RESEARCH PAPER

Formulation and Characterization of Dapoxetine Hcl Sublingual Tablets

Mitali Prajapati[1], Krishna Taretiya[2], Jitendra O. Bhangale[3*]

[1] Student, Smt. N. M. Padalia Pharmacy College, Ahmedabad, Gujarat - 382210, India.
Email: mitalip284@gmail.com

[2] Associate Professor, Smt. N. M. Padalia Pharmacy College, Ahmedabad, Gujarat - 382210, India.
Email: krishnataretiya@gmail.com

[3*] Professor and Principal, Smt. N. M. Padalia Pharmacy College, Ahmedabad, Gujarat - 382210, India.
(Corresponding Author) Email: jitu2586@gmail.com, ORCID: https://orcid.org/0000-0002-2049-3610

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ABSTRACT

The present study aimed to develop and optimize sublingual tablets of Dapoxetine HCl using solid dispersion technology and factorial design to enhance solubility, dissolution, and onset of action for the management of premature ejaculation. Premature ejaculation is a prevalent male sexual disorder significantly affecting quality of life, requiring rapid-acting therapeutic interventions. Dapoxetine HCl, a short-acting selective serotonin reuptake inhibitor, exhibits poor aqueous solubility and variable oral bioavailability due to extensive first-pass metabolism, making it a suitable candidate for sublingual delivery. Preformulation studies confirmed the identity and purity of the drug, with melting point observed in the range of 173–177°C and λmax at 291 nm. The calibration curve showed excellent linearity (R^2 = 0.9992). FTIR analysis confirmed compatibility between drug and excipients. Sublingual tablets were formulated using a 3^2 factorial design. Among all batches, DM9 exhibited optimal performance with rapid disintegration (14.63 sec) and 99.64% drug release within 14 minutes. Stability studies confirmed no significant changes under accelerated conditions. Thus, the optimized formulation demonstrated enhanced solubility, rapid disintegration, and improved drug release, making it a promising approach for fast-acting treatment of premature ejaculation.

Keywords: Dapoxetine HCl; Sublingual Tablets; Solid Dispersion; Factorial Design; Premature Ejaculation; Drug Release.

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INTRODUCTION

Premature ejaculation (PE) is one of the most common male sexual disorders, characterized by ejaculation that always or nearly always occurs before or within about one minute of vaginal penetration, or before the individual wishes it to occur. It significantly affects interpersonal relationships, self-esteem, and overall quality of life.[1-3]

Pharmaceutical research in recent years has therefore focused on the development of rapid-acting drug delivery systems capable of producing a prompt therapeutic effect, particularly for drugs like dapoxetine hydrochloride, which has a short half-life and is used on demand.[4] The development of an optimized formulation necessitates systematic investigation and rigorous empirical validation to ensure peak efficacy. Dapoxetine dose is 30-60mg orally as required but maximum once every 24 hours.[5] The oral bioavailability of dapoxetine hydrochloride is 42%. Dapoxetine is extensively bound to plasma proteins, with a binding rate of greater than 99%.[6-7] Dapoxetine hydrochloride is metabolized in the liver and kidneys through a process involving multiple enzymes.[8]

The sublingual tablets are usually small and flat, compressed lightly to keep them soft. The tablets must dissolve quickly allowing the drug to be absorbed. It is designed to dissolve in small quantity of saliva; after the tablet is placed in the mouth below the tongue, the patient should avoid

eating, drinking, smoking and possibly talking in order to keep the tablet in place.[9] Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological action.[10]

E. Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect.[11-12] Sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first pass metabolic processes.[13]

MATERIALS AND METHODS

Materials

Avicel PH 102 (MCC), Sodium lauryl sulfate, Aspartame, Citric acid and talc were provided by Grindley Merck: A Pharma Division, Ahmedabad. Magnesium stearate was supplied by Astron chemical, Ahmedabad. Methanol, Poloxamer 188, Soluplus and Indion 414 were supplied by Chemdyes Corporation, Rajkot. D-Mannitol and Sodium bicarbonate was supplied by Finar Chemicals, Ahmedabad.

DAPOXETINE HCl SUBLINGUAL TABLETS

Formulation design of Dapoxetine HCl Sublingual Tablets by Effervescent Method[14-16]

The effervescent system is generally composed of a dry acid and dry base. When reaction between dry acid and dry base takes place it facilitate a mild effervescent reaction when the tablets contact saliva. The effervescent reaction accelerates the disintegration of tablet through the release of carbon dioxide, water and salt.

Dapoxetine HCl Sublingual Tablet Tablets by Effervescent Method were prepared as follows:

A. **Dispensing:** All the ingredients were weighed as per the formulation design.

B. **Sieving:** After dispensing of the ingredients, all the ingredients were passed through sieve size of 44#. This step used for the uniformity of the ingredients and reduction in the size of particles gives uniform particle size distribution.

C. **Mixing:** After sieving, Dapoxetine HCl, Avicel PH 102, D-Mannitol, super disintegrants, Citric acid, Sodium bicarbonate were weighed and mixed in a geometric order in a mortar. Weighed quantity of Talc, Magnesium stearate and Sodium Lauryl Sulfate were mixed with the formulation blend.

D. **Compression:** Formulation blend was compressed using 8 mm flat round punch into a tablet using Rimek multi rotary 16 station tablet compression machine.

E. **Evaluation:** Prepared tablets were evaluated by various evaluation parameters.

The Composition of Various Solid Dispersions batches of Dapoxetine HCl with their ratio were as given in below table:

Calculation for Equivalent weight of drug for DS3 Batch:

Amount of Drug added: 1000 mg

Obtained weight of Solid Dispersion: 2453 mg

Actual dose of drug: 30 mg

Weight of drug (mg)		Weight of solid Dispersion (mg)
1000	→	2453
30	→	(?)

$$\text{Equivalent Weight of solid Dispersion} = \frac{30 \text{ X } 2453}{1000} = 73.59 \text{ mg}$$

3^2 FACTORIAL DESIGN

A 3^2 factorial design was applied to evaluate combined effect of Drug: Poloxamer 188 and Indion 414. In this design 2 independent variables were selected, where each variable was evaluated at three different levels –1, 0 and +1.

In 3^2 factorial design amount of Drug: Poloxamer 188 was taken as independent variable X_1 and the amount of Indion 414 was taken as independent variable X_2 and *In Vitro* Disintegration time and % CDR were selected as dependent variables Y_1 and Y_2 respectively.

Data of response (dependent variables) was recorded and analysis of data was carried out using ANOVA in the design expert 12 trial version provided by stat ease.[17-18]

The Quadratic equation for 3^2 factorial design is as follows:

$$Y = B_0 + B_1X_1 + B_2X_2 + B_{12}X_1X_2 + B_{11}X_{12} + B_{22}X_{22} + E$$

Where,

B_0 = Intercept Constant

B_1 and B_2 = Coefficient of X_1 and X_2 coefficient of first order term

B_{12} = Coefficient of interaction between X_1 and X_2 variable

B_{11} and B_{22} = Coefficient of Quadratic term

X_1 and X_2 = Independent variable

E = Error

Table 1: Coded and Actual value of formulations

Std.	Coded value		Actual value		
	X1 (DS6) Drug: Poloxamer 188	X2 (Indion 414)	X1 (DS6) Drug:Poloxamer 188		X2 (Indion 414) (mg)
			Ratio	Equivalent weight (mg)	
1.	-1	-1	1 : 1	44.07	1
2.	0	-1	1 : 2	59.22	1
3.	+1	-1	1 : 3	73.59	1
4.	-1	0	1 : 1	44.07	1.5
5.	0	0	1 : 2	59.22	1.5
6.	+1	0	1 : 3	73.59	1.5
7.	-1	+1	1 : 1	44.07	2
8.	0	+1	1 : 2	59.22	2
9.	+1	+1	1 : 3	73.59	2

Table 2: Formulation of Sublingual Tablet Tablets using 3^2 Factorial design

Ingredients (mg)	DM 1	DM 2	DM 3	DM 4	DM 5	DM 6	DM 7	DM 8	DM 9
Weight of solid dispersion (Batch DS 3) eq. to 30 mg	44.07	59.22	73.59	44.07	59.22	73.59	44.07	59.22	73.59
Avicel PH 102	30	30	30	30	30	30	30	30	30
D-Mannitol	36.93	21.78	7.41	36.43	21.28	6.91	35.93	20.78	6.41
Indion 414	1	1	1	1.5	1.5	1.5	2	2	2
citric acid	15	15	15	15	15	15	15	15	15
sod. Bi carvbonate	15	15	15	15	15	15	15	15	15
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	2	2	2	2	2	2	2	2	2
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Determination of Melting point of Dapoxetine HCl

Melting point of Dapoxetine HCl was measured by melting point apparatus.[19]

Determination of λ_{max} of Dapoxetine HCl in phosphate buffer at pH 6.8

Appropriate amounts (accurately weighed) of Dapoxetine HCl (10 mg) were quantitatively measured and then make the stock solution concentration of 100 µg/ml per IP. For determination of λ_{max}, stock solution was scanned between 200-400 nm against phosphate buffer (pH 6.8) as a blank in the UV-Visible spectrophotometer. Working solutions of concentration 2, 4, 6, 8 and 10 ppm were prepared by pipette outing 0.2, 0.4, 0.6, 0.8 and 1.0 ml respectively from the stock solution of 100 ppm and diluted up to 10 ml volumetric flask. Absorbance of working solutions was measured

in triplicate at λ_{max} at 291 nm against phosphate buffer (pH 6.8) as a blank.

Preparation of Phosphate buffer at pH 6.8: Dissolve 28.80 gm of Disodium Hydrogen Phosphate and 11.45 gm of Potassium Dihydrogen Phosphate in sufficient water to produce 1000 ml.[20]

PREFORMULATION STUDIES OF DAPOXETINE HCl

Determination of pre compression parameters

Bulk density: Accurately weighed the powder mixture and transferred to measuring cylinder carefully measure the volume of powder without compacting. It is expressed as gm/ml.[21]

$$\textbf{Bulk Density} = \frac{\textbf{Mass of powder (gm)}}{\textbf{Bulk Volume of powder (ml)}}$$

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 is not achieved. It is expressed as gm/ml. [21]

$$\textbf{Tapped Density} = \frac{\textbf{Mass of powder (gm)}}{\textbf{Tapped Volume of powder (ml)}}$$

Carr's index: Compressibility index is a ratio of difference of tapped density and bulk density to tapped density. It is expressed in percentage (%).[22]

$$\textbf{Compressibility Index} = \frac{\textbf{Tapped density} - \textbf{Bulk density}}{\textbf{Tapped density}} \times \mathbf{100}$$

Hausner's ratio: Hausner's ratio is a ratio of tapped density to bulk density. Generally, Glidant were added to improve the powder flow of the material. [22]

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

Angle of repose: 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. [22]

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

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

EVALUATION PARAMETERS OF OF DAPOXETINE HCL SUBLINGUAL TABLET

Post Compression Parameters

Thickness and Diameter: Thickness and diameter of tablets was important for uniformity of tablet size. The thickness and diameter of tablets were determined with the help of Vernier caliper. The average diameter and thickness of the tablet was calculated.[23]

Weight variation: 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.[23] (Table 3)

Table 3: Weight variation specification as per IP

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

Hardness: The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3 - 5 $kg/cm^2$is considered to be satisfactory for uncoated tablets. The crushing strength of tablets was measured by using Monsanto type hardness tester. [23]

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. [23]

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

Drug content: The amount of drug present in 30 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 291 nm. Drug concentration was determined from standard graph. [24]

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. [24]

***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. [24]

Cumulative Drug release study: % drug release of Dapoxetine HCl Sublingual Tablet Tablets was 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. 5 ml samples were withdrawn at di of time periods 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 291 nm. [24]

Stability study of optimized batch: 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 40 ± 2°C/ 75 ± 5% RH for 1 month as prescribed by ICH guidelines for accelerated stability study. After completion of 30 days tablets were evaluated for Hardness, Friability, Drug content, Wetting time, *In Vitro* Disintegration time and % Cumulative Drug release study. [25]

RESULTS AND DISCUSSION

Identification of Drug

Determination of Melting point of Dapoxetine HCl

Melting point determination is one of the popular techniques used to identify drug using melting point apparatus and melting point of Dapoxetine HCl was found in the range of 173 - 177°C. Reported melting point of Dapoxetine HCl is 175 - 183 °C and is thus similar to the melting point of Dapoxetine HCl. (Table 4)

Table 4: Melting point of Dapoxetine HCl

Sr. No.	Reported Melting Point	Observed Melting point
1.	175 – 183 ºC	174 – 177 ºC
2.		174 – 176 ºC
3.		173 – 175 ºC

Analytical method for Dapoxetine HCl

The absorbance of Dapoxetine HCl in phosphate buffer pH 6.8 was scanned between 200 - 400 nm by UV-Visible spectrophotometer. The spectrum showed λ_{max} at 291 nm. Calibration curve of Dapoxetine HCl, is constructed in phosphate buffer of pH 6.8. From stock solution of Dapoxetine HCl, working solution of concentration range i.e. 2, 4, 6, 8 and 10 ppm were prepared in phosphate buffer of pH 6.8.

Absorbance of prepared working solutions were measured at λ_{max} 291 nm against phosphate buffer of pH 6.8 as a blank in UV-Visible Spectrophotometer.

Calibration curve of prepared working solutions of Dapoxetine HCl, was constructed by plotting a graph between concentration and absorbance Reported λ_{max} of Dapoxetine HCl is 291 nm. So it can be concluded that the given drug was Dapoxetine HCl. (Fig. 1,2, Table 5)

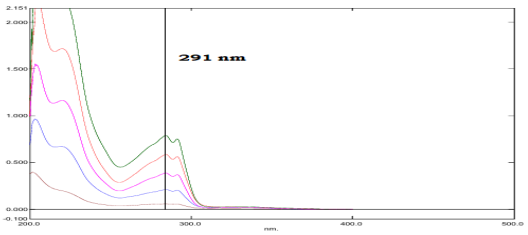


Fig. 1: Overlay Spectra of Dapoxetine HCl

Table 5 : Absorbance of different concentration of Dapoxetine HCl, in phosphate buffer at pH 6.8

Sr. No.	Concentration (ppm)	Absorbance			Mean Absorbance ± S.D.
		I	II	III	
1	2	0.079	0.081	0.08	0.080 ± 0.0010
2	4	0.288	0.291	0.285	0.288 ± 0.0030
3	6	0.484	0.489	0.488	0.487 ± 0.0026
4	8	0.681	0.682	0.685	0.683 ± 0.0021
5	10	0.872	0.875	0.874	0.874 ± 0.0015

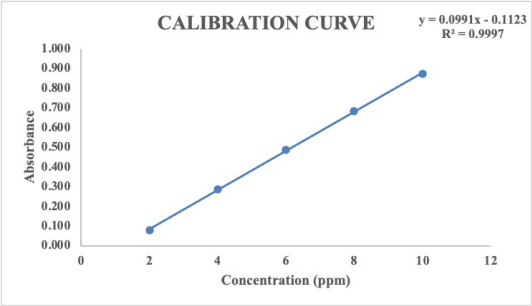


Fig. 2: Calibration curve of Dapoxetine HCl in phosphate buffer at pH 6.8

Results of Sublingual Tablets formulated by 3^2 Factorial Design

Precompression Parameters:

1. The **bulk density** values ranged from 0.50 ± 0.00 g/ml (DM2) to 0.89 ± 0.03 g/ml (DM5), while tapped density varied between 0.56 ± 0.00 g/ml and 1.14 ± 0.05 g/ml..
2. **Carr's** index values ranged from 4.38 ± 2.18% (DM1) to 21.28 ± 6.39% (DM5)**.** DM1 and DM3 exhibited excellent flow properties (≈4%), indicating minimal compressibility and low interparticle friction. DM2, DM4, DM6, DM7, and DM8 showed values within the good range (7–10%). DM9 (14.94%) demonstrated fair flow, whereas DM5 (21.28%) indicated comparatively poor flow characteristics.
3. **Hausner's ratio** values were observed between 1.05 ± 0.02 and 1.28 ± 0.10. A Hausner's ratio below 1.25 generally indicates good flow properties. DM1 and DM3 (1.05) showed excellent flow behavior, while DM2, DM4, DM6, DM7, and DM8 (≈1.08–1.11) exhibited good flow. DM9 (1.18) indicated fair flow, and DM5 (1.28) suggested poor flow, correlating well with its higher Carr's index value.
4. **The angle of repose** ranged from 27.36° to 31.48°**.** An angle below 30° indicates good flow, whereas values above 30° suggest passable to poor flow. Most batches (DM1–DM4, DM6–DM9) showed angles within acceptable limits (27–29°), confirming satisfactory flow behavior. DM5 exhibited a comparatively higher angle of repose (31.48°), indicating increased cohesiveness and reduced flowability
(Table 6)

Table 6: Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of repose data

Batch	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio	Angle of repose (°θ)
DM1	0.81 ± 0.05	0.85 ± 0.07	4.38 ± 2.18	1.05 ± 0.02	28.18 ± 0.37
DM2	0.50 ± 0.00	0.56 ± 0.00	10.00 ± 0.00	1.11 ± 0.00	27.16 ± 0.60
DM3	0.55 ± 0.01	0.58 ± 0.01	4.40 ± 2.15	1.05 ± 0.02	28.18 ± 0.37
DM4	0.54 ± 0.01	0.58 ± 0.00	7.85 ± 1.15	1.09 ± 0.01	28.18 ± 0.37
DM5	0.89 ± 0.03	1.14 ± 0.05	21.28 ± 6.39	1.28 ± 0.10	31.48 ± 0.45
DM6	0.53 ± 0.01	0.57 ± 0.01	7.74 ± 1.18	1.08 ± 0.01	27.97 ± 0.37
DM7	0.53 ± 0.01	0.57 ± 0.01	7.73 ± 2.33	1.08 ± 0.03	27.56 ± 0.35
DM8	0.53 ± 0.01	0.57 ± 0.00	7.03 ± 1.13	1.08 ± 0.01	27.36 ± 0.69
DM9	0.86 ± 0.00	1.01 ± 0.02	14.94 ± 1.99	1.18 ± 0.03	29.05 ± 0.00

POST-COMPRESSION STUDY:

The prepared tablet batches (DM1–DM9) were evaluated for post-compression parameters including thickness, weight variation, hardness, and friability to ensure compliance with pharmacopeial specifications and suitability for further development.

The thickness of tablets ranged from 2.93 ± 0.23 mm (DM4) to 3.57 ± 0.12 mm (DM5)**.** The relatively narrow variation among batches indicates uniform die filling and consistent compression during tablet punching. Minor differences in thickness may be attributed to variations in compressibility and bulk density of the powder blends. However, all values were within acceptable limits, confirming uniform tablet dimensions.

The average tablet weight for all batches was approximately 149.15–150.70 mg, with standard deviation values within acceptable range. According to pharmacopeial standards for tablets weighing around 150 mg, weight variation should not exceed ±7.5%. The observed values (149.15–150.70 mg) indicate excellent weight uniformity, suggesting proper flow of blends and uniform die cavity filling during compression.

Tablet hardness values ranged from 2.17 ± 0.29 kg/cm² (DM9) to 4.17 ± 0.58 kg/cm² (DM1)**.** Batches DM1 and DM4 showed comparatively higher hardness (above 4 kg/cm²), indicating good mechanical strength. DM6, DM8, and DM9 exhibited relatively lower hardness values, which may influence friability.

Friability values were observed between 0.43% (DM1) and 0.76% (DM6)**.** As per pharmacopeial limits, friability should be less than 1%. All batches complied with this specification, indicating satisfactory mechanical integrity. Weight variation, Thickness, Hardness and Friability data as per (Table 7)

Table 7: Weight variation, Thickness, Hardness and Friability data

Batch	Thickness (mm ± S.D.)	Weight Variation (mg ± S.D.)	Hardness (kg/cm² ± S.D.)	Friability (%)
DM1	3.23 ± 0.35	149.95 ± 1.61	4.17 ± 0.58	0.43
DM2	3.27 ± 0.29	149.50 ± 1.47	3.50 ± 0.50	0.51
DM3	3.07 ± 0.38	150.00 ± 1.56	2.83 ± 0.29	0.63
DM4	2.93 ± 0.23	150.15 ± 1.31	4.00 ± 0.87	0.48
DM5	3.57 ± 0.12	149.15 ± 1.31	3.17 ± 0.76	0.61
DM6	3.50 ± 0.17	150.70 ± 1.38	2.50 ± 0.87	0.76
DM7	3.20 ± 0.46	149.40 ± 1.64	3.33 ± 0.58	0.57
DM8	3.17 ± 0.55	150.20 ± 1.32	2.67 ± 0.29	0.68
DM9	3.27 ± 0.35	149.90 ± 1.74	2.17 ± 0.29	0.71

Wetting time (sec): Wetting time of the batches formulated was found to be in the range of 11.07 ± 0.36 sec. to 39.11 ± 1.21 sec. The batch DM9 was found to be having least (11.07 ± 0.36 sec) wetting time as compared to other batches.

The *in-vitro* disintegration time ranged from 14.63 ± 0.32 sec (DM9) to 41.77 ± 0.69 sec (DM1)**.** All batches disintegrated within one minute, which is acceptable for fast disintegrating formulations. A clear correlation between wetting time and disintegration time was observed; batches with lower wetting time exhibited faster disintegration.

Drug content across all batches ranged from 98.58 ± 0.43% (DM3) to 99.97 ± 0.89% (DM8)**.** All formulations complied with pharmacopeial limits (95–105%), confirming uniform drug distribution within the tablet matrix.

(Table 8)

Table 8: Wetting time, *In-Vitro* disintegration time and Drug Content

Batch	Wetting time (sec. ± S.D.)	*In-Vitro* disintegration time (sec. ± S.D.)	Drug content (%)
DM1	39.11 ± 1.21	41.77 ± 0.69	98.81 ± 0.88
DM2	32.82 ± 0.66	34.93 ± 0.38	99.39 ± 0.93
DM3	19.97 ± 0.32	22.84 ± 0.78	98.58 ± 0.43
DM4	36.01 ± 1.06	35.89 ± 0.55	99.16 ± 0.47
DM5	24.20 ± 0.10	27.63 ± 0.76	99.01 ± 0.30
DM6	12.85 ± 0.34	16.41 ± 0.31	98.84 ± 0.89
DM7	31.97 ± 0.60	29.80 ± 0.68	99.31 ± 1.06
DM8	18.19 ± 0.31	21.53 ± 0.26	99.97 ± 0.89
DM9	11.07 ± 0.36	14.63 ± 0.32	98.83 ± 0.83

***In-Vitro* Drug Release Profile:** The *In-Vitro* dissolution study of sublingual tablets (DM1–DM9), formulated using optimized solid dispersion of Dapoxetine HCl, was conducted to evaluate the rate and extent of drug release. Rapid drug release is a critical requirement for sublingual dosage forms to ensure quick onset of action and improved bioavailability.

All formulations demonstrated rapid initial drug release, confirming efficient tablet disintegration and immediate drug availability. At 2 minutes,

cumulative drug release ranged from 33.51% (DM1) to 46.70% (DM9**)**, indicating prompt wetting and drug diffusion from the tablet matrix.

A steady and concentration-dependent increase in drug release was observed during this period. At 10 minutes, cumulative drug release ranged from 71.85% (DM1) to 88.55% (DM9)**.** By 14 minutes, most formulations achieved more than 80% drug release, with DM9 (99.64%), DM6 (98.73%), and DM3 (92.88%) showing superior performance.

The enhanced dissolution during this phase may be attributed to rapid tablet disintegration, increased surface area due to solid dispersion, and improved solubility of Dapoxetine HCl in the dissolution medium.

Nearly complete drug release was achieved by 16–20 minutes in most batches. DM6 and DM9 exhibited almost complete release (approximately 99%) by 16 minutes, whereas DM1 required up to 20 minutes to reach 98.93% release.

DM9 demonstrated the fastest and highest cumulative drug release across all time points, indicating optimal formulation characteristics. The dissolution data confirm that all sublingual tablet batches achieved rapid and substantial drug release within 20 minutes, which is desirable for sublingual delivery systems. The incorporation of solid dispersion significantly improved the dissolution rate compared to conventional formulations. Among all batches, DM9 exhibited superior dissolution performance, making it the most promising formulation for further optimization and stability studies.

Overall, the study demonstrates that appropriate selection of formulation variables and utilization of solid dispersion technology effectively enhance the release characteristics of Dapoxetine HCl in sublingual tablets. (Table 9)

Table 9: Cumulative Drug Release of Factorial design DM1-DM9 batches

Time (min)	Cumulative % Drug release								
	DM1	**DM2**	**DM3**	**DM4**	**DM5**	**DM6**	**DM7**	**DM8**	**DM9**
0	0	0	0	0	0	0	0	0	0
2	33.51	36.94	40.62	35.56	39.68	45.13	38.31	42.92	46.7
4	47.52	52.28	56.43	50.89	55.05	60.59	53.66	57.82	63.36
6	53.05	58.76	64.59	56.89	62.72	70.01	60.63	65.18	73.7
8	62.15	67.73	72.97	65.93	71.59	78.62	69.54	74.89	81.85
10	71.85	77.02	82.62	75.42	79.63	85.39	78.61	84.42	88.55
12	77.22	81.95	86.7	80.57	83.71	89.66	83.32	88.48	92.28
14	80.73	87.41	92.88	83.96	90.35	98.73	88.88	94.06	99.64
16	89.06	91.49	98.78	90.69	96.89	99.72	94.08	98.36	-
18	92.72	98.48	-	93.48	99.81	-	98.92	-	-
20	98.93	-	-	99.15	-	-	-	-	-

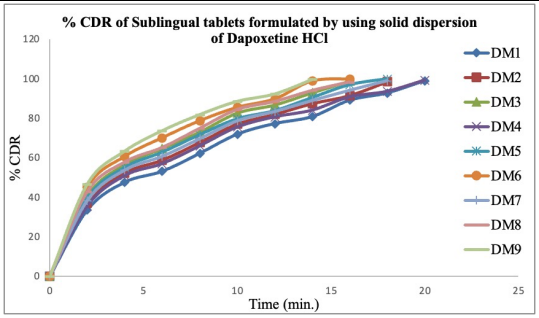


Fig. 3 : *In-Vitro* Drug Release profile of batches DM1 to DM9

STATISTICAL ANALYSIS

A statistical model incorporating polynomial and interactive terms is used to evaluate the response

$$Y= B_0 + B_1X_1 + B_2X_2 + B_{12}X_1X_2 + B_1^2X_1 + B_2^2X_2 + E$$

A polynomial equation is used to draw the conclusion after considering the magnitude of coefficient and mathematical signs (positive or negative).

Table 10: Observed Dependent Variables for 3^2Factorial Design

Batch code	*In-Vitro* disintegration time (sec.)	% CDR
DM1	41.77	80.73
DM2	34.93	87.41
DM3	22.84	92.88
DM4	35.89	83.96
DM5	27.63	90.35
DM6	16.41	98.73
DM7	29.80	88.88
DM8	21.53	94.06
DM9	14.63	99.64

Equations for 3^2 factorial design, summary of ANOVA analysis and summary of polynomial

equation as shown in Table 23 and Table 24 for all dependent variables was generated by using Microsoft excel 2010.

Table 11: Summary of polynomial equation

Response	B_0	B_1	B_2	B_{12}	B_{11}	B_{22}
***In-Vitro* Disintegration Time (Y_1)**						
Coefficient	27.40	.93	.60	9400	.14	9400
P Value rug: Poloxamer 188)	0.0005					
P Value (Indion 414)	0.0022					
% CDR at 14 minutes (Y2)						
Coefficient	90.88	6.28	3.59	3475	1961	4133
P Value rug: Poloxamer 188)	0.0011					
P Value (Indion 414)	0.0056					

Statistical analysis for *In-Vitro* Disintegration time

A quadratic model was applied to evaluate the effect of independent variables, namely X_1: Drug: Poloxamer 188 (B_1) and X_2: INDION 414 (B_2), on the response variable (*In-Vitro* disintegration time / swelling-related response). The polynomial equation generated in terms of coded factors is:

$$Y_1 = 27.40 - 8.93\ B_1 - 5.60\ B_2 + 0.9400\ B_{12} - 1.14\ B_1^2 + 0.9400\ B_2^2$$

The negative coefficients of B_1 (−8.93) and B_2 (−5.60) indicate that increasing the concentration of Drug: Poloxamer 188 and INDION 414 reduces the response value (disintegration-related parameter). The magnitude of the coefficient suggests that Drug: Poloxamer 188 exerts a comparatively greater influence than INDION 414.

The interaction term (B_1B_2 = +0.9400) shows a minor positive interaction effect, indicating that the combined influence of both polymers slightly increases the response when varied simultaneously.

The quadratic terms (B_1^2 and B_2^2) suggest curvature in the response surface. The negative coefficient for B_1^2 (−1.14) indicates a downward curvature, while the positive coefficient for B_2^2 (+0.9400) suggests a mild upward curvature.

From the result of ANOVA table it was found that Fcal values were much greater than Ftab for all formulations indicating that all factors had statistically significant effect on all dependent variables.

Summary of ANOVA Analysis

The ANOVA results confirmed the adequacy and statistical significance of the developed quadratic model. The model F-value of 70.53 indicates that the model is highly significant, while the corresponding p-value of 0.0026 (less than 0.05) further confirms its statistical validity. Both independent variables, A (Drug: Poloxamer 188) and B (INDION 414), exhibited significant p-values (< 0.05), demonstrating their substantial influence on the response. In contrast, the interaction term (AB) and the quadratic terms (A^2 and B^2) were found to be non-significant (p > 0.05), suggesting that the response is predominantly influenced by the linear effects of the formulation variables.

The coefficient of determination (R^2) was found to be 0.9910, indicating that 99.10% of the variability in the response is explained by the model.

The Adjusted R^2 value (0.9761) was in close agreement with the R^2, confirming the reliability of the model. Furthermore, the Predicted R^2 value of 0.8922 was reasonably close to the Adjusted R^2 (difference less than 0.2), indicating good predictive capability of the developed model.(Fig.4,5,6)

Contour plot and 3D surface graph for *In-Vitro* Disintegration time

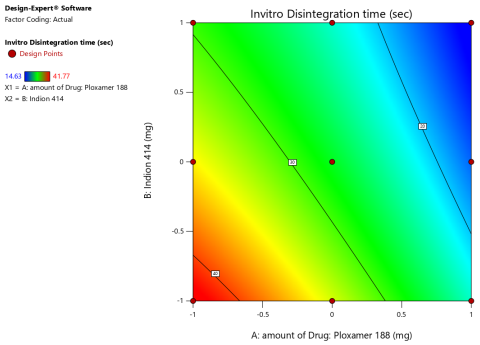


Fig. 4: Contour plot showing the effect of Drug: Poloxamer 188 (X1) and Indion 414 (X2) on *In-Vitro* Disintegration time

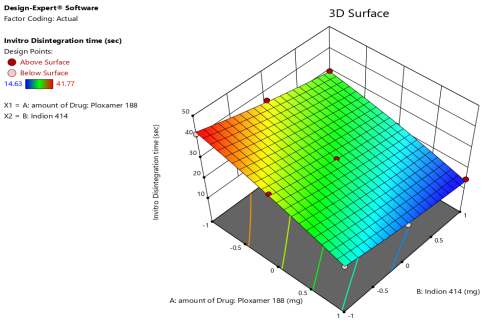


Fig. 5 : 3D surface plot showing the effect of Drug: Poloxamer 188 (X1) and Indion 414 (X2) on %CDR at 14 minutes

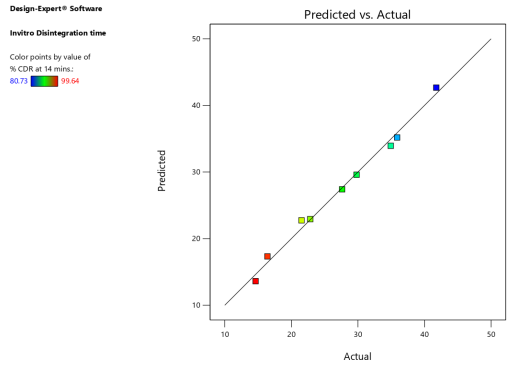


Fig. 6 :Actual value vs predicted value for *In-Vitro* Disintegration time.

The contour (2D) and three-dimensional surface plots clearly illustrate the effect of Drug: Poloxamer 188 and INDION 414 on the response. The color gradient from blue to red indicates a gradual increase in the response. Increasing levels of both factors significantly influence the response in a predictable manner. The surface appears moderately curved, supporting the presence of quadratic behavior. Maximum and minimum response regions are clearly distinguishable, enabling identification of optimized formulation conditions.

The 3D surface plot demonstrates a smooth response surface without abrupt irregularities, confirming the absence of outliers and validating model fitting.

The Actual vs. Predicted plot shows that experimental values are closely aligned along the straight reference line. This indicates:

Minimal residual error

High accuracy of model predictions

Strong agreement between observed and predicted values

The close clustering of points near the diagonal line confirms the reliability and robustness of the developed model.

Thus, the statistical analysis validates the optimization approach and confirms that the selected formulation variables significantly affect the performance characteristics of the developed sublingual tablet formulation.

Statistical analysis for % CDR at 14 minutes

The effect of formulation variables on percentage cumulative drug release (% CDR) at 14 minutes was evaluated using a quadratic model generated by Design-Expert® software. The polynomial equation obtained in terms of coded factors was:

$$Y_2 = 90.88 + 6.28\ B_1 + 3.59\ B_2 - 0.3475\ B_{12} + 0.1967\ B_1^2 - 0.4133\ B_2^2$$

The positive coefficients indicate that increasing the concentration of both Poloxamer 188 and Indion 414 leads to an increase in % CDR at 14 minutes. The negative interaction term (−0.3475) indicates a slight antagonistic interaction between the two variables when increased simultaneously.

The quadratic coefficients suggest minor curvature in the response surface, indicating that the response is not strictly linear within the studied design space.

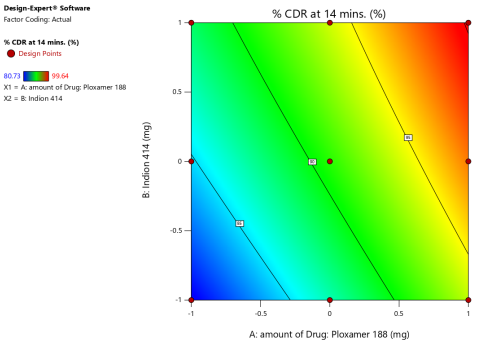
The ANOVA results confirmed the statistical significance and adequacy of the quadratic model. The model F-value of 41.85 and a p-value of 0.0056 indicate that the model is highly significant and that there is only a minimal probability that such a large F-value could occur due to noise.

Both main effects, A (Poloxamer 188) and B (Indion 414), as well as their interaction term (AB), were found to be statistically significant ($p < 0.05$), whereas the quadratic terms were non-significant, indicating that the primary contribution to % CDR arises mainly from linear and interaction effects.

The coefficient of determination (R^2) was found to be 0.9988, demonstrating that 99.88% of the variability in % CDR is explained by the model.

The Adjusted R^2 (0.9967) was in close agreement with the R^2 value, confirming the reliability of the model. Furthermore, the Predicted R^2 value (0.9850) was reasonably close to the Adjusted R^2, indicating excellent predictive capability.

Contour plot and 3D surface graph for %CDR at 14 minutes



. Fig. 7 : Contour plot showing the effect of Drug: Poloxamer 188 (X1) and Indion 414 (X2) on % CDR at 14 min

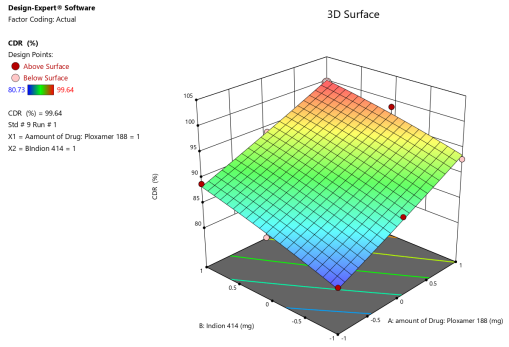


Fig. 8: 3D surface plot showing the effect of Drug: Poloxamer 188 (X1) and Indion 414 (X2) on % CDR at 14 minutes

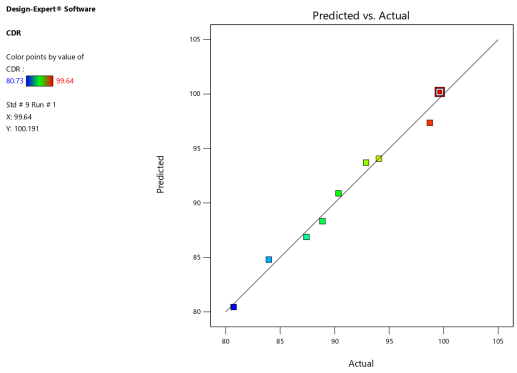


Fig. 14 : Actual value vs predicted value of %CDR at 14 minutes

The contour (2D) and three-dimensional response surface plots further illustrate the effect of formulation variables on % CDR at 14 minutes. The gradual transition of color from blue to red in the contour plot indicates a steady increase in drug release with increasing levels of Poloxamer 188 and Indion 414.

The 3D surface plot exhibits a smooth and uniformly inclined surface without abrupt irregularities, suggesting a stable and well-fitted model. Higher concentrations of both factors resulted in maximum % CDR values approaching 99%, indicating optimized drug release conditions within the experimental region.

The Predicted versus Actual plot demonstrated that the experimental values closely aligned along the diagonal reference line, indicating excellent agreement between predicted and observed responses. The minimal scatter of data points confirms low residual error and validates the robustness of the developed model.

Overall, the statistical analysis and graphical interpretation confirm that both Poloxamer 188 and Indion 414 significantly influence % CDR at 14 minutes, with Poloxamer 188 showing a comparatively stronger effect. The developed quadratic model is statistically significant, reliable, and suitable for optimization and prediction of drug release within the studied design space.

RESULTS OF STABILITY STUDY

On the basis of all above parameters of Factorial Design batches it was concluded that the batch DM9 was an optimized batch, as it had good surface appearance, Mechanical strength and Drug Content.

The stability study of the optimized batch (DM9) was carried out under accelerated conditions at 40°C and 75 ± 5% RH for a period of one month to evaluate the effect of storage on critical quality attributes. The evaluated parameters included hardness, wetting time, *In-Vitro* disintegration time, drug content, and cumulative drug release profile. The results obtained after one month were compared with the initial values to assess formulation stability.

Table 12 : Result of the Stability Study

Evaluation parameter	Results of optimized batch	Result after 1 month at 40 ± 2°C and 75 ± 5 % RH
Hardness (kg/cm^2 ± S.D.)	2.17 ± 0.29	2.23 ± 0.21
Wetting Time (sec. ± S.D.)	11.07 ± 0.36	11.17 ± 0.14
In-Vitro Disintegration Time (sec. ± S.D.)	14.63 ± 0.32	14.08 ± 0.10
Drug Content (%)	98.83 ± 0.83	99.22 ± 0.39

Table 13 : Cumulative Drug Release Study of

Stability Batch

Time (Min.)	% CDR of Optimized Batch (%)	% CDR of batch After Time Period of1 Month (%)
0	0	0
2	46.7	45.82
4	63.36	62.43
6	73.7	72.94
8	81.85	80.29
10	88.55	87.28
12	92.28	91.29
14	99.64	98.17

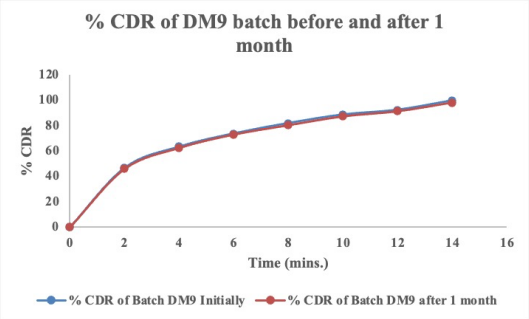


Fig. 9 : Comparison of Cumulative Drug Release study of Optimized batch and Stability batch

The hardness of the optimized batch showed a marginal decrease from 2.17 ± 0.29 kg/cm² to 2.23 ± 0.21 kg/cm², indicating no significant change in mechanical strength during the study period.

Wetting time exhibited a slight increase from 11.07 ± 0.36 seconds to 11.17 ± 0.14 seconds, which may be attributed to minor moisture uptake under accelerated conditions; however, the change was negligible and remained within acceptable limits.

Similarly, the *In-Vitro* disintegration time showed a minimal variation from 14.63 ± 0.32 seconds to 14.08 ± 0.10 seconds, indicating that the rapid disintegration property of the sublingual tablet was retained even after storage.

Drug content analysis demonstrated values of 98.83 ± 0.83% initially and 99.22 ± 0.39% after one month, confirming that no significant drug degradation occurred under accelerated storage conditions. The values remained within pharmacopeial limits (95–105%), indicating chemical stability of the formulation.

The cumulative drug release study further supported the stability of the optimized batch. At 14 minutes, % CDR was 99.64% initially and 98.17% after one month, showing only a slight reduction in drug release.

The dissolution profile before and after storage exhibited comparable release patterns at all time intervals, with only marginal variations. The similarity in dissolution curves indicates that the formulation maintained its rapid release characteristics and that the solid dispersion system remained stable without significant recrystallization or loss of solubility enhancement.

Overall, the stability study results demonstrate that the optimized batch (DM9) remained physically and chemically stable under accelerated conditions for one month.

No significant changes were observed in hardness, wetting time, disintegration time, drug content, or dissolution profile.

Therefore, it can be concluded that the developed sublingual tablet formulation possesses satisfactory short-term stability and retains its performance characteristics upon storage.

CONCLUSION

The present research work was undertaken with the objective of enhancing the solubility and dissolution rate of poorly water-soluble Dapoxetine HCl by employing optimizing sublingual tablets using a 3^2 factorial design approach.

Based on solid dispersion performance, sublingual tablets were formulated using a 3^2 factorial design (DM1–DM9). Precompression studies indicated acceptable flow properties for most blends. Post-compression parameters such as weight variation, thickness, hardness, and friability were within pharmacopeial limits.

All batches exhibited friability below 1%, confirming adequate mechanical strength.

Wetting time and *In-vitro* disintegration time were significantly influenced by formulation variables. Batch DM9 showed the fastest wetting and disintegration time, indicating efficient superdisintegrant action.

In-vitro drug release studies revealed rapid and substantial release from all formulations. DM9 demonstrated superior performance with 99.64% drug release at 14 minutes and nearly complete release within 16–18 minutes.

Statistical analysis using ANOVA confirmed that formulation variables significantly influenced both disintegration time and %CDR. High R^2

values (above 0.99) indicated excellent model fit and predictive capability.

Stability studies of optimized batch DM9 under accelerated conditions (40 ± 2°C / 75 ± 5% RH) for one month revealed no significant changes in hardness, wetting time, disintegration time, drug content, or dissolution profile.

Drug release after one month remained 98.17% at 14 minutes, confirming formulation stability.

Overall, the study successfully demonstrated that the combination of solid dispersion technology and factorial design optimization is an effective approach for developing rapidly disintegrating sublingual tablets of Dapoxetine HCl with enhanced dissolution and satisfactory stability characteristics.

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