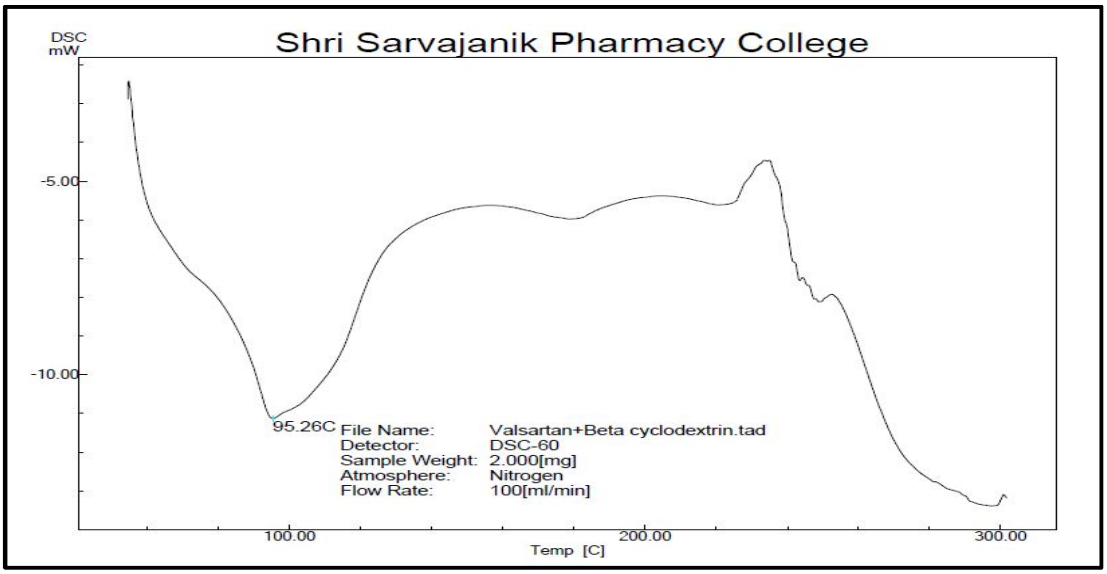

Figure 7: DSC spectrum of valsartan and beta-cyclodextrin

It was of interest to note that melting peak of beta-cyclodextrin appears at 95.26 ^{O}C but melting peak of valsartan did not appear. So it was concluded that valsartan was converted from crystalline to amorphous form.

Preliminary Trials for Formulation of Sublingual Tablets

Powder Characteristics of powder mixture with Valsartan + Beta-cyclodextrin

Table 9: Powder characteristics of powder mixture with Valsartan + Beta-cyclodextrin

Powder Mixture	Loose bulk density (g/ml)	Tapped bulk density (g/ml)	Carr's index	Hausner's ratio	Angle of Repose
	0.432	0.498	12.39	1.15	23.82

Powder mixture showed minimum carr's index, hausner's ratio and angle of repose. So the mixture have good flow properties and good compressibility. So we had gone through direct compression.

Optimization of Super Disintegrant

Evaluation of Tablets (F1 to F3)

Table 10: Pre-compression parameters for formulation (Batch F1 to F3)

Parameters	F1	F2	F3
Angle of repose (θ)	27.77	24.68	23.80
Bulk Density (gm/ml)	0.357	0.384	0.434
Tapped Density (gm/ml)	0.416	0.432	0.526
Compressibility (%)	14.18	11.13	17.49
Hausner's ratio	1.17	1.12	1.22

Table 11: Post-compression parameters for formulation (Batch F1 to F3)

Parameters	F1	F2	F3
Hardness (kg/cm2) ± SD (n=3)	4.2±0.2	3.2±0.23	4.06±0.12
Friability (% w/w) ±SD (n=3)	0.86±0.03	0.47±0.02	0.53±0.02
Thickness (mm) ±SD (n=3)	2.8±0.061	2.5±0.091	2.9±0.084
Wetting Time (Sec) ± SD (n=3)	35±1.54	22±0.98	26±1.02
Disintegration Time (Sec) ± SD (n=3)	47±1.73	28±1.01	34±1.15
Weight Variation ± SD (n=3)	150.7±1.87	150.6±2.19	150.9±1.53
Assay (%)	90.8	98.27	96.8

The optimization of super disintegrant was done based on the evaluation parameters like hardness, disintegration time, wetting time, friability and assay. In the preliminary trial for optimization of disintegrant, all the prepared batches were evaluated firstly for the hardness.

All the batches had hardness between 3.2 to 4.2 (kg/cm^2). Disintegration Time (sec) was observed minimum for batch F3 (containing Cross carmellose sodium).

Table 12: *In-vitro* drug release profile (Batch F1 to F3)

Sr. No.	Time (min)	% CPR (Mean±SD, n=3)		
		F1	F2	F3
1.	0	0	0	0
2.	5	33.42±0.61	41.02±1.15	37.54±0.72
3.	10	53.67±1.37	63.12±1.07	58.82±1.23
4.	15	71.61±3.07	82.53±0.55	74.98±1.79
5.	20	81.09±0.86	89.72±1.28	84.24±2.09
6.	25	91.15±1.09	98.14±0.82	93.17±0.87
7.	30	95.98±2.01	99.07±0.61	97.56±3.14

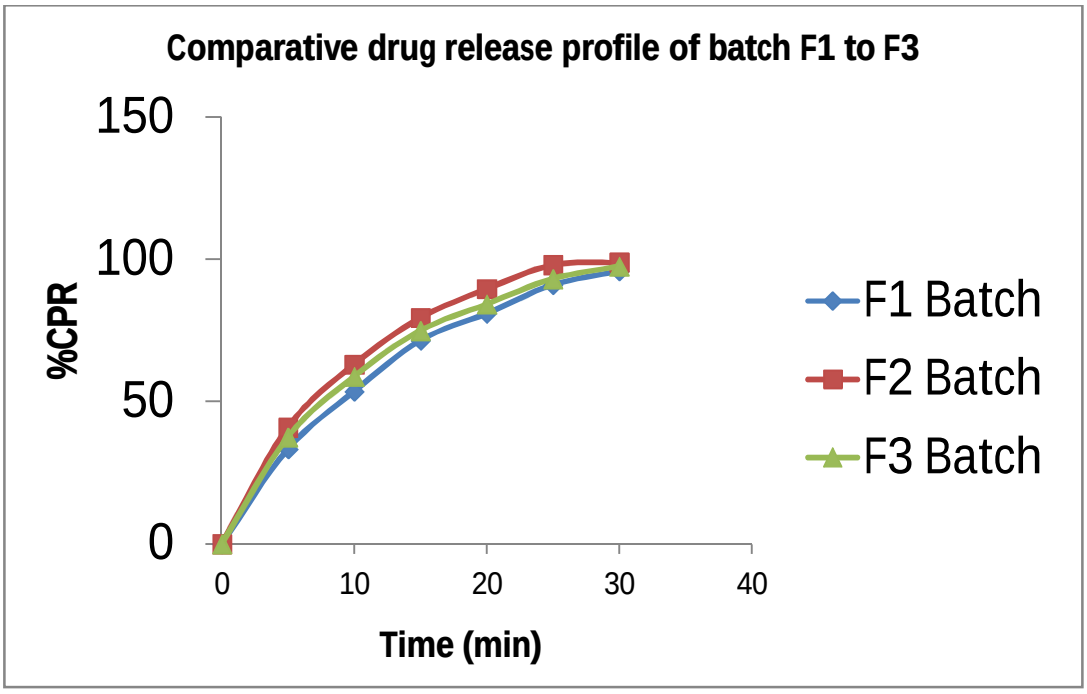

Figure 8: *In-vitro* drug release profile (F1 to F3)

All the batches contain 3% of super disintegrant. Among F1, F2 and F3 batches, F2 (Cross carmellose sodium) shown highest drug release. It released more than 80 % drug release in 15 min. So, Cross carmellose sodium was selected as super disintegrant for further study.

Drug Excipient Compatibility Study by FTIR

The FTIR spectra of valsartan showed a characteristic peaks of valsartan appeared at 1130-1210cm-1(N-H stretching), 1550-1640 cm-1 (N-H bending), 1670-1820 cm-1 (C=O stretching), 1080-1360 cm-1 (C-N stretching), 3000-3010 cm-1(Methyl bond).

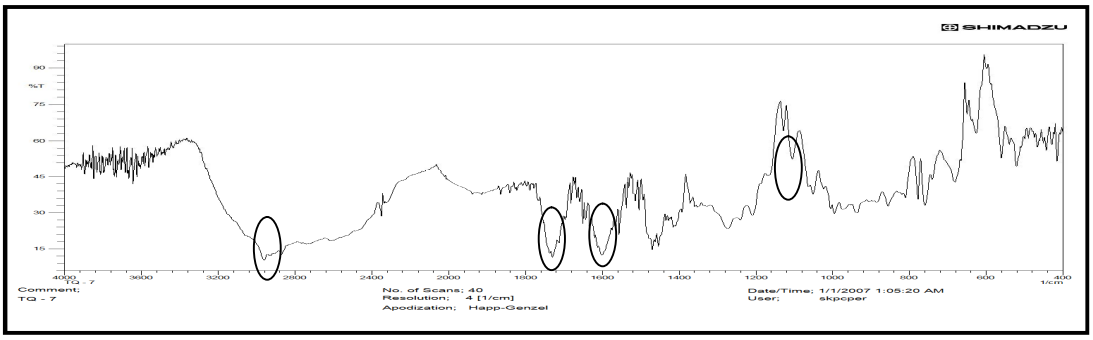

Figure 9: FTIR spectrum of valsartan

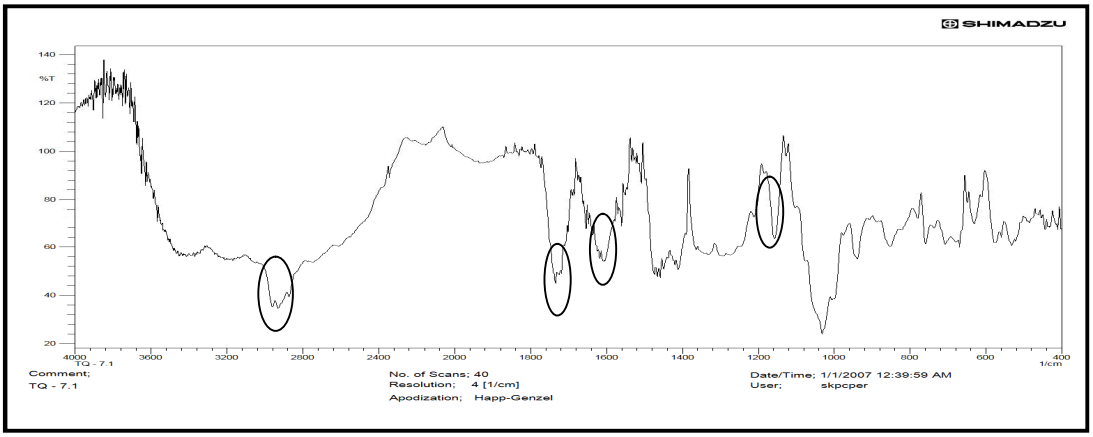

Figure10: FTIR spectrum of valsartan + excipient

Table 13: Functional group identification

Functional group	Standard range	Inference
N-N(stretch)	1130-1210 cm^{-1}	1160 cm^{-1}
N-H (bending)	1550-1640 cm^{-1}	1596 cm^{-1}
C=O (stretch)	1670-1820 cm^{-1}	1727 cm^{-1}
C-N (stretch)	1080-1360 cm^{-1}	1204 cm^{-1}
Methyl bond	3000-3010 cm^{-1}	2990 cm^{-1}

The frequencies of functional groups of the drug valsartan remained intact in physical mixture containing different excipients so it is concluded that there is no interaction occurred between the drug and excipients used in the study.

Optimization of Super Disintegrant Concentration

Evaluation of Tablets (Batch F4 to F6)

Table 14: Pre-compression parameters for Batch F4 to F6

Parameters	F4	F5	F6
Angle of repose (θ)	22.72	29.57	21.05
Tapped Density (gm/ml)	0.526	0.434	0.476
Compressibility (%)	13.68	11.52	8.82
Hausner's ratio	1.15	1.13	1.09

Table 15: Post-compression parameters for Batch F4 to F6

Parameters	F4	F5	F6
Hardness (kg/cm2) ± SD (n=3)	3.44± 0.422	3.28± 0.305	3.6± 0.20
Friability (% w/w) ±SD (n=3)	0.62±0.05	0.45±0.01	0.37± 0.02
Thickness (mm) ±SD (n=3)	2.6±0.064	2.9±0.078	2.7±0.048
Wetting Time (Sec) ± SD (n=3)	21±1.52	23±1.63	12±0.81
Disintegration Time (Sec) ± SD (n=3)	32± 1.58	27±1.44	19± 0.98
Weight Variation ± SD (n=3)	151.1± 1.79	150.5± 1.79	150.4±1.88
% Assay	93.4	98.54	99.37

The optimization concentration of super disintegrant was done based on the evaluation parameters like hardness, disintegration time, wetting time, friability and assay. Disintegration Time (sec) was observed minimum for batch F6, containing 5% Cross carmellose sodium among F4 to F6.

Table 16: *In-vitro* drug release profile of batches (F4 to F6**)**

Sr. No.	Time (min)	% CPR (Mean±SD, n=3)		
		F4	**F5**	**F6**
1.	0	0	0	0
2.	5	37.59±1.57	40.98±1.98	48.36±0.41
3.	10	61.87±0.63	63.27±2.05	69.54±0.94
4.	15	77.16±0.19	81.01±0.23	86.23±1.25
5.	20	85.14±1.54	89.91±2.69	96.48±1.09
6.	25	96.89±2.36	98.12±3.17	100.37±2.54
7.	30	97.33±0.49	99.15±0.64	101.45±1.37

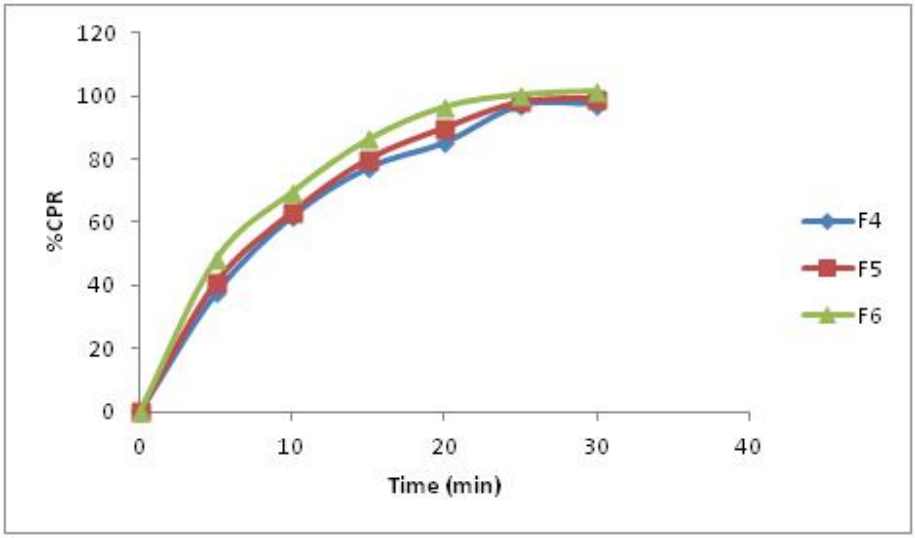

Figure 11: *In-vitro* drug release profile of batches (F4 to F6**)**

Batch F4, F5 and F6 contain 1%, 3% and 5% super disintegrant respectively. Among all batches, batch F6 showed highest drug release as compared to other batches. It also shown more than 85 % drug release in 15 min. So, formuation F6 can be considered optimized.

***Ex-vivo* Permeation Study**

Results for *Ex-Vivo* Permeation study showed that drug permeation of 97.89% in 30 min was observed for optimized formulation of solid dispersion whereas pure drug showed only 48.62%. S0 permeability of drug was increased after preparation of solid dispersion.

Table 17: *Ex-vivo* Permeation Study

Time (min)	Drug permeation (%)	
	Pure drug (without solid dispersion)	Optimized formulation of solid dispersion
0	0	0
5	17.89	52.10
10	26.59	74.59
15	31.12	82.27
20	36.54	93.45
25	40.01	95.19
30	48.62	97.89

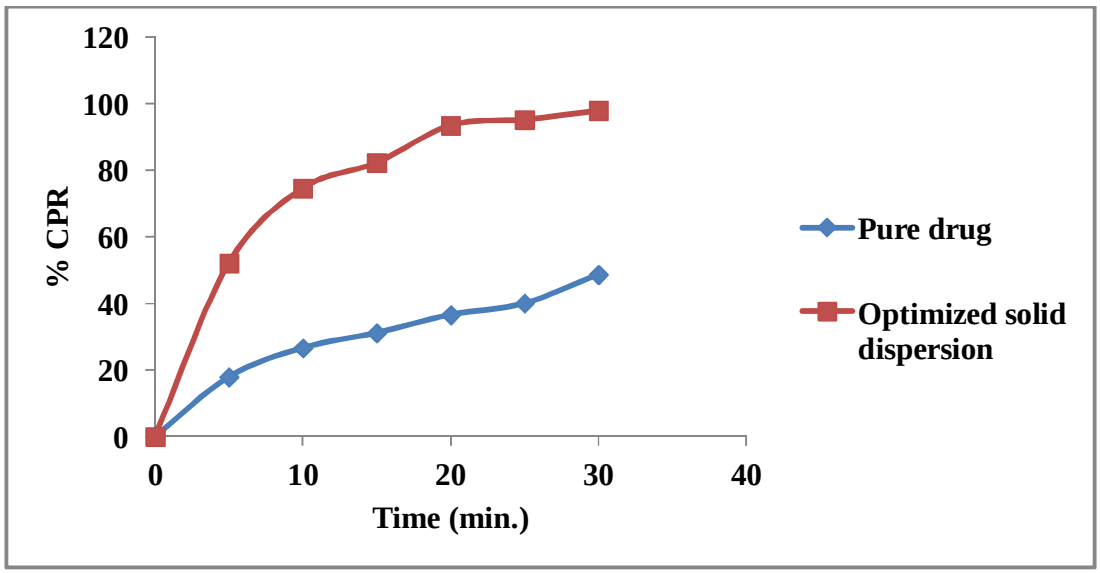

Figure 12: Plot of *ex-vivo* drug permeation study

Stability Studies of the Optimized Formulation

The stability studies were carried out on the most satisfactory formulations (Batch F6) as per ICH guidelines Q1C. The stability studies were performed at 40 ± 2 °C / 75 ± 5 % RH conditions for 1 month. At the end of studies, samples were analyzed for the weight variation, thickness, friability, hardness, wetting time, Disintegration time, drug content and *in vitro* dissolution. The optimized formulations stored at 40 ± 2 °C / 75 ± 5 % were found stable. After storage at 40 ± 2 °C / 75 ± 5 %, no shape deformation in the tablets was found. Assay of drug as well as

cumulative percentage drug release was nearly similar before and after storage. (Figure 5.17). similarity factor f_2 value was found to be 84.75 So, it was clear that drug was thermally stable as well as not affected by high humidity at 40 ± 2 °C / 75 ± 5 %.

Table 18: Evaluation data after stability study of optimized batch (F6)

Parameter	F6
weight variation (mg)	150.37±1.72
Thickness	2.8±0.041
Friability	0.32±0.028
Hardness	3.9±0.49
Wetting time (Sec)	15±1.52
Disintegration time (Sec)	21±0.57
Assay	99.11

All values are mean ± S.D (n=3)

Table 19: *In-vitro* drug release studies after stability study

Time (min)	%CPR (Initial)	%CPR (After storage at 40 ± 2 °C / 75 ± 5 % RH) for 30 days
0	0	0
5	48.36	47.54
10	69.54	68.33
15	86.23	85.14
20	96.48	96.21
25	100.37	99.05
30	101.45	99.43

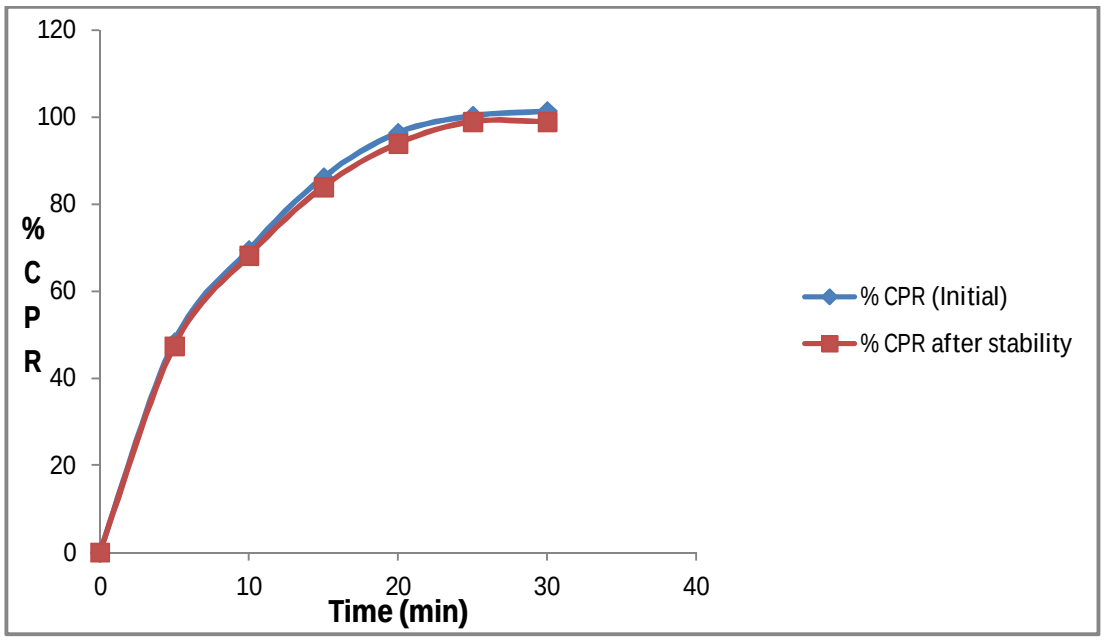

Figure 13: Plot of *In-vitro* drug release studies after stability study

CONCLUSION:

Valsartan sublingual tablets were prepared successfully by using of solid dispersion of valsartan-Beta cyclodextrin (1:1) complex by solvent evaporation method using cross carmellose sodium as a superdisintegrant. It was also concluded that there was no physical and chemical interaction between drug and excipients. Similarly, *ex vivo* permeation studies showed 97.89% drug release from the sublingual tablet. The prepared formulation is stable at 40 ± 2 °C / 75 ± 5 % for 1 month. Thus, sublingual tablet of Valsartan could be an alternative route to avoid hepatic first pass metabolism offered by conventional tablets and it may act as a potential alternate for the valsartan oral tablet.

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