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Formulation and Evaluation of Sublingual Tablets of Tolvaptan

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ABSTRACT:
Objective: The present study aimed to develop a Tolvaptan solid dispersion–based sublingual tablet using an effervescent approach to enhance dissolution and improve bioavailability, which is limited to approximately 56% due to poor aqueous solubility and extensive first-pass metabolism. S**olid dispersions** of Tolvaptan were prepared with carriers like **Guar gum**, **Xanthan gum**, **Eudragit RS100**, and **PEG 6000**at 1:1 and 1:2 ratio using the solvent evaporation method. The prepared solid dispersion batches were evaluated for pre formulation and post formulation parameters, including drug content uniformity and *in vitro* dissolution studies and were characterized to identify an optimized batch. Based on results, Solid dispersions with Guar gum gave better solubility, content uniformity and drug release. Therefore, this combination was further formulated into sublingual tablets and was evaluated for post compression parameters such as weight variation, hardness, friability, drug content, disintegration time, and *in-vitro* drug release. The optimized formulation **F9,** containing **Drug: Guar gum (1:2)** ratio, showed **disintegration time** of **24.33 ± 1.150 seconds**, **wetting time** of **18.33 ± 1.150 seconds**, and *in-vitro* **drug release** of **98.77% ± 0.144** in**12 minutes**. Among all the batches, **Batch F9** exhibited the best performance in terms of solubility and dissolution. Stability studies of batch **F9** showed no significant changes in post-compression parameters after a period of one month when stored at **40 ± 2°C**and**75 ± 5% RH**. From the study, it was concluded that **Sublingual tablets of Tolvaptan** can be successfully formulated to enhance its solubility, providing a **rapid drug release** within a short period of time, making it an acceptable dosage form for the treatment of **hyponatremia**and autosomal dominant polycystic kidney disease (ADPKD).

INTRODUCTION:
Hyponatremia is a common medical condition in which the level of sodium in the blood falls below normal (less than135 mmol/L). It is more frequently seen in hospitalized patients and elderly people. Hyponatremia can occur due to excess body water or loss of sodium and is commonly caused by conditions such as heart failure, liver disease, kidney disorders, excessive fluid intake, or the use of certain medicines like diuretics,

antidepressants, and antipsychotics. The symptoms may range from mild signs such as nausea, tiredness, headache, and muscle weakness to serious complications including confusion, seizures, brain swelling, and coma in severe cases.[1-2]

Tolvaptan, a BCS Class IV drug, is used to treat hyponatremia and autosomal dominant polycystic kidney disease (ADPKD). However, its bioavailability is limited to 56% due to poor solubility and extensive first-pass metabolism. To address these challenges, a formulation incorporating **solid dispersions** has been developed to enhance solubility and improve bioavailability.[3-4,]
An additional strategy to improve Tolvaptan's bioavailability is the use of **sublingual tablets as dosage form**. The sublingual route bypasses the hepatic first-pass effect, allowing the drug to be absorbed directly into the bloodstream through the sublingual mucosa. This provides a faster onset of action and higher bioavailability compared to oral tablets, making it ideal for critical conditions like hyponatremia, where rapid intervention is crucial. Sublingual tablets offer the added advantage of not requiring water, making them useful for patients with swallowing difficulties or in emergency situations.[5-6] so objective of the study was to formulate sublingual tablets of Tolvaptan using solid dispersion.

MATERIALS AND METHODS:

Materials:

Tolvaptan was procured from Amneal Pharmaceuticals, Ahmedabad, India as gift sample. Eudragit RS 100, Xanthan gum, Guar gum, and PEG 6000, Sodium Starch Glycolate Avicel PH 102, D-Mannitol, Citric acid, Sodium bicarbonate, Aspartame, Sodium Lauryl Sulfate, Talc, Magnesium stearate and Methanol were purchased by Chemdyes Corporation, India.

Methods:

Formulation method for solid dispersion[7-8]

Solid dispersions of Tolvaptan were prepared with Xanthan Gum, Guar Gum, Eudragit RS100, and PEG 6000 in drug-to-polymer ratios of 1:1 and 1:2 using the solvent evaporation method. A weighed quantity of Tolvaptan was dissolved in a minimum volume of methanol, to which the required amount of polymer was gradually added with continuous stirring to obtain a uniform solution or dispersion. The mixture was stirred for 1 hour and subsequently subjected to solvent evaporation on a water bath maintained at 45–50 °C until a dry mass was obtained. The dried solid dispersion was then kept in a desiccator containing anhydrous calcium chloride until a constant weight was achieved, after which it was pulverized using a mortar and pestle, passed through a 60# sieve, and stored in a desiccator for further evaluation. Composition of different formulations of Tolvaptan Solid Dispersion were showed in Table 1.

Table 1: Composition of Various Solid Dispersions of Tolvaptan

Sr. No.	Formulation code	Composition	Ratio
1.	SD1	Drug : Xanthan gum	1 : 1
2.	SD2	Drug : Xanthan gum	1 : 2
3.	SD3	Drug : Guar gum	1 : 1
4.	SD4	Drug : Guar gum	1 : 2
5.	SD5	Drug : Eudragit RS 100	1 : 1
6.	SD6	Drug : Eudragit RS 100	1 : 2
7.	SD7	Drug : PEG 6000	1 : 1
8.	SD8	Drug : PEG 6000	1 : 2

Formulation method for sublingual tablet[9-10]

Tolvaptan sublingual tablets were prepared by the direct compression method incorporated with effervescent material, in which all ingredients were accurately weighed according to the formulation design and passed through a 44# sieve to ensure uniform particle size distribution. Tolvaptan solid dispersions were blended with Avicel PH 102, D-mannitol, superdisintegrants, citric acid, and sodium bicarbonate using geometric dilution to obtain a homogeneous mixture. Subsequently, talc, magnesium stearate, and sodium lauryl sulfate were incorporated and gently mixed to improve flow and lubrication. The final blend was compressed into sublingual tablets using 8 mm flat round punches on a Rimek multi-rotary 16-station tablet compression machine, and the prepared tablets were evaluated for various physicochemical parameters to ensure suitability for sublingual administration. All formulation compositions are listed in Table 2.

Table 2: Composition of Formulation of Tolvaptan Sublingual Tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Solid Dispersion Equivalent to 15 mg Tolvaptan	27.49	36.61	41.93	27.49	36.61	41.93	27.49	36.61	41.93
Avicel pH 102	30	30	30	30	30	30	30	30	30
SSG	3	3	3	4.5	4.5	4.5	6	6	6
D-Mannitol	35.5	26.4	21.07	34.0	24.9	19.57	32.5	23.4	18.07
Citric Acid	5	5	5	5	5	5	5	5	5
Sodium Bicarbonate	10	10	10	10	10	10	10	10	10
Aspartame	3	3	3	3	3	3	3	3	3
SLS	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3	3	3	3	3	3	3	3	3
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**

Identification of Tolvaptan by melting point determination[11]

The melting point of **Tolvaptan** was determined using the capillary method. A small quantity of the drug was filled into a thin-walled capillary tube sealed at one end and placed in a melting point apparatus. The temperature was gradually increased, and the temperature range at which the drug sample completely melted was recorded as the melting point of **Tolvaptan**.

Identification of Tolvaptan by UV Spectroscopy[12-14]

Ten milligrams of **Tolvaptan** was dissolved in one hundred milliliters of pH 6.8 phosphate buffer to create a standard stock solution with a concentration of 100µg/ml. By pipetting out 0.5, 1.0, 1.5, 2.0, and 2.5 ml of the stock solution of 100 µg/ml and diluting it up to 10 ml in a volumetric flask, working solutions with concentrations of 5, 10, 15, 20, and 25 µg/ml were created. Prepared working solutions were measured at λ_{max} 269 nm against phosphate buffer of pH 6.8 as a blank in UV−Visible Spectrophotometer.

Evaluation parameters of solid dispersions[15-17]

Bulk density: Accurately weighed the powder mixture and transferred to measuring cylinder carefully and then the volume of powder was measured without compacting.

$$\textbf{Bulk density (gm/ml)} = \frac{\textbf{Mass of powder (gm)}}{\textbf{Bulk volume of powder (ml)}}$$

Tapped density: Tapped density was measured by placing graduated cylinder containing formulation blend on mechanical tapping apparatus. Tapped volume was measured until constant tapped volume achieved.

$$\textbf{Tapped density (gm/ml)} = \frac{\textbf{Mass of powder (gm)}}{\textbf{Tapped volume of powder (ml)}}$$

Hausner's ratio: Hausner's ratio is a ratio of tapped density to bulk density.

$$\textbf{Hausner's ratio} = \frac{\textbf{Tapped density}}{\textbf{Bulk density}}$$

Compressibility index: Carr's index is 100 times the ratio of the difference of tapped density and bulk density to tapped density.

$$\textbf{Compressibility Index (\%)} = \frac{\textbf{Tapped density} - \textbf{Bulk density}}{\textbf{Tapped density}} \textbf{ X 100}$$

Angle of repose: It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane; Angle of repose was determined by funnel method. Powder blend was poured from funnel that can be raised vertically until it reaches maximum cone height (h) was obtained. Radius (r) of the pile was measured. Angle of repose was measured by following formula.

$$\textbf{Tan } \theta = \frac{h}{r} \qquad \theta = \tan^{-1}\frac{h}{r}$$

Where, **θ** = Angle of repose, **h** = Height of pile, **r** = Radius of pile

Void volume: The volume of the space between particles was determined by applying the following formula:

$$\textbf{Void volume} = \textbf{Bulk volume} - \textbf{Tapped volume}$$

% Porosity: The % porosity of the granules of each prepared batch was determined using the following formula:

$$\% \textbf{ Porosity } = \textbf{ 1} - \frac{\textbf{Tapped volume}}{\textbf{Bulk volume}} \textbf{ X 100}$$

% Practical yield: The prepared solid dispersion were collected and weighed. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the solid dispersion.

$$\% \textbf{ Practical yield } = \frac{\textbf{Actual weight of solid dispersion obtained}}{\textbf{Total weight of drug and polymer added}} \textbf{X 100}$$

% Drug Content: The amount of drug present in 15 mg equivalent amount of solid dispersion was determined by dissolving the powder mixture in 100 ml of pH 6.8 phosphate buffer and suitably diluted with pH 6.8 phosphate buffer and UV absorbance was measured at 269 nm. Drug concentration was determined from standard graph.

***In-vitro* Drug Release Studies:** Dissolution studies of solubility enhanced dispersions were determined by USP type II (paddle type) dissolution apparatus. This test performed using 900 ml of phosphate buffer (pH 6.8) at 37 ± 0.5 °C at 50 rpm which was maintained throughout the experiment. 5 ml samples were withdrawn at 5 min of time interval and the same quantity of sample was replaced with fresh dissolution media. The sample was filtered through 0.45 µm membrane filter. Absorbance of these samples was analyzed by using UV spectrophotometer at 269 nm.

Solubility studies: Solid Dispersion of drug equivalent to 15 mg of Tolvaptan was added to 100 ml of pH 6.8 phosphate buffer in a beaker. The contents of the beaker were stirred for 6 hours using a mechanical stirrer (1000 rpm) at 37 ± 0.5 ºC. After stirring, the beaker was allowed to stand for 12 hours for equilibration at 37 ± 0.5 ºC. The resultant solution was filtered through a 0.45 μm membrane filter, and the filtrate was analyzed by UV spectrophotometer at 269 nm.

Pre-compression parameters for powder blend of sublingual tablets[18-24]

Hausner's ratio, bulk density, tapped density, compressibility index, and angle of repose were all measured. Good flow qualities were indicated by the powder mixture's minimum Carr's index, Hausner's ratio, and angle of repose.

Post compression parameters for sublingual tablet[18-24, 6]

General appearance

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. It includes tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Thickness and diameter

Vernier calipers were used to measure the tablet's diameter and thickness. Six tablets were chosen at random, and two arms of Vernier calipers were used to measure each tablet's thickness and diameter.

Hardness

The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The crushing strength of tablets was measured by using Monsanto type hardness tester.

Weight Variation[19-20]

20 tablets selected at random were weighed and the average weight was calculated. Not more than two of the individual weights deviated from the average weight by more than the percentage showed in Table 3.

Table 3: Weight variation limit

Average weight of tablet	% Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250mg or more	±5

% Friability

Friability test: The friability of tablets was measured by Roche type friabilator. 20 tablets were initially weighed and then tablets were placed in friabilator at 25 rpm for 4 min then tablets were deducted and weighed again. Loss in weight should not be more than 1 %. Friability determined by using following equation.

$$\% \textbf{ Friability} = \frac{\textbf{Initial weight} - \textbf{Final weight}}{\textbf{Initial weight}} \times \textbf{100}$$

Drug content

The amount of drug present in 15 mg equivalent amount of tablet was determined by dissolving the powder mixture in 100 ml of pH 6.8 phosphate buffer and suitably diluted with pH 6.8 phosphate buffer. The solution was filtered through 0.45 mm membrane filter and UV absorbance was measured at 269 nm. Drug concentration was determined from standard graph.

Wetting time

Six circular tissue papers of 10 cm diameter were placed in a petridish. 10 ml of phosphate buffer (pH 6.8) containing amaranth dye was added to petridish. A tablet was carefully placed on the surface of tissue paper. Time required for water to reach the upper surface of tablet was noted as a wetting time.

***In-vitro* Disintegration test**

This test performed on six tablets using digital tablet disintegration test apparatus. 500 ml Phosphate buffer (pH 6.8) at 37 ± 0.5 °C was used as a disintegration media and time in sec. was recorded for complete disintegration of tablet with no residue remaining in apparatus.

***In-vitro* Drug release study**

In vitro drug release of Tolvaptan Sublingual Tablets was determined by USP type II (paddle type) dissolution apparatus. This test was performed using 900 ml of phosphate buffer (pH 6.8) at 37 ± 0.5 °C at 50 rpm. 5 ml samples were withdrawn 5 min of time interval and the same quantity of sample was replaced with fresh dissolution media. The sample was filtered through 0.45 µm membrane filter. Absorbance of these samples was analyzed by using UV spectrophotometer 269 nm.

Stability study

In the present study, stability study of optimized batch was carried out at 40 ± 2°C/ 75 ± 5% RH for time period of 1 month by wrapping the formulation in aluminum foil to prevent the formulation from exposure to light under the as prescribed by ICH guidelines for accelerated stability study. After completion of 30 days tablets were evaluated for Hardness, Drug content, Wetting time, *In vitro* Disintegration time and *In-vitro* Drug release study.

RESULTS AND DISCUSSION

Determination of melting point of Tolvaptan

Melting point determination is one of the popular techniques used to identify drug using melting point apparatus and melting point of Tolvaptan was found in the range of 222 – 231 °C. Reported melting point of Tolvaptan is 225-230°Cand is thus similar to the melting point of Tolvaptan (Table 4).

Table 4: Melting point of Tolvaptan

Sr. No.	Reported Melting Point[18]	Observed Melting point
1.	225-230°C	225-227 °C
2.		224-227 °C
3.		229-230 °C

Identification of drug by UV Spectroscopy Method

Drug overlay spectra were acquired by scanning solutions with varying concentrations (5, 10, 15, 20, and 25 µg/ml) at 269 nm. The overlain spectra obtained confirmed that the model drug was Tolvaptan as it gave linearity at 269 nm wavelength with R^2 value of 0.997 as showed in Table 5 and Figure 1.

Table 5: Absorbance of different concentration of Tolvaptan in phosphate buffer at pH 6.8

Sr. No.	Concentration (ppm)	Absorbance			Mean Absorbance ± S. D.
		I	II	III	
1.	5	0.318	0.321	0.317	0.319 ± 0.002
2.	10	0.439	0.436	0.438	0.438 ± 0.001

3.	15	0.587	0.587	0.586	0.587 ± 0.005
4.	20	0.701	0.704	0.702	0.702 ± 0.002
5.	25	0.860	0.860	0.862	0.861 ± 0.001

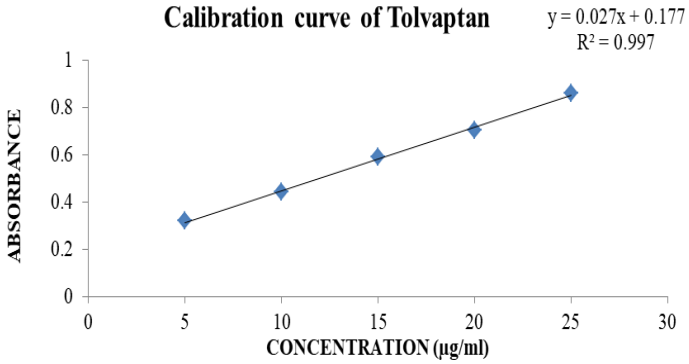

Figure 1: Calibration curve of Tolvaptan in phosphate buffer at pH 6.8

Solubility Study of Tolvaptan in Different Media

Tolvaptan shows very low solubility across various media. In water, it is practically insoluble with a solubility of 0.37 ± 0.07 µg/ml. In 0.1 N HCl, simulating gastric conditions, it is slightly soluble (0.04 ± 0.03 µg/ml), and in phosphate buffer at pH 6.8, it remains slightly soluble (0.03 ± 0.02 µg/ml). These low solubility values across different environments suggest that Tolvaptan bioavailability may be limited (Table 6).

Table 6: Solubility of Tolvaptan in Different Media

Sr. No.	Media	Reported Solubility[13] (µg/ml)	Observed Solubility (n=6) (µg/ml ± S.D.)	Remarks
1.	Water	0.4	0.37 ± 0.07	Practically insoluble
2.	0.1 N HCl	0.05	0.04 ± 0.03	Slightly soluble
3.	Phosphate Buffer pH 6.8	0.02	0.03 ± 0.02	Slightly soluble

Results of solid dispersion:

The solid dispersions SD1 to SD8 were evaluated for powder flow and packing properties. Bulk density ranged from 0.53 ± 0.005g/ml to 0.58 ± 0.004g/ml, and tapped density ranged from 0.62 ± 0.005 g/ml to 0.70 ± 0.005g/ml. The Carr's index was between 14.51 ± 0.026 % and 18.57 ± 0.026 %, while the Hausner's ratio varied from 1.16 ± 0.101 to 1.2 ± 0.131, indicating good flow characteristics. The angle of repose was observed between 26.44 ± 0.212°θ and 29.74 ± 0.216 °θ, supporting acceptable flowability. The void volume was minimal (0.10 ± 0.040 –0.40 ± 0.050), and porosity ranged from 17.64 ± 1.009% to 35.29 ± 1.252%, reflecting proper packing and uniformity of the solid dispersions. All Results are demonstrated in Table 7.

Table 7: Flow Properties of Tolvaptan Solid Dispersions

Batch	Bulk Density (gm/ml ± S.D.) (n=6)	Tapped Density (gm/ml ± S.D.) (n=6)	Carr's Index (% ± S.D.) (n=6)	Hausner's Ratio ± S.D. (n=6)	Angle of Repose (°θ ± S.D.) (n=6)	Void Volume ± S.D. (n=6)	% Porosity ± S.D. (n=6)
SD1	0.56 ± 0.005	0.66 ± 0.002	15.15 ± 0.046	1.17 ± 0.061	27.75 ± 0.482	0.20 ± 0.050	33.33 ± 1.035
SD2	0.57 ± 0.004	0.70 ± 0.005	18.57 ± 0.026	1.22 ± 0.106	28.07 ± 0.252	0.30 ± 0.100	26.31 ± 1.753
SD3	0.58 ± 0.004	0.68 ± 0.005	14.70 ± 0.010	1.17 ± 0.104	27.14 ± 0.151	0.20 ± 0.092	27.77 ± 0.690
SD4	0.57 ± 0.002	0.68 ± 0.004	16.17 ± 0.030	1.19 ± 0.115	28.39 ± 0.254	0.40 ± 0.050	17.64 ± 1.009
SD5	0.53 ± 0.010	0.63 ± 0.005	15.87 ± 0.020	1.18 ± 0.111	28.72 ± 0.193	0.40 ± 0.050	26.31 ± 1.536
SD6	0.54 ± 0.010	0.66 ± 0.002	18.18 ± 0.040	1.22 ± 0.108	29.74 ± 0.216	0.30 ± 0.050	27.77 ± 0.751
SD7	0.54 ± 0.004	0.65 ± 0.002	16.92 ± 0.030	1.20 ± 0.131	26.44 ± 0.212	0.10 ± 0.040	35.29 ± 1.252
SD8	0.53 ± 0.005	0.62 ± 0.005	14.51 ± 0.026	1.16 ± 0.101	28.19 ± 0.285	0.20 ± 0.080	29.41 ± 1.508

The solid dispersions SD1 to SD8 demonstrated a practical yield ranging from 89.69 ± 0.165 to 96.21 ± 0.259. The solubility of the dispersions was found to be between 0.88 ± 0.072µg/mL to 1.32 ± 0.072 µg/mL, while the drug content ranged from 96.17 ± 0.294% to 98.67 ± 0.769%, indicating good efficiency of the preparation method and uniform distribution of Tolvaptan in the solid dispersions. All Results are demonstrated in Table 8.

Table 8: Practical yield, Solubility of Various Solid Dispersions of Tolvaptan and % Drug content

Batch	% Practical Yield ± S.D. (n=6)	Solubility of Various Solid Dispersions of Tolvaptan (µg/ml ± S.D.)(n=6)	% Drug Content (% ± S.D.) (n=6)
SD1	92.69 ± 0.599	1.03 ± 0.035	97.67 ± 0.769
SD2	96.12 ± 0.278	1.17 ± 0.061	96.36 ± 0.624
SD3	95.36 ± 0.314	1.24 ± 0.051	97.64 ± 0.720
SD4	96.21 ± 0.259	1.32 ± 0.072	98.67 ± 0.769
SD5	90.67 ± 0.580	0.88 ± 0.072	97.67 ± 0.769
SD6	93.11 ± 0.573	0.97 ± 0.025	96.99 ± 0.608
SD7	89.69 ± 0.165	0.91 ± 0.015	96.17 ± 0.294
SD8	95.22 ± 0.203	1.06 ± 0.053	98.25 ± 0.433

In-vitro Drug Release Profile of Tolvaptan Solid Dispersion

In vitro drug release study stated that more than 50% of the drug was released within 15 minutes for all formulations. Formulations SD1–SD8 showed 5 min drug release ranging from 12.25 ± 0.447% to 28.55 ± 0.077% and achieved over 94% release within 25–40 minutes. The results indicated that the polymer type influenced the release profile, with batches containing guar gum showing the fastest and most complete release, achieving over 95% drug release in 30 minutes (Figure 2).

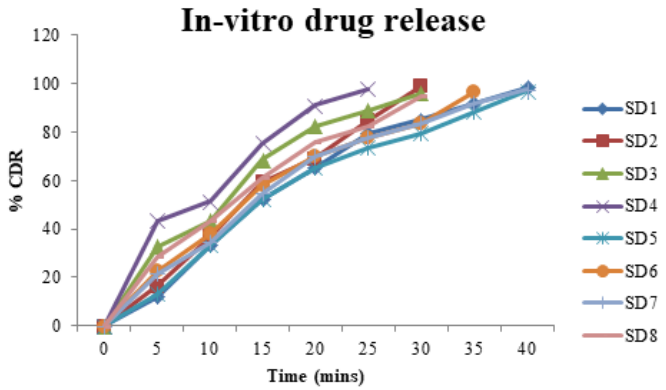

Figure 2: *In-vitro* Drug Release of Batches SD1& SD8

In conclusion, the study demonstrated that solid dispersions of Tolvaptan with guar gum in various ratios significantly enhanced the drug's dissolution rate compared to the pure drug. The best dissolution was achieved with the 1:2 ratio of Tolvaptan to guar gum, where nearly 98%-99% of the drug dissolved within the first 25 minutes. Formulation Batch SD4 (1:2 ratio) showed excellent taste-masking properties and a high drug release of 97.55 ± 0.071 % in 25 minutes, making it the most promising candidate for the development of sublingual tablets. Overall, the solid dispersion approach successfully improved both the dissolution rate and the taste masking of Tolvaptan.

Results of sublingual tablet

Pre-compression Parameters of sublingual Tablet

The formulation blends of batches F1 to F9 exhibited bulk densities ranging from 0.52 ± 0.026g/ml to 0.60 ± 0.044g/ml and tapped densities ranging from 0.64 ± 0.026g/ml to 0.73 ± 0.050g/ml. The Carr's index ranged from 17.39 ± 0.357% to 23.28 ± 0.330% and Hausner's ratio ranged from 1.18 ± 0.020 to 1.3 ± 0.020, indicating powder flow from excellent to passable. The angle of repose ranged from 26.45 ± 0.328°θ to 34.21 ± 0.215°θ, suggesting flow properties from excellent to poor, overall showing acceptable characteristics for tablet compression. All results were demonstrated in table 9.

Table 9: Pre-compression parameters

Batch	Bulk density (g/ml ± S.D.) (n=6)	Tapped density (g/ml ± S.D.) (n=6)	Carr's index (%± S.D.) (n=6)	Hausner's Ratio ± S.D. (n=6)	Angle of repose (°θ ± S.D.) (n=6)
F1	0.58 ± 0.026	0.71 ± 0.066	18.30 ± 0.755	1.22 ± 0.026	30.45 ± 0.328
F2	0.57 ± 0.053	0.71 ± 0.062	19.71 ± 0.711	1.24 ± 0.026	29.43 ± 0.403
F3	0.52 ± 0.026	0.64 ± 0.026	18.75 ± 0.250	1.23 ± 0.030	31.68 ± 0.159
F4	0.54 ± 0.053	0.69 ± 0.036	21.73 ± 0.252	1.27 ± 0.010	26.45 ± 0.328
F5	0.57 ± 0.056	0.71 ± 0.046	19.71 ± 0.301	1.24 ± 0.020	29.43 ± 0.403

F6	0.56 ± 0.036	0.73 ± 0.030	23.28 ± 0.330	1.30 ± 0.010	33.42 ± 0.386
F7	0.56 ± 0.036	0.73 ± 0.050	23.28 ± 0.330	1.30 ± 0.020	33.42 ± 0.330
F8	0.60 ± 0.044	0.71 ± 0.053	15.49 ± 0.254	1.18 ± 0.020	34.21 ± 0.215
F9	0.57 ± 0.056	0.69 ± 0.053	17.39 ± 0.357	1.21 ± 0.020	32.11 ± 0.315

Post-compression Parameters of sublingual Tablet

The formulated batches F1 to F9 exhibited tablet thickness ranging from 2.96 ± 0.020 mm to 3.02 ± 0.010 mm and diameters ranging from 5.99 ± 0.010 mm to 6.06 ± 0.060 mm. Weight variation was found between 118.00 ± 1.340 mg and 122.00 ± 1.410 mg, complying with the ±7.5 mg limits specified in the Indian Pharmacopoeia. Hardness values ranged from 2.57 ± 0.060kg/cm² to 2.97 ± 0.060 kg/cm², reflecting adequate mechanical strength suitable for sublingual tablets. Friability was observed between 0.21± 0.080% and 0.71 ± 0.130%, which is well within the pharmacopeial limit of less than 1%, indicating good mechanical stability of the tablets (Table 10).

Table 10: Post compression parameters of Tolvaptan Sublingual tablets

Batch	Thickness (mm ± S.D.) (n=6)	Diameter (mm ± S.D.) (n=6)	Weight Variation (mg ± S.D.) (n=6)	Hardness (kg/cm²± S.D.) (n=6)	Friability (%± S.D.) (n=6)
F1	2.97 ± 0.030	6.02 ± 0.070	120.00 ± 1.200	2.63 ± 0.050	0.54 ± 0.120
F2	2.99 ± 0.025	6.03 ± 0.050	121.05 ± 1.640	2.67 ± 0.120	0.21 ± 0.080
F3	2.99 ± 0.025	6.04 ± 0.050	120.30 ± 1.420	2.86 ± 0.200	0.71 ± 0.130
F4	2.98 ± 0.025	5.99 ± 0.010	119.70 ± 1.450	2.87 ± 0.200	0.42 ± 0.090
F5	3.01 ± 0.030	6.02 ± 0.070	120.75 ± 1.410	2.73 ± 0.110	0.54 ± 0.070
F6	2.99 ± 0.020	6.06 ± 0.060	118.00 ± 1.340	2.93 ± 0.060	0.37 ± 0.100
F7	3.02 ± 0.010	6.00 ± 0.010	120.45 ± 1.190	2.57 ± 0.060	0.66 ± 0.080
F8	2.98 ± 0.010	6.03 ± 0.050	122.00 ± 1.410	2.97 ± 0.060	0.46 ± 0.110
F9	2.96 ± 0.020	6.03 ± 0.050	120.00 ± 1.200	2.67 ± 0.050	0.25 ± 0.050

The formulated batches F1 to F9 showed wetting times ranging from 18.33 ± 1.150 s to 47.33 ± 1.530 s, with batch F9, containing a combination of solid dispersion and 6 mg sodium starch glycolate, exhibiting the shortest wetting time of 18.33 ± 1.150 s. *In vitro* disintegration times ranged from 24.33 ± 1.150 s to 51.33 ± 0.580 s, with batch F9 again showing the fastest disintegration at 24.33 ± 1.150 s. Drug content of all batches was between 93.41 ± 1.530% and 99.55 ± 1.200%, indicating uniform distribution of the active ingredient and accurate dosing in the sublingual tablets. (Table 11)

Table 11: Wetting time, *In vitro* disintegration time and % Drug Content

Batch	Wetting time(sec. ± S.D.) (n=6)	*In vitro* disintegration time (sec. ± S.D.)(n=6)	% Drug content (% ± S.D.)(n=6)
F1	47.33 ± 1.530	51.33 ± 0.580	93.41 ± 1.530
F2	38.33 ± 0.580	42.33 ± 0.330	96.05 ± 1.320
F3	23.33 ± 1.530	26.33 ± 1.150	98.96 ± 1.420
F4	41.33 ± 0.580	47.33 ± 0.580	94.56 ± 1.450
F5	39.67 ± 1.150	42.67 ± 1.150	98.24 ± 1.410
F6	21.67 ± 0.580	26.67 ± 1.150	97.22 ± 1.340
F7	44.33 ± 0.580	45.33 ± 0.580	94.90 ± 1.190
F8	33.33 ± 1.530	37.67 ± 1.150	96.50 ± 1.410
F9	18.33 ± 1.150	24.33 ± 1.150	99.55 ± 1.200

***In-vitro* Drug Release study**

In vitro Drug Release study of formulations F1 to F9 was performed using USP Type II (paddle) apparatus in 900 ml phosphate buffer (pH 6.8) at 37 ± 0.5 °C and 50 rpm. The results are indicated in Table 12 and Figure 3, which shows that increasing the concentration of superdisintegrant enhanced drug release, with more than 50% of the drug released within 4 minutes and over 90% released within 10 minutes. Formulations F1 to F3 showed 2 min drug release of 30.48 ± 0.212%, 37.2 ± 0.283%, and 41.08 ± 0.172%, reaching 96.25 ± 0.288%, 96.39 ± 0.222%, and 97.25 ± 0.187% at 12–16 minutes. Formulations F4 to F6 released 32.03 ± 0.211%, 37.46 ± 0.179%, and 43.93 ± 0.541% at 2 minutes, achieving 97.47 ± 0.174% to 99.26 ± 0.179 % and 96.25 ± 0.217 by 14–16 minutes. Formulations F7 to F9 showed 29.77 ± 0.149 %, 36.68 ± 0.150%, and 43.41 ± 0.262% release at 2 minutes, reaching 98.23 ± 0.199% to 98.37 ± 0.328%, **and 98.77 ± 0.144 %** by 12–16 minutes. Overall, the drug release profile confirmed that higher superdisintegrant concentrations (up to 6 mg) lead to faster and more complete drug release.

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Table 12: *In-vitro* Drug Release study of Tolvaptan Sublingual Tablets (F1-F4)

Time (min)	F1 (% ± S.D.) (n=6)	F2 (% ± S.D.) (n=6)	F3 (% ± S.D.) (n=6)	F4 (% ± S.D.) (n=6)	F5 (% ± S.D.) (n=6)	F6 (% ± S.D.) (n=6)	F7 (% ± S.D.) (n=6)	F8 (% ± S.D.) (n=6)	F9 (% ± S.D.) (n=6)
0	0.00	0.00	0.00	0.00	0	0	0	0	0
2	30.48 ± 0.212	37.20 ± 0.283	41.08 ± 0.172	32.03 ± 0.211	37.46 ± 0.179	43.93 ± 0.541	29.77 ± 0.149	36.68 ± 0.150	43.41 ± 0.262
4	47.03 ± 0.402	56.60 ± 0.253	60.48 ± 0.206	48.48 ± 0.172	57.37 ± 0.174	61.25 ± 0.187	42.37 ± 0.340	50.65 ± 0.226	57.89 ± 0.067
6	67.72 ± 0.210	71.60 ± 0.228	77.55 ± 0.235	64.10 ± 0.200	71.6 ± 0.228	74.96 ± 0.484	53.75 ± 0.266	61.25 ± 0.187	68.24 ± 0.136
8	82.46 ± 0.242	86.34 ± 0.247	91.25 ± 0.476	82.46 ± 0.237	85.82 ± 0.619	92.29 ± 0.243	66.68 ± 0.181	79.36 ± 0.192	84.53 ± 0.207
10	83.89 ± 0.288	92.72 ± 0.150	95.55 ± 0.207	85.41 ± 0.144	91.77 ± 0.174	94.87 ± 0.183	88.13 ± 0.174	93.48 ± 0.206	96.29 ± 0.222
12	90.21 ± 0.243	95.21 ± 0.228	97.25 ± 0.187	91.25 ± 0.476	93.58 ± 0.226	96.25 ± 0.187	92.29 ± 0.222	95.39 ± 0.229	98.77± 0.144
14	94.10 ± 0.248	96.39 ± 0.222	-	93.58 ± 0.226	98.22 ± 0.206	96.25 ± 0.217	96.22 ± 0.192	98.37 ± 0.328	-
16	96.25 ± 0.288	-	-	97.47 ± 0.174	99.26 ± 0.179	-	98.23 ± 0.199	-	-

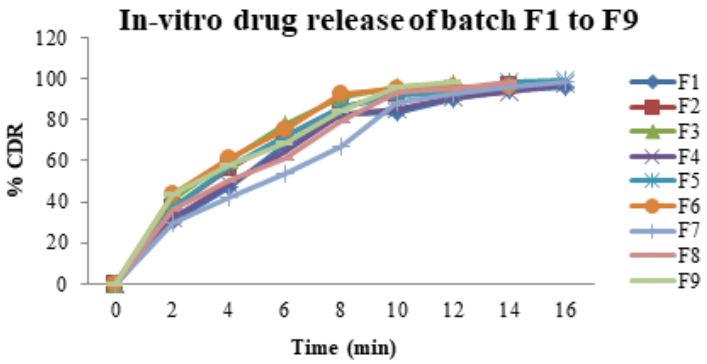

Figure 3: *In-vitro* drug release of Batch F1 to F9

Results of stability study

Based on the evaluation of all batches F9 was identified as the optimized batch due to its good surface appearance, mechanical strength, and uniform drug content. It exhibited **98.77% ± 0.103**% drug release in just 12 minutes, with the shortest wetting time of 18.33 ± 0.330 sec and the fastest *in vitro* disintegration time of 24.33 ± 0.330 seconds compared to all other batches. Therefore, batch F9 was selected as the optimized formulation. A stability study of the optimized batch was conducted at 40 ± 2 °C and 75 ± 5% RH for one month, after which hardness, wetting time, *in vitro* disintegration time, drug content, and *In-vitro* drug release was evaluated to assess its stability.

Table 13: Result of the Stability Study

Evaluation parameter	Results of optimized study (n=6)	Result after 1 month at 40 ± 2°C and 75 ± 5 % RH(n=6)
Hardness (kg/cm^2± S.D.)	2.67 ± 0.070	2.66 ± 0.060
Wetting Time (sec. ± S.D.)	18.33 ± 0.330	19.33 ± 0.330
In vitro Disintegration Time (sec. ± S.D.)	24.33 ± 0.330	24.67 ± 0.170
% Drug Content (%± S.D.)	99.55 ± 0.250	99.21 ± 0.210

Table 14: *In-vitro* Drug Release Study of Stability Batch

Time (Min.)	*In-vitro* Drug Release of Optimized Batch(% ± S.D., n=6)	*In-vitro* Drug Release of batch After 1 Month (% ± S.D., n=6)
0	0	0
2	43.41 ± 0.086	42.38 ± 0.121
4	57.89 ± 0.139	56.92 ± 0.051
6	68.24 ± 0.139	68.12 ± 0.140
8	84.53 ± 0.075	83.53 ± 0.051
10	96.29 ± 0.169	96.29 ± 0.169
12	98.77 ± 0.103	97.42 ± 0.068

The results of the stability study, as presented in Tables 13 and 14, indicated no significant changes in hardness, wetting time, *in vitro* disintegration time, drug content, or *In-vitro* drug release. This confirms that the selected optimized formulation is stable over an extended period. A comparative analysis of the optimized batch before and after the stability study is graphically illustrated in Figure 4.

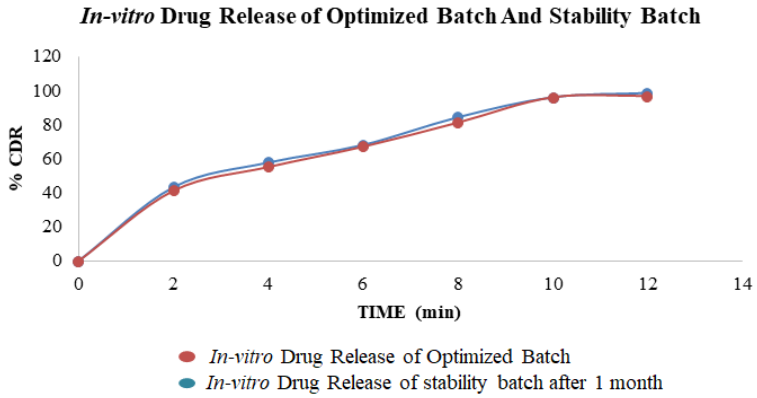

Figure 4: Comparison of *In-vitro* Drug Release of Optimized batch and stability study After1 month

Stability data showed that all the parameters were in acceptable limits as there was minor change in the results. Thus, the prepared batch F9 was stable over period of 1 month.

CONCLUSION:

In conclusion, Tolvaptan, a poorly soluble BCS Class IV drug, showed significantly improved solubility and dissolution when formulated as solid dispersions with carriers such as Guar gum, Xanthan gum, Eudragit RS100, and PEG 6000 using the solvent evaporation method. Among the solid dispersions, SD4 (Tolvaptan:Guar gum 1:2) demonstrated the highest drug content, solubility, and *In-vitro* drug release and was used for formulating sublingual tablets. Sublingual tablets prepared by the effervescent method with superdisintegrants exhibited excellent pre-compression and post-compression properties, rapid disintegration (24.33 ± 1.150 s), wetting time (18.33 ± 1.150 s), and **98.77% ± 0.144** % drug release within 12 minutes. Batch F9 was optimized on the basis of post compression parameters. Stability studies confirmed that it retained its mechanical and dissolution properties over period of one month. Overall, the study demonstrates that Tolvaptan solid dispersions can be effectively formulated into sublingual tablets, providing rapid drug release and improved patient compliance for the management of hyponatremia andautosomal dominant polycystic kidney disease.

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