RESEARCH PAPER

Design and Optimization of Procyclidine HCl Sublingual tablets

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ABSTRACT

Objective: The objective of the present investigation was to develop and optimize sublingual tablets of Procyclidine HCl using the direct compression method. **Materials and Method:** In this study, sublingual tablets were prepared by using different superdisintegrants such as Crospovidone and Sodium Starch Glycolate (SSG) in varying concentrations. The powder blend was evaluated for precompression parameters including Carr's Index, Hausner's Ratio, and Angle of Repose. FTIR spectroscopy was employed to evaluate drug-excipient compatibility and to confirm the absence of any significant interaction between drug and excipients. A Central Composite Design (CCD) was applied to optimize the formulation by studying the effect of Crospovidone (X_1) and Sodium Starch Glycolate (X_2) on in vitro disintegration time (Y_1) and percentage cumulative drug release (Y_2). The prepared tablets were further evaluated for post-compression parameters such as weight variation, hardness, friability, drug content, disintegration time, and dissolution study. **Results and Discussion:** Precompression parameters indicated good flow properties, while post-compression results complied with compendial standards, confirming satisfactory tablet characteristics. Among all the formulations, the optimized batch F6 showed the best performance with a disintegration time of 16.34 ± 1.02 seconds and cumulative drug release of 98.12 % within 14 minutes. Stability studies of batch F6 revealed no significant changes in hardness, friability, weight variation, drug content, disintegration time, and dissolution profile after one month of storage under conditions of 40 ± 2°C and 75 ± 5% RH. **Conclusion:** From the study, it was concluded that sublingual tablets of Procyclidine HCl prepared by the direct compression method are an effective approach to achieve rapid disintegration and enhanced drug release, making it a promising dosage form for the treatment of Parkinson's disease.

Keywords: Procyclidine HCl, Sublingual Tablets, Central Composite Design (CCD), *In vitro* Disintegration Time, % CDR.

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INTRODUCTION

Parkinson's disease is a progressive neurological disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra, leading to a deficiency of dopamine in the brain. It is one of the most common movement disorders and represents a significant cause of disability, particularly among the elderly population. The cardinal symptoms include tremors at rest, muscular rigidity, bradykinesia (slowness of movement), and postural instability. In addition to motor symptoms, patients may also experience non-motor manifestations such as cognitive impairment, depression, sleep disturbances, and autonomic dysfunction. The exact etiology of Parkinson's disease is multifactorial, involving genetic predisposition, environmental factors, and oxidative stress. If not adequately managed, the disease can lead to severe functional impairment and reduced quality of life.[1, 2]

The management of Parkinson's disease primarily focuses on symptomatic relief and improving patient quality of life. Pharmacological therapy includes dopaminergic agents and anticholinergic drugs such as Procyclidine, which are effective in reducing tremors and rigidity. However, conventional oral dosage forms may present limitations such as delayed onset of action, first-pass metabolism, and variable bioavailability, which can affect therapeutic efficacy and patient compliance.[3, 4]

Sublingual tablets have emerged as a promising alternative for drug delivery, offering rapid onset of action by allowing direct absorption of the drug through the sublingual mucosa into the systemic circulation, thereby bypassing hepatic first-pass metabolism.[5,6] This route is particularly beneficial in conditions like Parkinson's disease, where rapid symptom control is essential. Additionally, sublingual tablets improve patient compliance, especially in elderly patients who may have difficulty swallowing conventional tablets.[7, 8]

Procyclidine HCl is a BCS Class I drug with high solubility and high permeability, exhibiting an oral bioavailability of approximately 75% and a half-life of about 12 hours. It undergoes hepatic metabolism mainly via the cytochrome P450 (CYP450) enzyme system. However, conventional oral dosage forms may show delayed onset of action due to first-pass metabolism. Therefore, sublingual tablets offer a

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promising alternative by enabling rapid drug absorption through the sublingual mucosa, bypassing hepatic metabolism and improving therapeutic response in the management of Parkinson's disease.[9,10] To overcome the problem, objective of the study was to develop and optimize sublingual tablets of Procyclidine HCl.

MATERIALS AND METHOD

Materials

Procyclidine HCl was supplied by Greenson Pharma, Kalol, Ahmedabad, Gujarat, India. Crospovidone, Sodium Starch Glycolate (SSG), Mannitol, Aspartame, Magnesium stearate and Talc were provided by Chemdyes Corporation, Rajkot, Gujarat, India.

Formulation of Procyclidine HCl Sublingual Tablets by Direct Compression Method

Direct compression is used for sublingual tablets because it produces rapidly disintegrating tablets without heat or moisture, preserving drug stability and ensuring fast drug release.

All ingredients were sieved to ensure uniform particle size; Procyclidine HCl, Mannitol, Crospovidone, Sodium Starch Glycolate, and Aspartame were passed through a #60 sieve, while Magnesium stearate and Talc were passed through a #80 sieve. The materials were accurately weighed, and the drug was first blended with Mannitol to achieve uniform distribution. Superdisintegrants and Aspartame were then added and mixed thoroughly to obtain a homogeneous blend. Finally, Magnesium stearate and Talc were incorporated as lubricants and mixed gently to avoid over-lubrication. The resulting blend was directly compressed into tablets using a Cronimach lab scale compression machine, with optimized compression force to obtain tablets with adequate hardness, low friability, and rapid disintegration suitable for sublingual administration.[11, 12]

Central Composite Design (CCD)

Central Composite Design (CCD) is used in formulation design to systematically study the effects and interactions of variables and optimize the formulation with minimal experiments, making it important for efficient, accurate, and cost-effective development.

A Central Composite Design was applied to evaluate combine effect of superdisintegrants: Crospovidone and Sodium Starch Glycolate. In this design two dependent variable were selected and studied at three different levels: low (-1), medium (0) and high (+1). In Central Composite Design amount of superdisintegrantes: Crospovidone and Sodium Starch Glycolate was taken as independent variable X_1 and X_2, whereas *in vitro* disintegration time and % CDR were selected as dependent variable Y_1 and Y_2 respectively. The experimental design consisted of 4 factorial points, 4 axial points, and 5 center points. The data obtained for the responses were analyzed using ANOVA through Design-Expert® software (Version 11, Stat-Ease Inc., USA). A face-centered Central Composite Design ($\alpha = 1$) was used, with axial points at the face centers, suitable for limited factor ranges (Table 1 and table 2).[13, 14, 15]

Table 1: Coded and Actual value of Formulations

Sr. No.	Coded value		Actual value	
	X1 Crospovidone	X2 Sodium Starch Glycolate	X1 Crospovidone (mg)	X2 Sodium Starch Glycolate (mg)
1.	-1	-1	2	2
2.	0	-1	3	2
3.	+1	-1	4	2
4.	-1	0	2	3
5.	0	0	3	3
6.	+1	0	4	3
7.	-1	+1	2	4
8.	0	+1	3	4
9.	+1	+1	4	4
10.	0	0	3	3
11.	0	0	3	3
12.	0	0	3	3
13.	0	0	3	3

Table 2: Formulation Design for Procyclidine HCl Sublingual Tablets using Central Composite Design

Materials	Formulation Batches												
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Procyclidine HCl	5	5	5	5	5	5	5	5	5	5	5	5	5
Crospovidone	2	3	4	2	3	4	2	3	4	3	3	3	3
Sodium Starch Glycolate (SSG)	2	2	2	3	3	3	4	4	4	3	3	3	3
Mannitol	86	85	84	85	84	83	84	83	82	84	84	84	84

Aspartame	2	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1	1	1	1	1
Total	100	100	100	100	100	100	100	100	100	100	100	100	100

Pre Formulation Parameters

Determination of Melting Point of Procyclidine HCl

Melting point of Procyclidine HCl was measured by Melting Point Apparatus, Bhavana, India. Minimum amount of drug was placed in a thin-walled capillary tube closed at one end. This capillary was then mounted in a melting point apparatus with thermometer and then their temperature range over which Procyclidine HCl melts is measured. The readings taken in triplicate.[16]

Estimation of Procyclidine HCl by UV-Visible Spectrophotometry

Estimation by UV–Visible spectrophotometry is done because it provides a simple, rapid, and accurate method to quantify drug concentration based on its absorbance.

Preparation of standard stock solution in Phosphate Buffer at pH 6.8

Standard stock solution of Procyclidine HCl was prepared by dissolving 10 mg of Procyclidine HCl in 100 ml Phosphate Buffer at pH 6.8, which make the stock solution of concentration of 100 ppm**.** For determination of λ_{max}, stock solution was scanned between 200–400 nm against distilled Phosphate Buffer at pH 6.8 as a blank in the UV-Visible spectrophotometer, Shimadzu 1900, Japan (UV Prob-2 Software). Working solution 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 258 nm against Phosphate Buffer at pH 6.8 as a blank.[17]

Identification of drug by FTIR

Drug identification by FTIR is done because it provides a characteristic molecular "fingerprint" of functional groups, confirming the drug's identity and detecting possible impurities.

FTIR of drug was carried out to identify the drug through peaks using Shimadzu IR Affinity-1S Japan.[18]

Compatibility Study of Drug and Excipients

Compatibility study of drug and excipients is done to ensure there are no interactions that could affect the drug's stability, efficacy, or safety in the final formulation.

FTIR spectroscopy was used for drug and excipients identification and to evaluate its compatibility. FTIR spectroscopy of pure drug and physical mixture of drug and excipients was carried out to check the compatibility of drug and excipients.[18]

Pre Compression Parameters

Pre compression parameters are important to evaluate the flow properties and compressibility of the powder blend, which ensures proper die filling, uniform tablet weight, adequate mechanical strength, and consistent quality of the final dosage form.[19]

Bulk density

Bulk density is measured to evaluate powder packing and flow properties, which helps in proper die filling and dosage uniformity during tablet formulation.

Accurately weighed the powder mixture, transferred it to a measuring cylinder, and measured the volume without compacting. Bulk density was calculated, and the experiment was repeated six times.[19, 20, 21]

Tapped density

Tapped density is measured to assess powder compressibility and packing behavior, helping predict flow properties and tablet uniformity.

Tapped density was measured by placing a graduated cylinder containing the formulation blend on a mechanical tapping apparatus. The tapped volume was recorded until a constant volume was achieved to calculate tapped density, and the experiment was repeated six times.[19, 20, 21]

Hausner's ratio

Hausner's ratio is determined to evaluate powder flowability, as it indicates the degree of interparticle friction affecting uniform tablet formation.

Hausner's ratio is a ratio of tapped density to bulk density.[20, 21]

Compressibility index

Carr's index is determined to assess powder flowability and compressibility, helping predict its suitability for tablet manufacturing.

Compressibility index is defined as the ratio of the difference between tapped density and bulk density to tapped density, expressed in percentage (%), and the experiment was repeated six times.[19, 20, 21]

Angle of repose

Angle of repose is measured to evaluate powder flow properties, ensuring proper flow during tablet manufacturing.

It is defined as the maximum angle between the surface of a pile of powder and the horizontal plane. The angle of repose was determined by the funnel method, in which the powder blend was poured through a funnel raised vertically until a maximum cone height (h) was obtained. The radius (r) of the pile was measured, the angle of repose was calculated using the appropriate

formula, and the experiment was repeated six times.[19, 20]

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

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

Post Compression Parameters

Thickness and diameter

Thickness and diameter of tablets are measured to ensure uniform size, proper packaging, and consistent drug dose.

Tablet thickness and diameter were measured using Aerospace Digimatic Vernier callipers. Six tablets were randomly selected, and their thickness and diameter were measured by placing them between the two arms of the Vernier callipers.[20]

Hardness

Tablet hardness is measured to ensure sufficient mechanical strength to withstand handling while allowing proper disintegration and drug release.

Six Tablet hardness was defined as the force required to break a tablet in a diametric compression test. The crushing strength of the tablets was measured using a Monsanto-type hardness tester by D. K. Scientific, Ahmedabad, India.[20, 21, 22]

Friability test

Friability test is performed to assess the tablet's resistance to abrasion and mechanical stress during handling, packaging, and transport.

The friability of the tablets was measured using a Roche-type friabilator, Bhavana, India. tablets were initially weighed, placed in the friabilator, and rotated at 25 rpm for 4 minutes. The tablets were then dedusted and weighed again. The loss in weight was not more than 1%. The percentage friability was determined using initial and final weight.[20, 21, 22, 23]

Weight variation

Weight variation is tested to ensure uniform drug content in each tablet for accurate dosing.

Twenty tablets were randomly collected and average weight was determined by using an electronic digital weighing balance, Scale-tech, Vadodara, India.[20, 21, 22]

***In vitro* disintegration test**

In vitro disintegration test is performed to ensure the tablet breaks down within a specified time for proper drug release and absorption.

The disintegration test was performed on six tablets using a digital tablet disintegration test apparatus, Bhavana, India. Phosphate buffer pH 6.8 maintained at 37 ± 0.5 °C was used as the disintegration medium, and the time in seconds required for complete disintegration of the tablet, with no residue remaining in the apparatus, was recorded.[20, 21, 22, 24]

***In vitro* dissolution study**

In vitro dissolution test is performed to measure the rate and extent of drug release from the tablet, ensuring proper bioavailability.

The percentage drug release of Six Procyclidine HCl sublingual tablets was determined using a USP type II (paddle-type) dissolution apparatus, DKB Instruments, India. The test was performed using 900 ml of phosphate buffer pH 6.8 maintained at 37 ± 0.5 °C and a paddle speed of 50 rpm. A 5 ml sample solution was withdrawn from the dissolution apparatus at regular time intervals and replaced with an equal volume of fresh dissolution medium. Each sample was filtered through a 0.45 µm membrane filter, and the absorbance was measured using a UV spectrophotometer at 258 nm.[20, 21, 22]

Drug content

Drug content is determined to ensure each tablet contains the correct amount of active drug for accurate dosing and efficacy.

Ten tablets were powdered and equivalent to 5 mg of Procyclidine HCl was weighed and dissolved in 100 ml of phosphate buffer pH 6.8. The solution was filtered and 1 ml from filtrate was diluted to 10 ml and absorbance of this solution was analyzed by UV spectrophotometer at 258 nm.[20, 21, 22]

Stability study

Stability study is performed to determine how the drug's quality, safety, and efficacy are affected over time under various environmental conditions.

In the present study, stability study of optimized batch was carried by Stability chamber, Patel Scientific Instrument Pvt. Ltd. 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, *in vitro* disintegration time and % CDR study.[20, 21]

RESULTS AND DISCUSSION

The objectives of Preformulation studies are to develop a portfolio of information about the drug substance. So that this information is useful to develop formulation.

Preformulation investigations are designed to identify the physicochemical properties and excipients that may influence the formulation design, method of manufacturing and pharmacokinetic properties of resulting formulation.[19]

Determination of Melting Point of Procyclidine HCl

Melting point determination is one of the popular techniques used to identify drug using melting point apparatus and melting point of Procyclidine HCl was found in the range of 213-226°C. Reported melting point of Procyclidine HCl is 226-227°C and is thus similar to the melting point of Procyclidine HCl.

Estimation of Drug by UV Overlay Spectra

The absorbance of Procyclidine HCl in a phosphate buffer at pH 6.8 was scanned between 200-400 nm by UV-Visible Spectrophotometer. The reported λ_{max} of Procyclidine HCl is 258 nm (Figure 1).

Analytical Method for Procyclidine HCl

The absorbance of Procyclidine HCl in phosphate buffer at pH 6.8 was measured between 200-400 nm, revealing its maximum absorbance at 258 nm. A calibration curve was then established using working solutions ranging from 2 to 10 ppm. These solutions' absorbance at 258 nm was measured against the buffer as a blank (Table 3).

The resulting concentration-absorbance curve underwent regression analysis, yielding a regression equation (y = 0.0484x + 0.5135) with a correlation coefficient (R^2) of 0.9989, signifying a strong correlation between concentration and absorbance (Figure 2).

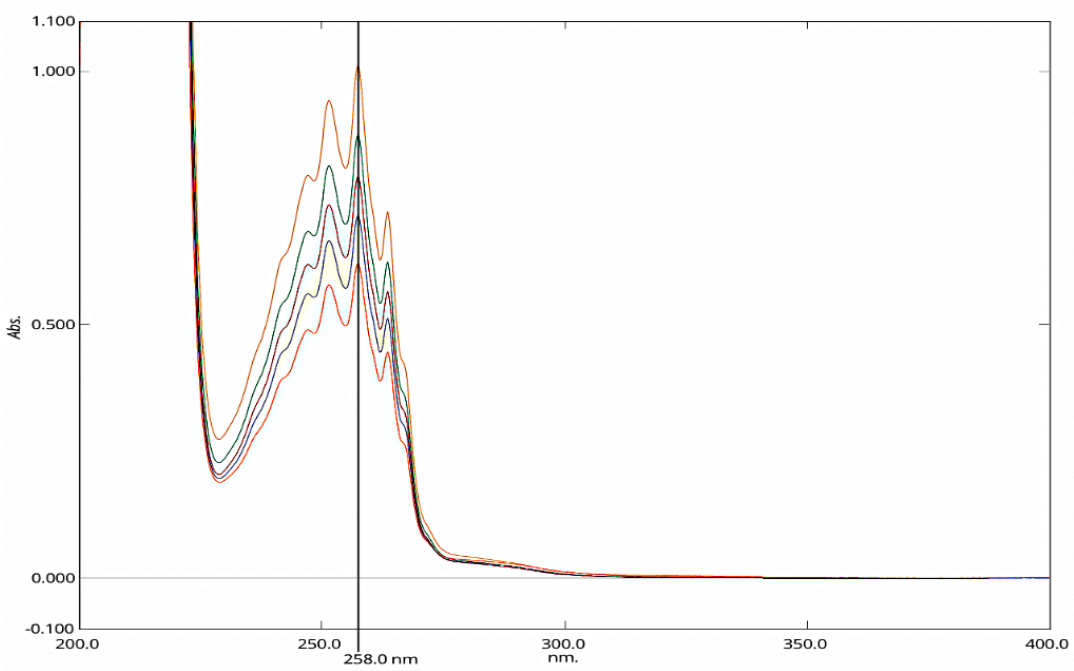

Figure 1: Overlay Spectra of Procyclidine HCl

Table 3: Absorbance of Different Concentration of Procyclidine HCl in Phosphate Buffer at pH 6.8

Sr. No.	Concentration (ppm)	Absorbance			Mean Absorbance ± S. D.
		I	II	III	
1.	2	0.612	0.616	0.617	0.615 ± 0.003
2.	4	0.702	0.706	0.707	0.705 ± 0.003
3.	6	0.797	0.799	0.801	0.799 ± 0.002
4.	8	0.893	0.897	0.898	0.896 ± 0.003
5.	10	1.004	1.000	1.005	1.003 ± 0.003

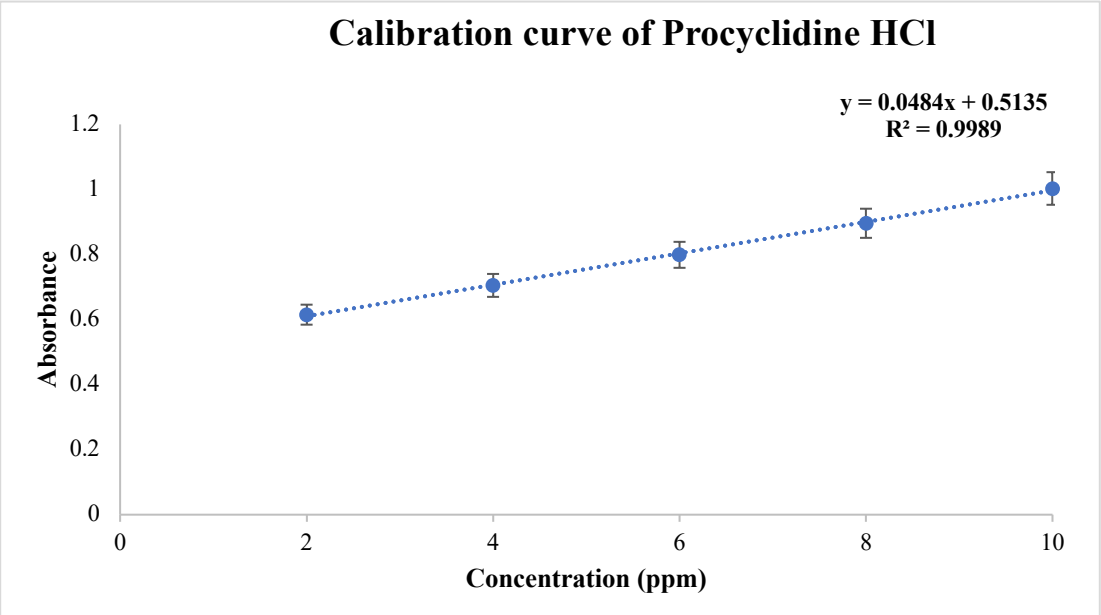

Figure 2: Calibration Curve of Procyclidine HCl in Phosphate Buffer at pH 6.8

Identification of Procyclidine HCl by FTIR Spectra

The FTIR of Procyclidine HCl shows band at 1124.50 cm^{-1}, 1124.50 cm^{-1}, 1598.99 cm^{-1}, 2497.82 cm^{-1}, 2850.78 cm^{-1}, 3088.03 cm^{-1} and 3300.00 cm^{-1} corresponding to the functional groups C-O Stretch, C-N Stretch, C=O Stretch (Aromatic), N-H Stretch, C-H Stretch (Alkyl), C-H Stretch (Aromatic), O-H Stretch. From the above interpretation it is found that major functional groups are presents in the reported structure (Figure 3) of Procyclidine HCl so, above result identifies that used API is Procyclidine HCl (Figure 4).

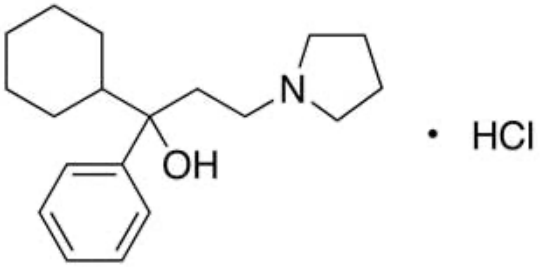

Figure 3: Structure of Procyclidine HCl

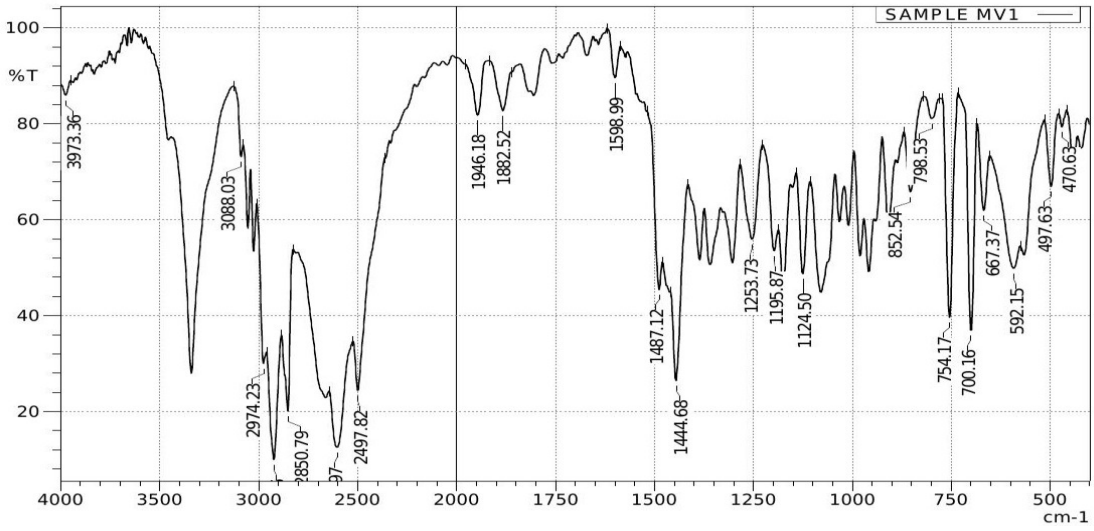

Figure 4: FTIR of Procyclidine HCl

Compatibility study of Procyclidine HCl and Excipients by FTIR Spectra

The FTIR of Procyclidine HCl and Excipients shows band at 1124.50 cm^{-1}, 1124.50 cm^{-1}, 1546.91 cm^{-1}, 2497.82 cm^{-1}, 2852.72 cm^{-1}, 3053.32 cm^{-1} and 3554.81 cm^{-1} corresponding to the functional groups C-O

Stretch, C-N Stretch, C=O Stretch (Aromatic), N-H Stretch, C-H Stretch (Alkyl), C-H Stretch (Aromatic), O-H Stretch. From the above interpretation it is found that major functional groups are present in the reported structure (Figure 3) of Procyclidine HCl and are present in the FTIR of Procyclidine HCl and Excipients with no significant change in band width (Figure 5).

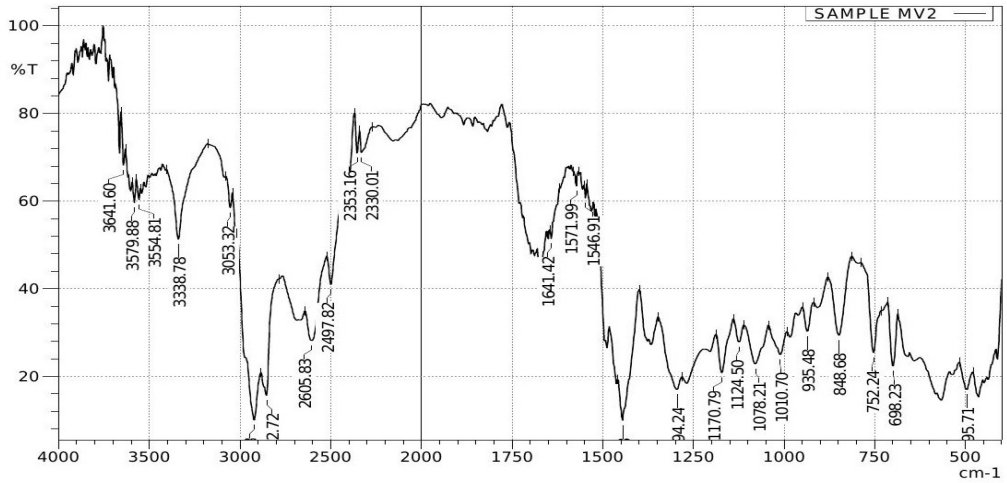

Figure 5: FTIR spectra of Procyclidine HCl and Excipients

Pre Compression Parameters

Batches F1-F13 were evaluated for bulk and tapped density. The bulk density was found to be in the range of 0.546 ± 0.009 gm/ml to 0.570 ± 0.010 gm/ml, whereas the tapped density ranged from 0.652 ± 0.009 gm/ml to 0.679 ± 0.014 gm/ml. These values indicate uniform packing and acceptable flow characteristics of all powder blends. The Hausner's ratio for batches F1-F13 was found in the range of 1.17 ± 0.03 to 1.21 ± 0.02. Based on these values, the powder blends exhibit good to fair flow properties, with most formulations closer to good flow behavior. The % Carr's Index for batches F1-F13 ranged from 14.21 ± 2.53 % to 17.09 ± 1.58 %. These results suggest that all batches possess fair to good flowability. The angle of repose for batches F1-F13 was observed in the range of 24.30 ± 0.64 ºθ to 27.10 ± 0.40 ºθ. Which indicate good to excellent flow properties for all formulations (Table 4).

Table 4: Bulk Density, Tapped Density, Hausner's Ratio, Carr's Index and Angle of Repose Data

Batch	Bulk Density (gm/ml ± S.D.)	Tapped Density (gm/ml ± S.D.)	Hausner's Ratio ± S.D.	Carr's Index (%± S.D.)	Angle of Repose (ºθ ± S.D.)
F1	0.556±0.017	0.664±0.015	1.20±0.03	16.26±1.87	26.85±0.75
F2	0.554±0.016	0.661±0.013	1.19±0.05	16.17±3.21	26.50±0.18
F3	0.570±0.010	0.679±0.014	1.19±0.02	15.97±1.34	25.37±0.48
F4	0.562±0.016	0.656±0.020	1.17±0.03	14.21±2.53	26.52±0.69
F5	0.546±0.009	0.658±0.015	1.21±0.02	17.09±1.58	25.92±0.83
F6	0.566±0.015	0.667±0.019	1.18±0.02	15.09±1.07	24.30±0.64
F7	0.562±0.017	0.670±0.018	1.19±0.03	16.07±2.28	27.10±0.40
F8	0.546±0.009	0.652±0.009	1.20±0.01	16.36±1.02	27.08±0.34
F9	0.558±0.012	0.658±0.016	1.18±0.03	15.22±2.36	26.88±0.62
F10	0.554±0.009	0.664±0.014	1.20±0.04	16.57±2.85	26.18±0.37
F11	0.560±0.010	0.670±0.009	1.20 ±0.03	16.38±2.42	25.72±0.83
F12	0.552±0.013	0.661±0.017	1.20±0.02	16.53±1.72	26.15±0.37
F13	0.556±0.011	0.652±0.014	1.17±0.03	14.80±2.13	25.43±0.54

All values are expressed as mean ± SD; (n=6)

Post Formulation Parameters

The thickness of batches F1-F13 was found to be in the range of 2.79 ± 0.02 mm to 2.85 ± 0.01 mm. The diameter of batches F1-F13 was in the range of 6.48 ± 0.01 mm to 6.56 ± 0.02 mm. The hardness of the formulated batches F1-F13 was found to be in the range of 2.27 ± 0.12 kg/cm² to 2.65 ± 0.10 kg/cm². These values are appropriate for sublingual tablets, providing sufficient mechanical strength while maintaining rapid disintegration. The friability of batches F1-F13 ranged from 0.40 % to 0.77 %. Since all values are below the USP limit of 1%, the tablets exhibit good mechanical resistance and durability. According to USP limits (±7.5% for 100 mg tablets), the weight variation for batches F1-F13 ranged from 99.12 ± 2.77 mg to 101.89 ± 2.84 mg. All batches were within acceptable limits. The *in vitro* disintegration time of batches F1-F13 was found to be in the range of 16.34 ± 1.02 sec to 22.13 ± 1.50 sec. All formulations exhibited rapid disintegration. The drug content of batches F1-F13 ranged from 95.92 ± 0.83 % to 99.08 ± 0.93 %. All formulations were within acceptable pharmacopeial limits, indicating uniform distribution of the drug throughout the

tablets (Table 5 & 6).

Table 5: Thickness, Diameter, Hardness and Friability, Weight Variation Data

Batch	Thickness (mm ± S.D.)	Diameter (mm ± S.D.)	Hardness (kg/cm^2 ± S.D.)	Friability (%)	Weight Variation (mg ± S.D.)
F1	2.85 ± 0.01	6.48 ± 0.01	2.52 ± 0.10	0.55	101.89 ± 2.84
F2	2.82 ± 0.03	6.53 ± 0.02	2.43 ± 0.15	0.63	100.53 ± 2.75
F3	2.83 ± 0.01	6.51 ± 0.03	2.37 ± 0.10	0.72	100.71 ± 2.68
F4	2.79 ± 0.01	6.56 ± 0.02	2.47 ± 0.16	0.59	99.73 ± 2.00
F5	2.83 ± 0.02	6.50 ± 0.01	2.35 ± 0.11	0.68	100.87 ± 2.84
F6	2.80 ± 0.01	6.55 ± 0.02	2.27 ± 0.12	0.77	101.41 ± 2.30
F7	2.84 ± 0.02	6.49 ± 0.02	2.65 ± 0.10	0.40	99.96 ± 1.86
F8	2.81 ± 0.01	6.52 ± 0.03	2.62 ± 0.13	0.46	100.39 ± 2.81
F9	2.79 ± 0.02	6.54 ± 0.02	2.57 ± 0.12	0.51	99.67 ± 2.72
F10	2.82 ± 0.03	6.49 ± 0.01	2.28 ± 0.13	0.72	99.12 ± 2.77
F11	2.80 ± 0.01	6.52 ± 0.03	2.32 ± 0.12	0.70	100.44 ± 2.54
F12	2.79 ± 0.01	6.50 ± 0.02	2.35 ± 0.16	0.65	100.52 ± 2.94
F13	2.83 ± 0.02	6.54 ± 0.01	2.42 ± 0.15	0.69	101.07 ± 2.13

All values are expressed as mean ± SD; (n=6)

Table 6: *In vitro* Disintegration Time and Drug Content Data

Batch	*In vitro* Disintegration Time (sec. ± S.D.)	Drug Content (%)
F1	19.76 ± 1.24	98.70 ± 0.73
F2	18.45 ± 1.59	99.08 ± 0.93
F3	17.09 ± 1.13	96.95 ± 0.89
F4	19.14 ± 1.88	95.92 ± 0.83
F5	17.88 ± 1.35	97.98 ± 0.82
F6	16.34 ± 1.02	98.59 ± 0.65
F7	22.13 ± 1.50	96.72 ± 0.88
F8	21.57 ± 1.37	98.77 ± 0.84
F9	20.73 ± 1.41	99.01 ± 0.70
F10	17.43 ± 1.24	97.73 ± 0.90
F11	17.58 ± 1.09	96.44 ± 0.64
F12	18.11 ± 1.47	98.18 ± 0.82
F13	17.73 ± 1.21	97.55 ± 0.73

All values are expressed as mean ± SD; (n=6)

Cumulative Drug Release study (%): The % CDR study was carried out using USP dissolution apparatus (Type II-paddle) in 900 ml phosphate buffer (pH 6.8) at 37 ± 0.5 °C with a rotation speed of 50 rpm. The results indicate that drug release increased progressively with time for all batches (F1–F13). More than 50% drug release was achieved within 6-8 minutes, and more than 90 % drug release was observed within 14 minutes for most formulations. For formulations F1 to F3, Drug release ranged from 17.52 % to 25.42 % at 2 minutes, which increased to 87.39 % to 96.88 % at 14 minutes.

For formulations F4 to F6, Drug release ranged from 19.67 % to 27.66 % at 2 minutes, which increased to 90.49 % to 98.12 % at 14 minutes. For formulations F7 to F9, Drug release ranged from 11.34 % to 15.75 % at 2 minutes, which increased to 69.37 % to 78.52 % at 16 minutes. For formulations F10 to F13, Drug release ranged from 21.85 % to 25.01 % at 2 minutes, which increased to 94.18 % to 96.84 % at 14 minutes (Table 7) (Figure 6).

Table 7: Percentage Cumulative Drug Release of Batch F1 to F13

Time (min.)	Batches												
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	17.52	21.12	25.42	19.67	23.14	27.66	11.34	13.42	15.75	21.85	24.32	22.67	25.01
4	30.28	36.41	41.7	33.43	39.62	44.13	19.16	21.98	26.08	37.94	40.87	38.55	41.76
6	39.34	45.55	52.64	41.74	49.73	56.78	33.43	35.37	37.23	48.26	51.14	47.89	52.38
8	58.47	66.07	73.13	62.39	68.89	76.34	40.86	47.73	53.19	66.72	70.05	67.48	71.26
10	64.15	75.33	84.36	69.52	80.37	88.35	48.12	54.09	59.41	78.91	81.92	79.64	82.47
12	72.66	81.69	87.96	77.71	84.45	91.6	54.35	59.78	63.34	83.62	85.76	84.02	86.21
14	87.39	92.74	96.88	90.49	95.27	98.12	61.43	65.24	69.46	94.18	96.11	94.73	96.84

16	-	-	-	-	-	-	69.37	73.81	78.52	-	-	-	-

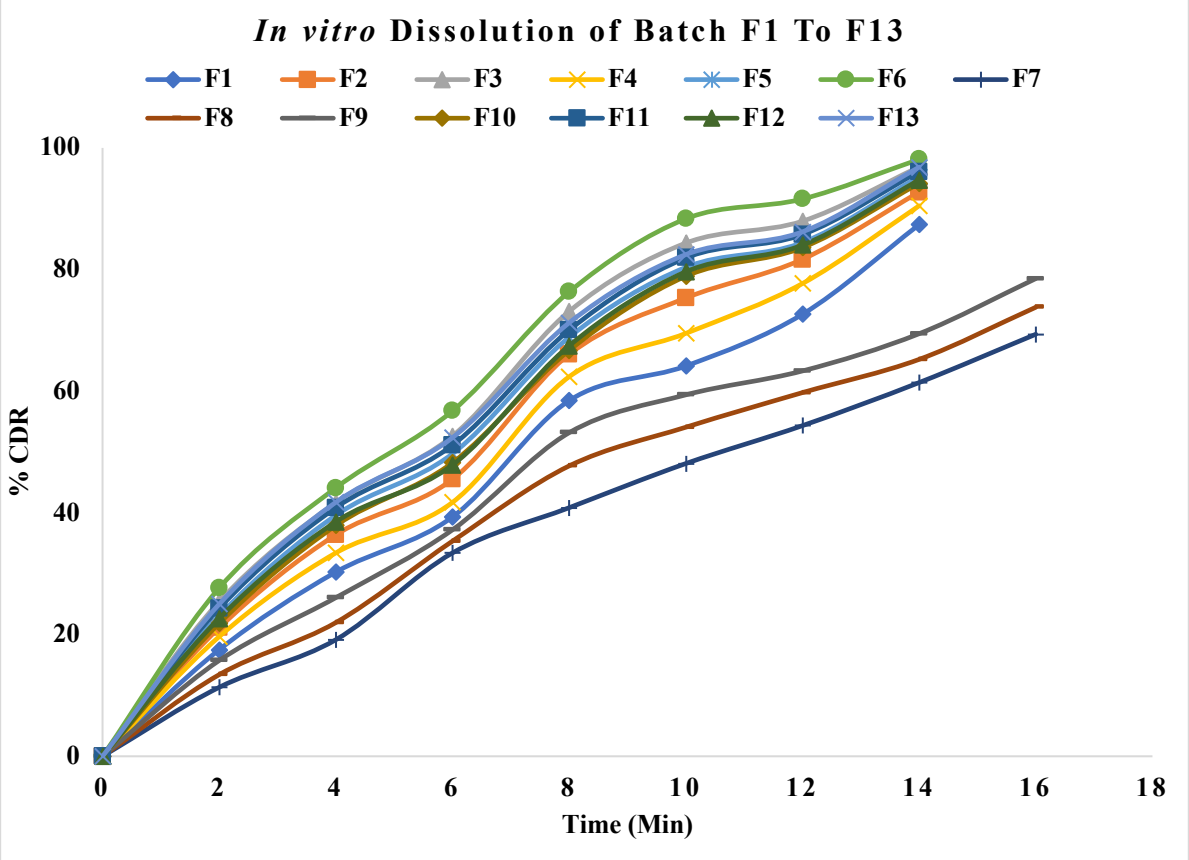

Figure 6: % Cumulative Drug Release of Batches F1 to F13

Statistical Analysis

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

$$Y = B_0 + B_1X_1 + B_2X_2 + B_{12}X_1X_2 + B_{11}X_1^2 + B_{22}X_2^2 + E$$

Utilizing a polynomial equation, conclusions are drawn by assessing the magnitude and mathematical signs (positive or negative) of coefficients.

The R^2 values for *In vitro* Disintegration time (sec.) and % CDR were 0.9875 and 0.9872, respectively, indicating a strong correlation between dependent and independent variables. Terms with p-values less than 0.05 were considered statistically significant and retained in the full model.

In the Central Composite design, *In vitro* Disintegration time and % CDR at 14 minutes were chosen as dependent variables Y_1 and Y_2, respectively. Formulation batches F1 to F13 underwent evaluation for *in vitro* disintegration time and % CDR, as detailed in Table 8.

Table 8: Observed Dependent Variables for Contral Composite Design

Batches	*In vitro* Disintegration Time (sec.)	% CDR at 14 mins
F1	19.76	87.39
F2	18.45	92.74
F3	17.09	96.88
F4	19.14	90.49
F5	17.88	95.27
F6	16.34	98.12
F7	22.13	61.43
F8	21.57	65.24
F9	20.73	69.46
F10	17.43	94.18
F11	17.58	96.11
F12	18.11	94.73
F13	17.73	96.84

Tables present the equations for the Central Composite design, along with a summary of ANOVA analysis and polynomial equations for all dependent variables. The ANOVA results revealed that the calculated F-values were considerably higher than the tabulated F-values for all formulations. This suggests that all factors had a statistically

significant impact on all dependent variables (Table 9).

Table 9: Summary of ANOVA Analysis

Source	Sum of Square	Degree of Freedom	Mean Square	F Value	P Value
***In vitro* Disintegration Time (Y_1)**					
Regression	37.96	5	7.59	110.33	< 0.0001
Residual	0.4816	7	0.0688		
Total	38.44	12			
% CDR (Y_2)					
Regression	2050.50	5	410.10	498.57	< 0.0001
Residual	5.76	7	0.8225		
Total	2056.26	12			

Statistical Analysis for *In vitro* Disintegration Time

Polynomial equation for *In vitro* Disintegration Time**:**

$$\mathbf{Y_1 = 17.76 - 1.15B_1 + 1.52B_2 + 0.3175B_{12} - 0.0429B_1^2 + 2.23B_2^2}$$

The multiple linear regression analysis showed that coefficients B_1 is negative sign which suggests that as the quantity of B_1 increase there is a decrease in *in vitro* disintegration time, and B_2 is positive sign which suggests that as the quantity of B_2 increase there is an increase in *in vitro* disintegration time.

Further examination of the equation showed that variable B_1 had a p-value of < 0.0001 ($p < 0.05$) and variable B_2 had a p-value of < 0.0001 ($p < 0.05$). Variables with p-values less than 0.05 are deemed to have significant effects. Thus, in this case, both X_1 and X_2 significantly affect the *in vitro* disintegration time in the formulation.

The Contour plot and 3D surface graph generated from the design expert software are depicted in Figure 7. Both graphs illustrate that an increase in the amount of Crospovidone leads to decrease *in vitro* disintegration time and an increase in the amount of SSG leads to increase *in vitro* disintegration time (Figure 7).

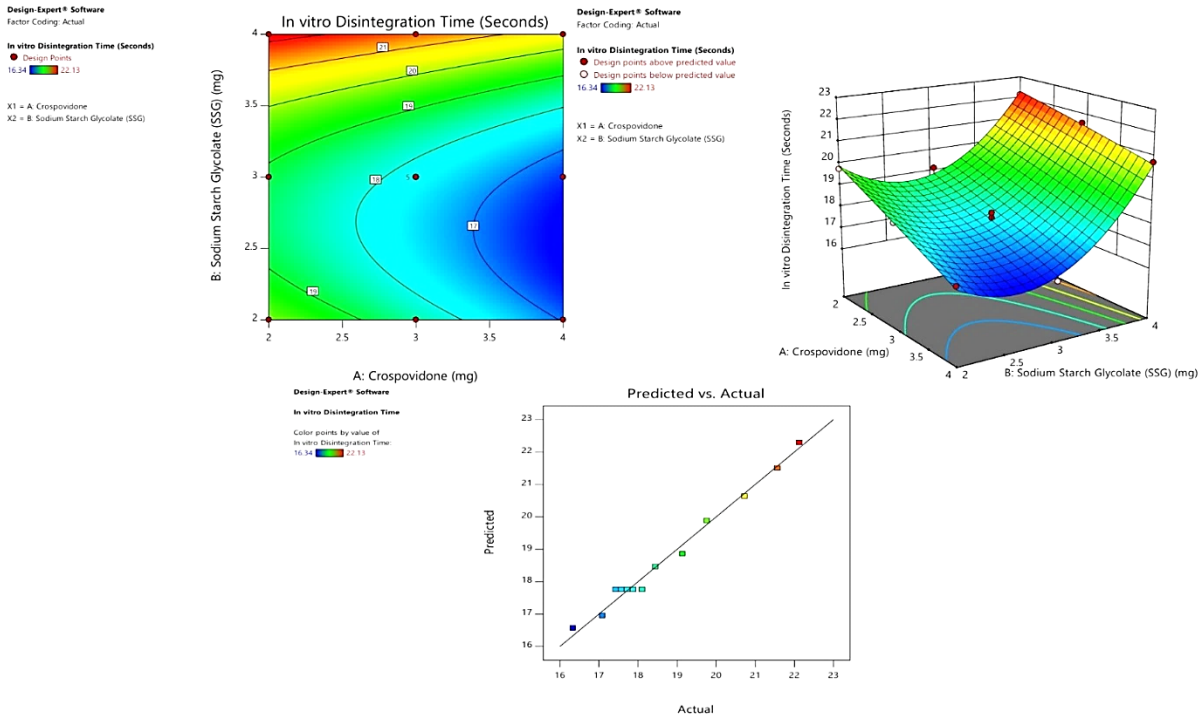

Figure 7: Contour plot, 3D surface plot, and Actual value vs Predicted value plot showing the effect of Crospovidone (X_1) and SSG (X_2) on *In vitro* Disintegration Time

Statistical Analysis for % Cumulative Drug Release

Polynomial equation for % CDR:

$$\mathbf{Y_2 = 95.30 + 4.19B_1 - 13.48B_2 - 0.3650B_{12} - 0.6764B_1^2 - 15.99B_2^2}$$

The multiple linear regression analysis showed that coefficient B_1 is positive sign which suggests that as the quantity B_1 increase there is an increase in % CDR and B_2 is negative sign which suggest that as increase B_1 there is a decrease in % CDR.

From the above equation it was found that variable B_1 have p value < 0.0001 ($p < 0.05$), variable B_2 have p value < 0.0001 ($p < 0.05$). Variables which have p value less than 0.05, have significant effects. So, here X_1 and X_2 significantly affects the % CDR in the formulation.

Contour plot and 3D surface graph taken from the design expert software are shown in this Figure 8 that an increase in the amount of Crospovidone leads to

increase in % CDR and an increase in the amount of SSG leads to decrease in % CDR (Figure 8).

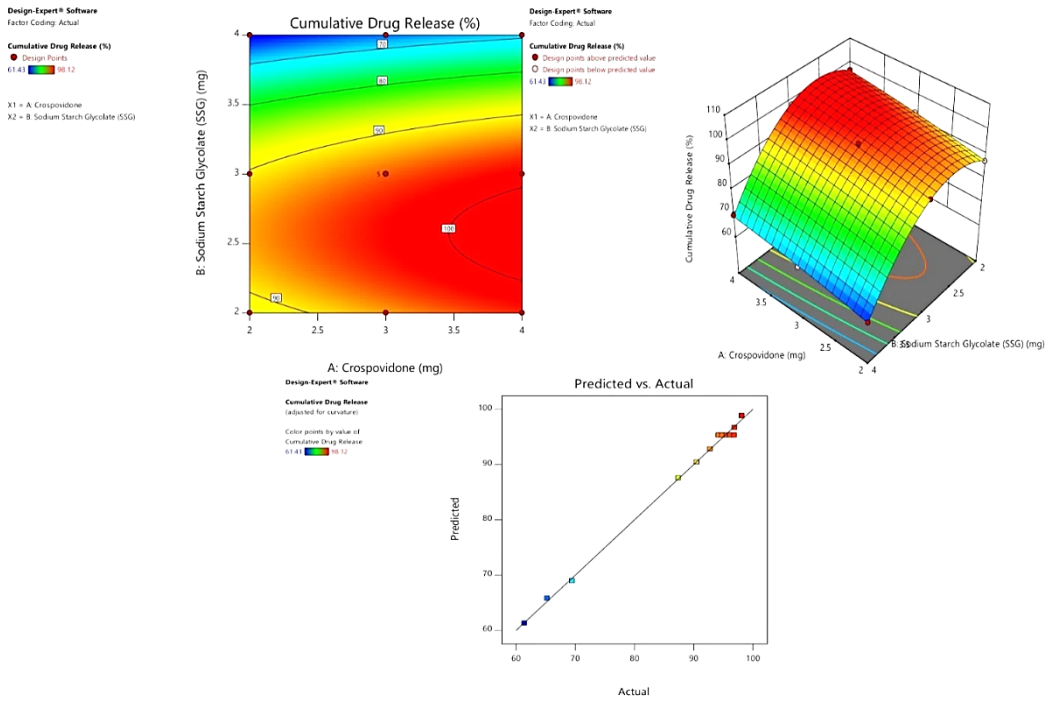

Figure 8: Contour plot, 3D surface plot, Actual value vs Predicted value plot showing the effect of Crospovidone (X_1) and SSG (X_2) on % CDR

Above graph shows the correlation of Actual value vs predicted value for % CDR. From the graph it can be concluded that the values of actual and predicted are nearer to the central diagonal and hence the statistical model is significant.

Based on the aforementioned parameters of the Central Composite Design batches, it was determined that batch F6 emerged as the optimized batch due to its favorable surface appearance, mechanical strength, and drug content. Additionally, it demonstrated a rapid drug release of 98.12 % within just 14 minutes and an *in vitro* disintegration time of merely 16 seconds, the shortest among all batches.

Results of Stability Study

Consequently, batch F6 was chosen as the optimized batch. To assess the stability of the sublingual tablets of the optimized batch, a stability study was conducted under conditions of 40 ± 2°C and 75 ± 5% RH for one month. Following this period, evaluations were performed on hardness, friability, weight variation, drug content, *in vitro* disintegration time and % CDR.

Table 10: Result of the Stability Study

Evaluation Parameters	Results of Optimized Batch	Result after 1 month at 40 ± 2 ºC and 75 ± 5 % RH
Hardness (kg/cm^2 ± S.D.)	2.27 ± 0.12	2.25 ± 0.10
Friability (%)	0.77	0.78
Weight variation (mg ± S.D.)	101.41 ± 2.30	101.52 ± 1.69
Drug Content (%)	98.59 ± 0.65	97.82 ± 0.84
***In vitro* Disintegration Time (sec. ± S.D.)**	16.34 ± 1.02	16.39 ± 1.06

All values are expressed as mean ± SD; (n=6)

Table 11: Cumulative Drug Release Study of Stability Batch

Time (Min.)	% CDR of Optimized Batch F6 (%)	% CDR of Optimized Batch F6 After Time period of 1 Month (%)
0	0	0
2	27.66	27.24
4	44.13	43.94
6	56.78	56.19
8	76.34	75.85
10	88.35	87.65
12	91.6	91.34
14	98.12	97.98

Based on the stability study results presented in Table 10 and Table 11, it can be inferred that there are no noteworthy variations in the parameters of hardness, friability, weight variation, drug content, *in vitro* disintegration time and % CDR. Thus, it can be deduced that the chosen formulation remains stable over an extended period.

A comparison between the results of the optimized batch and the same batch after the stability testing period is visually depicted in Figure 9.

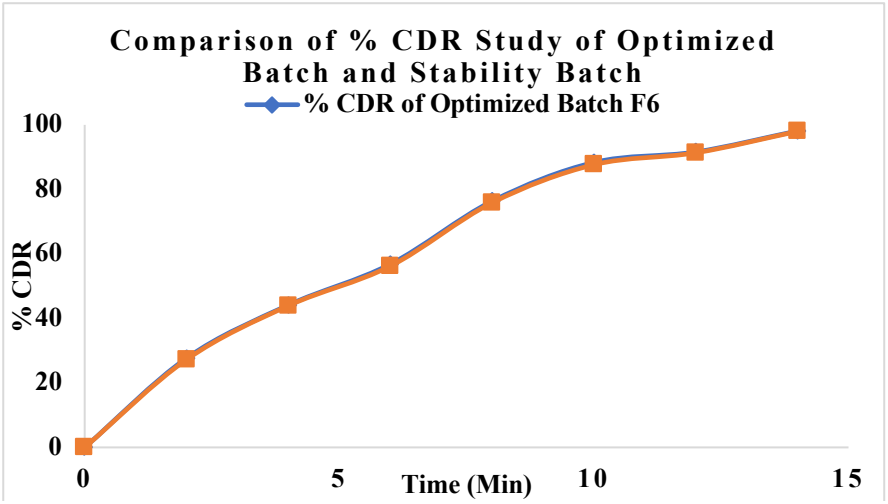

Figure 9: Comparison of Cumulative Drug Release study of Optimized Batch and Stability Batch

After evaluating the tablets placed for stability study, it was found that there were negligible changes in the before and after data for hardness, friability, weight variation, drug content, *in vitro* disintegration time and % CDR at the end of 1 month. Thus, it was concluded that the batch F6 was found to be stable.

CONCLUSION

Parkinson's Disease is commonly managed using Procyclidine HCl, a BCS Class I drug that undergoes extensive hepatic first-pass metabolism, leading to a bioavailability of approximately 75%. Therefore, the present study was focused on developing sublingual tablets of Procyclidine HCl using different superdisintegrants through the direct compression technique to enhance the onset of action and bypass first-pass metabolism. Drug–excipient compatibility studies were performed using FT-IR analysis, which confirmed that Procyclidine HCl was compatible with all selected excipients. The formulations were prepared using superdisintegrants such as Crospovidone and Sodium Starch Glycolate (SSG), which contributed significantly to reducing *in vitro* disintegration time. Pre-compression parameters like Angle of Repose and Carr's Index indicated good flow properties of the powder blends. The development of sublingual tablets offers a convenient and efficient approach for rapid therapeutic action. Additionally, the use of water-soluble excipients enhances patient acceptability and ease of administration. A Central Composite Design (CCD) was applied for optimization, where Crospovidone (X1) and Sodium Starch Glycolate (X2) were selected as independent variables. The responses studied were *in vitro* disintegration time (Y1) and percentage cumulative drug release at 14 minutes (Y2). Evaluation of pre-compression parameters such as Carr's Index, Hausner's Ratio, and Angle of Repose showed compliance with standard limits, confirming good flowability. Post-compression parameters including weight variation, hardness, and friability were within pharmacopeial limits, indicating adequate mechanical strength. Drug content uniformity was also within acceptable limits, ensuring consistent drug distribution. Among all formulations, batch F6 was identified as the optimized formulation based on overlay contour plot analysis. It exhibited a rapid disintegration time of 16.34 ± 1.02 seconds and achieved 98.59% drug release within 14 minutes. This formulation contained 4% Crospovidone and 3% SSG. The optimized batch F6 was further validated using the desirability function, showing close agreement between predicted and experimental results. Additional evaluation included stability testing. Statistical analysis using Design Expert software and ANOVA confirmed the significance of the model and validated that the selected independent variables were within acceptable ranges. Both contour and overlay plots supported the selection of batch F6 as the optimal formulation. Stability studies conducted at 40 ± 2 °C and 75 ± 5% RH for one month demonstrated no significant changes in hardness, friability, weight variation, disintegration time, drug content, or dissolution profile. Overall, the study concluded that Procyclidine HCl can be successfully formulated as sublingual tablets using superdisintegrants via direct compression, providing rapid drug release and improved onset of action. This approach is expected to enhance patient compliance, which is crucial for the effective management of Parkinson's Disease.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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