RESEARCH PAPER

FORMULATION AND OPTIMIZATION OF SUBLINGUAL TABLET OF PRASUGREL HCl

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ABSTRACT
The main objective of current research work is to formulate and optimize sublingual tablets of Prasugrel HCl for the treatment of heart attack. Compatibility studies were performed through FT-IR. For the formulation of sublingual tablets of Prasugrel HCl 3^2 factorial design was applied to optimize formulation where Cross carmellose sodium was selected as an independent variable (X_1) and Crospovidone was selected an independent variable (X_2) and Wetting time, *In Vitro* Disintegration time and % CDR at 15 mins were selected as dependent variables Y_1, Y_2 and Y_3 respectively. Direct compression method is used for preparation of sublingual tablet. All precompression parameters like Carr's Index, Hausner's Ratio and Angle of Repose meets the standard values of powder indicating good flow properties. The average weight, friability and hardness were within compendial limits which showed that all formulations possessed good mechanical strength. Sublingual tablet formulation batch F9 was optimized from the overlay contour plot which showed minimum Wetting time 13.21 ±1.17 sec, disintegrating time of 18.82 ±1.14 and % CDR is 99.43 in 15 min among all other batches of tablets. The result of stability study of the batch F9 showed that there was no significant change in all the parameter for a period of one month when stored in stability chamber at 40 ± 2 °C/ 75 ± 5 % RH for period of one month. The study concluded that sublingual tablets formulated using superdisintegrants by the direct compression method exhibited rapid drug release within a short period of time.

Keywords: Prasugrel HCl, Sublingual tablet, factorial design

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INTRODUCTION

A heart attack, also called myocardial infarction, is a serious condition that happens when blood flow to the heart muscle is suddenly blocked. This usually occurs because of a buildup of fatty deposits (plaque) in the heart arteries, which can break and form a blood clot.[1] This blockage stops oxygen from reaching the heart muscle, causing damage to the tissue. If treatment is not given quickly, the damage can become permanent.[2] Heart attack is categorised into three types Type I segment elevation myocardial infraction (STEMI) and type II non-segment elevation myocardial infraction (NSTEMI) and Silent heart attack.[3]

Prasugrel hydrochloride is an antiplatelet drug, which means it helps prevent blood clots. It acts as a blood thinner and is used to treat conditions like blood clots, Acute Coronary Syndrome (ACS), myocardial infarction (heart attack). It works by permanently blocking P_2Y_{12} ADP receptors on platelets, which stops them from sticking together and forming clots. Because of this action, it reduces the risk of heart attack, stroke, and other serious heart-related problems.[4] The drug has a half-life of about 7 hours due to strong first-pass metabolism and shows around 79% oral bioavailability. It belongs to BCS Class II. It is usually given once daily in a dose of 5-10 mg.[5] These limitations indicate the need to improve its bioavailability, and faster onset of action, which is why Prasugrel hydrochloride is selected for this study.Although conventional tablets of Prasugrel hydrochloride are available (5 mg,10 mg), they undergo first-pass metabolism in the liver, which can reduce their effectiveness.[5] In contrast, sublingual administration (under the tongue) allows the drug to be absorbed directly into the blood vessels, leading to a faster effect. This route bypasses the liver's first-pass metabolism, improving bioavailability.[6] Sublingual tablets can therefore provide quicker absorption and faster therapeutic action compared to conventional dosage forms.[7] This happens because the drug directly enters systemic circulation through sublingual blood vessels and lymphatic pathways without passing through the liver.[8] As a result, drugs taken under the tongue act more quickly and efficiently. The objective of current research work is to formulate and optimize sublingual tablet of prasugrel HCl.

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MATERIALS AND METHODS

MaterialsPrasugrel HCl was procured as gift sample from Intas pharmaceuticals limited, Ahmedabad, Gujarat, India. Croscarmellose sodium, Crospovidone, Aspartame, Talc, Magnesium stearate, Mannitol procured from Chemdyes corporation, Rajkot, Gujarat, India.

Formulation of sublingual tablets by Direct Compression Method

Direct compression is used for sublingual tablet formulation because it is a simple, cost-effective method that enables rapid disintegration and fast drug release without the need for heat or moisture.

In this formulation, two superdisintegrants were used: croscarmellose sodium and crospovidone. The accurately weighed drug and excipients were passed through a #60 sieve and mixed uniformly using the geometric dilution method. The final blend was then directly compressed into tablets using a multi-rotary tablet compression machine (Cronimach, Ahmedabad, Gujrat, India). The tablet weight and compression force were kept constant during the process. Each tablet contained 10 mg of Prasugrel HCl.[8](Table 1)

Calculation for Equivalent weight of drug

Amount of Drug added: 1000 mg

Obtained weight of Solid Dispersion: 6.8 gm (6870.5 mg)

Actual dose of drug: 10 mg

Weight of drug (mg)		**Weight of solid Dispersion (mg)**
1000	→	6870.5
10	→	(?)

$$\text{Equivalent Weight of solid Dispersion} = \frac{10 \text{ X } 6870.5}{1000} = 68.7 \text{ mg}$$

Table 1: Formulation of Sublingual Tablets using 3^2 Factorial design

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Solid Dispersion of Prasugrel HCl (Drug = 10 mg)	68.7	68.7	68.7	68.7	68.7	68.7	68.7	68.7	68.7
Cross carmellose sodium	2	2.5	3	2	2.5	3	2	2.5	3
Crospovidone	1	1	1	1.5	1.5	1.5	2	2	2
Mannitol	23.3	22.8	22.3	22.8	22.3	21.8	22.3	21.8	21.3
Aspartame	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	100

3^2 FACTORIAL DESIGN

A 3^2 factorial design is used to study the combined effect of two independent variables at three levels each on the formulation and to optimize the final product. A 3^2 full factorial design was adopted to optimize the variables in Design of experiment (D.O.E)11version.

A 3^2 factorial design was applied, in this design 2 Independent variables were selected, where each variable was evaluated at three different levels −1, 0 and +1.[9] Amount of Cross carmellose sodium was taken as independent variable X_1 and the amount of Crospovidone was taken as independent variable X_2 and Wetting time, *In Vitro* Disintegration time and % CDR were selected as dependent variables Y_1, Y_2 and Y_3 respectively.[10] Data of response (dependent variables) was recorded and analysis of data was carried out using ANOVA. (Table 2)

Table 2: Coded and Actual value of formulations

Std.	Coded value		Actual value	
	X_1: Cross carmellose sodium	X_2 : Crosspovidone	X_1: Cross carmellose sodium (mg)	X_2 : Crosspovidone (mg)
1	-1	-1	2	1
2	0	-1	2.5	1
3	+1	-1	3	1
4	-1	0	2	1.5
5	0	0	2.5	1.5
6	+1	0	3	1.5
7	-1	+1	2	2
8	0	+1	2.5	2
9	+1	+1	3	2

Determination of Melting point of Prasugrel HCl

Melting point is used in drug evaluation to confirm the purity and identity of a substance, as pure drugs have a sharp and characteristic melting range. melting point was determined using a capillary device (Bhawana, India).

Melting point of Prasugrel HCl was measured by digital melting point apparatus. 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 Prasugrel HCl melts is measured. The readings were taken in triplicate.[11]

Estimation of Prasugrel HCl by UV-Visible Spectrophotometer

UV-Visible spectrophotometry is used to quantify drug content by measuring the intensity of light absorbed at a specific wavelength.

Standard stock solution of Prasugrel HCl was prepared by dissolving 10 mg of Prasugrel HCl in 100 ml Phosphate buffer 6.8, which make the stock solution of concentration of 100 µg/ml.

Determination of λ_{max} of Prasugrel HCl in Phosphate buffer 6.8:- For determination of λ_{max}, stock solution was scanned between 200-400 nm against Phosphate buffer 6.8 as a blank in the UV-Visible spectrophotometer. Working solution of concentration 10, 20, 30, 40 and 50 ppm were prepared by pipette outing 1, 2, 3, 4 and 5 ml respectively from the stock solution of 100ppm and diluted up to 10 ml volumetric flask. Absorbance of working solutions was measured in triplicate at λ_{max} 252 nm against Phosphate buffer 6.8 as a blank. The above performed using UV spectroscopy is Shimadzu UV-1900, Japan and the Software was used UVprob-2.[12]

Determination of drug by FTIR

FTIR spectroscopy is used in drug evaluation to identify functional groups and detect any drug–excipient interactions.

FTIR was performed for determination of Prasugrel HCl and was estimated for standard FTIR peaks. FTIR spectroscopy was used for drug and excipients identification and to evaluate their compatibility. FTIR spectroscopy of pure drug and physical mixture of drug and excipients was carried out to check the compatibility of drug and excipients. To determine whether the drug and excipients were compatible, FTIR spectroscopy was performed By Shimadzu IR Affinity-1S, Japan.[13]

EVALUATION PARAMETERS OF SUBLINGUAL TABLET

Precompression parameters

Pre-compression parameters help evaluate the flow and compressibility characteristics of the powder blend, ensuring efficient die filling, uniform tablet weight, adequate strength, and consistent quality in the final tablets.[14]

Bulk density: Bulk density is used to evaluate the flow properties and packing ability of powder in tablet formulation. Accurately weighed the powder mixture and transferred to measuring cylinder carefully measure the volume of powder without compacting, and the experiment was repeated six times.[15]

Tapped density: Tapped density is used to assess the compressibility and flow characteristics of powder by measuring its density after tapping. 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, and the experiment was repeated six times.[15]

Hausner's ratio: Hausner's ratio is used to evaluate powder flowability by comparing tapped density to bulk density, and the experiment was repeated six times.[15]

Compressibility index: Compressibility index (Carr's index) is used to assess powder flowability and compressibility based on the difference between bulk and tapped density, and the experiment was repeated six times.[15]

Angle of repose: Angle of repose is used to evaluate the flow properties of powder by measuring the maximum angle formed between the surface of a powder pile 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, and the experiment was repeated six times.[15]

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

Post compression studies

Thickness and Diameter: Thickness and diameter are used to ensure uniformity and consistency in tablet size, which is important for proper dosing and packaging.

Aerospace Digi Matic 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.[16]

Weight Variation: Weight variation is used to ensure uniform distribution of drug content by checking consistency in tablet weight. Uniformity of weight was evaluated by weighing individual tablets to ensure consistency within the batch and compliance with pharmacopeial limits. Weighing of the tablets in Scale-Tec Gujrat, India.[16,17]

Hardness: Hardness is used to measure the mechanical strength of tablets to withstand handling, packaging, and transportation. A Monsanto hardness tester (D.K Scientific, Ahmedabad, Gujrat, India) was used to measure the tablets' hardness. Each formulation's six tablets were chosen at random, and the tablets' hardness was assessed. Tablet hardness was evaluated using a

hardness tester to determine resistance to crushing or breaking under mechanical stress. [18,19]

% Friability: Friability is used to evaluate the ability of tablets to resist breakage during handling and transport. The Roche friabilator (Bhawana, India) was used to assess the tablets' friability, and the percentage weight loss was calculated to evaluate tablet durability.[18-20]

Wetting Time: Wetting time is used to measure how quickly a tablet absorbs moisture, indicating its ability to disintegrate rapidly. Each formulation's six tablets were chosen at random, and the tablets' Wetting Time was measured. Wetting time was measured as the time required for the tablet to become completely wetted when placed in contact with a liquid medium.[18,19]

In-Vitro Disintegration Time: In-vitro disintegration time is used to determine how quickly a tablet breaks down into smaller particles in a specified medium. Using a digital tablet disintegration test device Bhawana, India, this test was conducted on six tablets to evaluate how quickly the tablets disintegrated under simulated physiological conditions.[18,21]

Drug Content: Drug content is used to ensure the amount of active drug present in each tablet is accurate and uniform. Ten tablets were crushed in a mortar. Take an amount equivalent to the drug dose and transfer to a volumetric flask. The solution was filtered with Whatman filter paper. The drug content of the sample was ascertained using UV Spectrophotometry by Shimadzu UV-1900, Japan and the Software was used UVprob-2 at 252 nm.[18]

In-Vitro Dissolution Study: In-vitro dissolution study is used to determine the rate and extent of drug release from the tablet in a specified medium. Dissolution studies were determined by USP type II (paddle type) dissolution apparatus (DKB Instruments, India). 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. 10 ml samples were withdrawn at 3 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 252 nm. [18]

Stability Study of optimized batch: Stability study is used to evaluate how the drug formulation maintains its quality, safety, and efficacy over time under different environmental conditions. 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 (Patel Scientific Instruments Pvt. Ltd Ahmedabad, Gujrat, India). After completion of 30 days tablets were evaluated for Hardness, Weight Variation, Friability, Wetting Time, *In Vitro* Disintegration time, Drug Content and % Cumulative Drug release study.[19]

RESULTS AND DISCUSSION

Melting point of Prasugrel HCl

Melting point determination is one of the popular techniques used to identify drug using digital melting point apparatus and melting point of Prasugrel HCl was found in the range of 185-187 °C.

Reported melting point of Prasugrel HCl is 185-187 °C and is thus like the melting point of Prasugrel HCl (Table 3).

Table 3: Melting point of Prasugrel HCl

Sr. No.	Reported Melting Point	Observed Melting point
1.	185-187 °C	174-178 °C
2.		176-184 °C
3.		182-188 °C

Estimation of drug by UV overlay spectra

The overlay spectra of drug were obtained by scanning different concentrations of solutions viz. 10, 20, 30, 40 and 50 ppm showed maximum absorption at 252 nm. Reported λ_{max} is 252 nm so it can be concluded that the given drug was Prasugrel HCl. (Figure 1) (Table 4). Calibration curve is mentioned in figure 2.

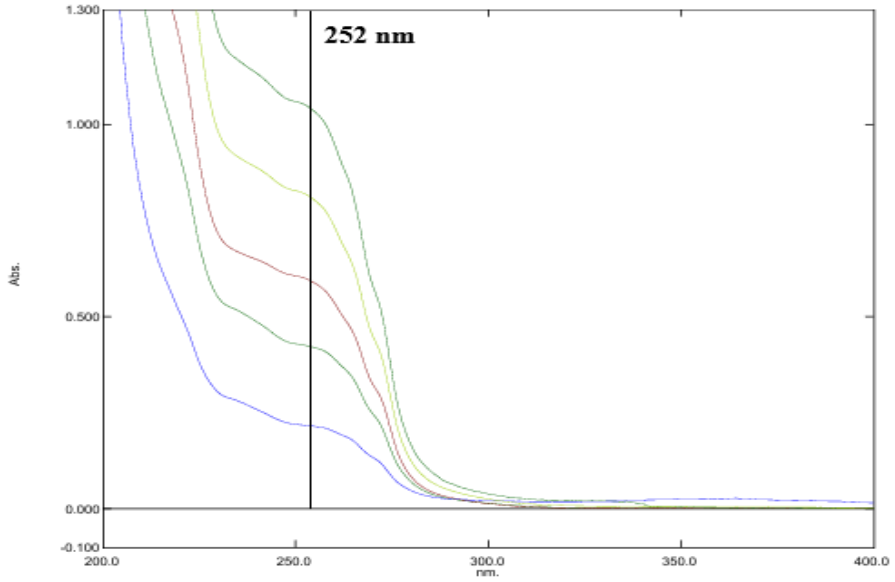

Figure 1: Overlay Spectra of Prasugrel HCl

Table 4: Absorbance of different concentration of Prasugrel HCl in phosphate buffer at pH 6.8

Sr. No.	Concentration (ppm)	Absorbance			Mean Absorbance ± S. D.
		I	II	III	
1.	10	0.217	0.219	0.215	0.217 ± 0.002
2.	20	0.426	0.42	0.423	0.423 ± 0.003
3.	30	0.609	0.611	0.613	0.611 ± 0.002
4.	40	0.819	0.822	0.816	0.819 ± 0.003
5.	50	1.042	1.05	1.046	1.046 ± 0.004

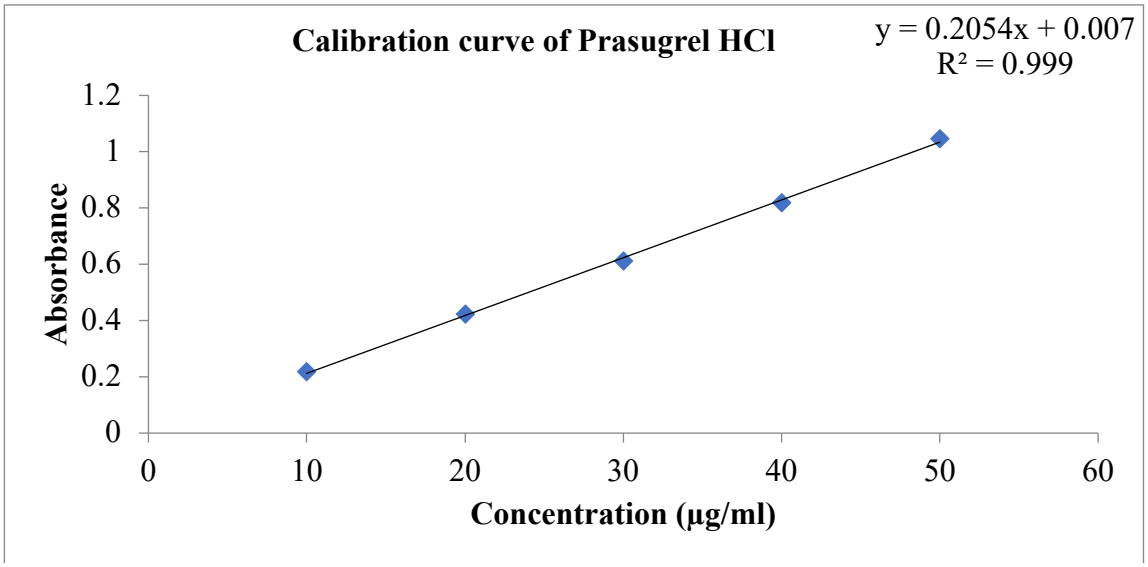

Figure 2: Calibration curve of Prasugrel HCl in Phosphate buffer 6.8

Identification of drug by FTIR

- The FTIR of Prasugrel HCl shows band at 607 cm^{-1}, 1070 cm^{-1}, 1155 cm^{-1}, 1217 cm^{-1}, 1450 cm^{-1}, 1687 cm^{-1}, 1757 cm^{-1} and 3005 cm^{-1} corresponding to the functional groups C-S Strech, C-O Strech, C-F Strech, C-N Strech, C=C Aromatic, C=O ketone, C=O Ester, C-H Aromatic.
- From the above interpretation it is found that major functional groups are presents in the reported structure of Prasugrel HCl So, above result identifies that used API is Prasugrel HCl. (Figure 3)

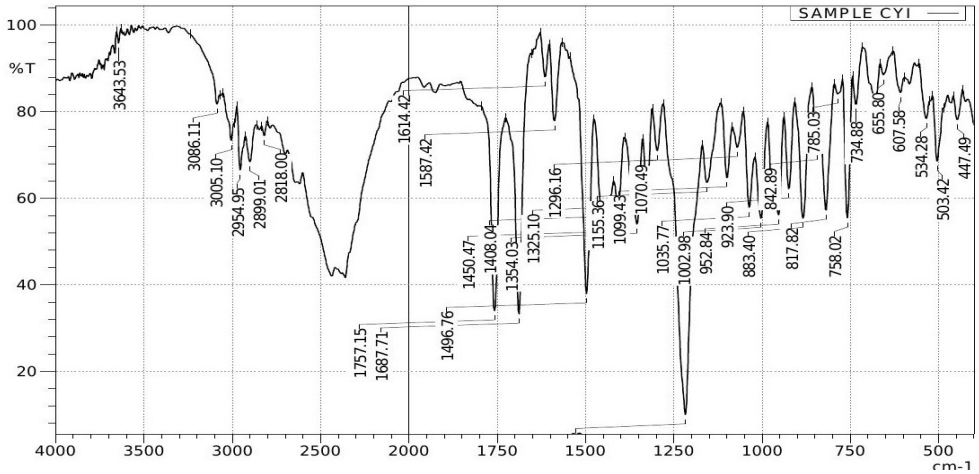

Figure 3: FTIR spectra of Prasugrel HCl

COMPATIBILITY STUDY OF PRASUGREL HCl AND EXCIPIENTS

- The FTIR of Prasugrel HCl and Excipients shows peaks at 1064 cm^{-1}, 1107 cm^{-1} ,1217 cm^{-1}, 1460 cm^{-1}, 1687 cm^{-1}, 1757 cm^{-1} corresponding to the functional groups C-O Strech, C-F Strech, C-N Strech, C=C Aromatic, C=O ketone, C=O Ester.
- From the above interpretation it is found that major functional groups are present in the reported structure of Prasugrel HCl and are present in the FTIR of Prasugrel HCl and Excipients with no significant change in band width.(Figure 4)

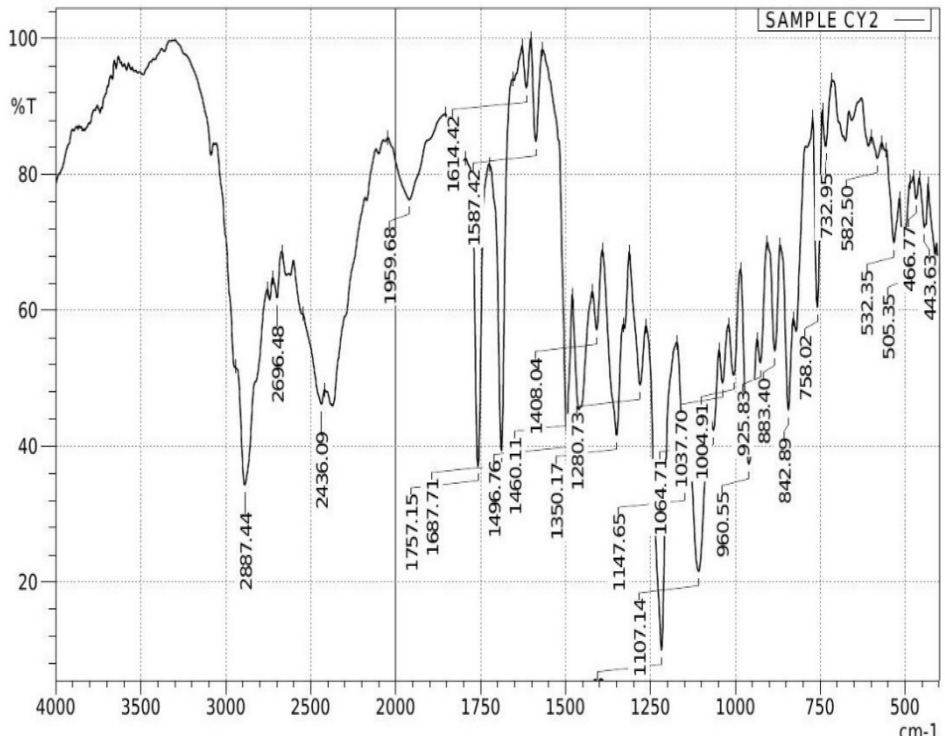

Figure 4: FTIR spectra of Prasugrel HCl and Excipients

- The FTIR of Prasugrel HCl and Excipients shows peaks at 655 cm^{-1}, 1145 cm^{-1}, 1217 cm^{-1}, 1280 cm^{-1}, 1462 cm^{-1}, 1687 cm^{-1}, 1757 cm^{-1}, 3084 cm^{-1} corresponding to the functional groups C-S Strech, C-O Strech, C-F Strech, C-N Strech, C=C Aromatic, C=O ketone, C=O Ester, C-H Aromatic.
- From the above interpretation it is found that major functional groups are present in the reported structure of Prasugrel HCl and are present in the FTIR of Prasugrel HCl and Excipients with no significant change in band width.(Figure 5)

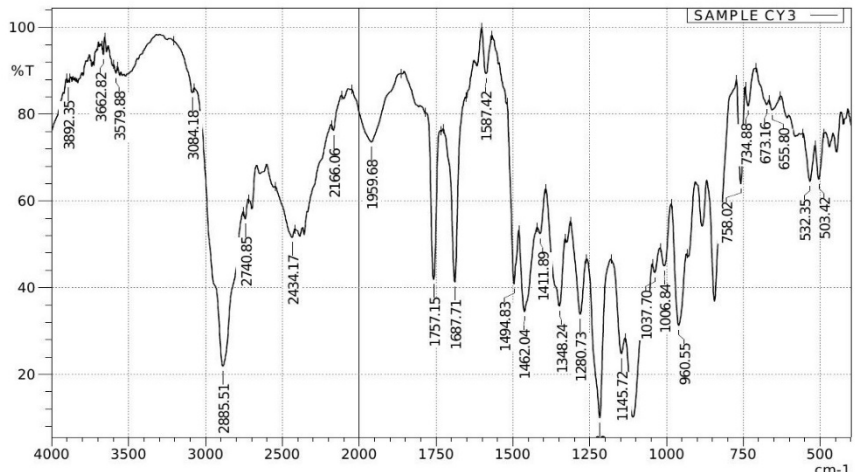

Figure 5: FTIR spectra of Prasugrel HCl and Excipients

RESULTS OF SUBLINGUAL TABLETS FORMULATED BY 3^2 FACTORIAL DESIGN

PRECOMPRESSION PARAMETERS

Bulk density and Tapped density: All formulation blends of F1 toF9 batches were evaluated for bulk density and tapped density. Bulk density was found to be 0.54 ±0.012 gm/ml to 0.56 ±0.010 gm/ml and tapped density was found to be 0.65 ±0.016 gm/ml to 0.68 ±0.008 gm/ml.

Hausner's ratio: Hausner's ratio of formulated batches F1 to F9 was found in the range of 1.18 ±0.026 to 1.23 ±0.027. From Hausner's ratio flow of powder was found to be Good to Fair.

Carr's index: % Carr's Index of formulated batches F1 to F9 was found in the range of 15.51 ±1.91 % to 19.11 ±1.79 %. From Carr's Index flow of powder was found to be Good to Fair.

Angle of repose: Angle of repose of formulated batches F1 to F9 was in the range of 23.78 ±0.72°θ to 33.14 ±0.69°θ. From observed Angle of repose flow of powder was found to be excellent to passable. (Table 5)

Table 5: Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of repose data

Batch	Bulk density (gm/ml ± SD)	Tapped density (gm/ml ± SD)	Hausners ratio ± SD	Carr's index (% ± SD)	Angle of repose (°θ ± SD)
F1	0.54 ±0.010	0.67 ±0.010	1.23 ±0.004	19.21 ±0.29	32.58 ±1.29
F2	0.55 ±0.012	0.68 ±0.008	1.23 ±0.027	19.11 ±1.79	32.49 ±0.72
F3	0.54 ±0.012	0.67 ±0.012	1.23 ±0.005	19.31 ±0.34	33.14 ±0.69
F4	0.55 ±0.013	0.66 ±0.016	1.20 ±0.023	17.19 ±1.67	28.07 ±0.46
F5	0.55 ±0.011	0.67 ±0.011	1.21 ±0.004	17.69 ±0.30	27.86 ±0.63
F6	0.54 ± 0.011	0.66 ±0.011	1.22 ±0.004	18.14 ±0.31	28.73 ±0.92
F7	0.55 ±0.014	0.66 ±0.015	1.20 ±0.010	17.08 ±0.73	24.52 ±0.80
F8	0.55 ±0.016	0.65 ±0.016	1.18 ±0.026	15.51 ±1.91	23.78 ±0.72
F9	0.56 ±0.010	0.67 ±0.007	1.20 ±0.012	16.71 ±0.84	24.44 ±0.84

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

POST-COMPRESSION PARAMETERS

Thickness (mm): Thickness of the formulated batches F1 to F9 was found to be in the range of 2.77 ±0.03 mm to 2.81 ±0.01 mm.

Diameter (mm): Diameter of the formulated batches F1 to F9 was in the range of 6.48 ±0.02 mm to 6.52 ±0.01 mm.

Weight variation (mg): Weight variation limits for tablet Weight 100 mg is ± 7.5 mg according to Indian Pharmacopoeia. Weight variation of the formulated batches F1 to F9 was found to be in the range of 99.76 ±3.08 mg to 102.14 ±2.26 mg. Thus, all the formulated batches prepared comply with the Weight variation limits of the pharmacopeia.

Hardness (kg/cm2): It is well known that tablets with more hardness shows longer disintegration time. Mechanical integrity is of paramount importance in successful formulation of sublingual tablet; hence

hardness of tablets was determined. Hardness of the formulated batches F1 to F9 was found to be in the range of 2.45 ±0.05 kg/cm2 to 2.67 ±0.02 kg/cm2.

Friability (%): Friability of the formulated batches F1 to F9 was found to be in the range of 0.28 to 0.68 %. According to IP, Friability limits is less than 1%. Observed values of friability indicated that tablets were having a good mechanical stability.

Wetting time (seconds): Wetting time of the formulated batches F1 to F9 was found to be in the range of 13.21 ±1.17 sec to 25.58 ±1.36 sec. The batch F9 having combination of Cross carmellose sodium 5 mg and crospovidone 5 mg was found to be having least 13.25 ±1.1 sec wetting time as compared to other batches.

In vitro Disintegration time (seconds): In vitro Disintegration time of the formulated batches F1 to F9 was found to be in the range of 18.82 ±1.14 sec. to 30.83 ±1.45 sec. The batch F9 having combination of Cross carmellose sodium 5 mg and crospovidone 5 mg was found to be having least 15.82 ±1.14 sec In vitro Disintegration time as compared to other batches.

Drug content (%): Drug content of the formulated batches F1 to F9 was found to be in the range of 93.88 ±0.63 % to 98 ±0.81%. These results of drug content indicated that sublingual tablet had uniform distribution and proper dose of active ingredient. (Table 6,7)

Table 6: Weight variation, Thickness, Diameter, Hardness and Friability data

Batch	Thickness (mm ± SD)	Diameter (mm ± SD)	Weight Variation (mg ± SD)	Hardness (kg/cm^2 ± SD)	Friability (%)
F1	2.77 ±0.03	6.48 ±0.02	100.51 ±2.75	2.67 ±0.02	0.28
F2	2.80 ±0.01	6.50 ±0.02	99.76 ±3.08	2.63 ±0.02	0.32
F3	2.78 ±0.02	6.49 ±0.02	102.14 ±2.26	2.60 ±0.02	0.36
F4	2.81 ±0.01	6.5 ±0.02	100.17 ±2.28	2.58 ±0.03	0.4
F5	2.8 ±0.01	6.49 ±0.02	100.53 ±2.20	2.55 ±0.03	0.45
F6	2.77 ±0.01	6.52 ±0.01	99.83 ±3.14	2.52 ±0.04	0.52
F7	2.79 ±0.01	6.50 ±0.01	100.86 ±2.47	2.51 ±0.03	0.55
F8	2.8 ±0.01	6.49 ±0.02	101.30 ±2.39	2.47 ±0.02	0.62
F9	2.80 ±0.01	6.50 ±0.02	100.96 ±2.24	2.45 ±0.05	0.68

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

Table 7: Wetting time, *In vitro* disintegration time and Drug Content

Batch	Wetting time (sec. ±S.D.)	*In vitro* disintegration time (sec. ±S.D.)	Drug Content (%)
F1	25.58 ±1.36	30.83 ±1.45	94.12 ±0.55
F2	23.85 ±1.31	29.34 ±1.07	93.88 ±0.63
F3	22.59 ±1.14	27.71 ±1.13	94.79 ±0.79
F4	21.51 ±1.34	26.64 ±1.33	95.39 ±0.30
F5	19.63 ±1.09	24.84 ±1.01	96.01 ±0.62
F6	17.95 ±1.53	22.77 ±1.09	95.31 ±0.57
F7	16.56 ± 1.07	21.68 ±1.40	97.94 ±0.73
F8	14.46 ±1.10	20.42 ±1.46	97.95 ±0.75
F9	13.21 ±1.17	18.82 ±1.14	98 ±0.81

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

% Cumulative drug release study:

% CDR study is performed by using dissolution test apparatus type II (paddle) in 900 ml of the phosphate buffer at pH 6.8 as a dissolution medium at 37° ± 0.5 °C at 50 rpm. Results shown in Table 9 indicated that as the concentration of superdisintegrant increases there is increase in the drug release from the tablet also more than 50% of drug released in less than 9 mins. Drug release profile indicates that as concentration of super disintegrant Cross carmellose sodium increases from 2 mg to 3 mg and Crospovidone 1 mg to 2 mg CDR profile also increases as shown in figure 6. (Table 8)

Table 8: Percentage Cumulative Drug Release of Batches F1 to F9

Time (Min.)	Batch								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
3	21.58	24.23	27.79	31.45	35.64	39.78	43.53	47.61	51.3
6	40.46	42.85	46.12	48.27	51.58	54.97	58.12	60.79	63.61
9	66.73	69.26	71.78	73.34	74.97	77.21	79.24	81.16	82.93

12	80.54	82.24	84.54	86.15	87.43	89.64	91.35	92.84	94.66
15	85.91	88.12	90.15	91.76	93.48	95.11	96.78	97.98	99.43
18	88.46	90.76	92.85	94.84	-	-	-	-	-

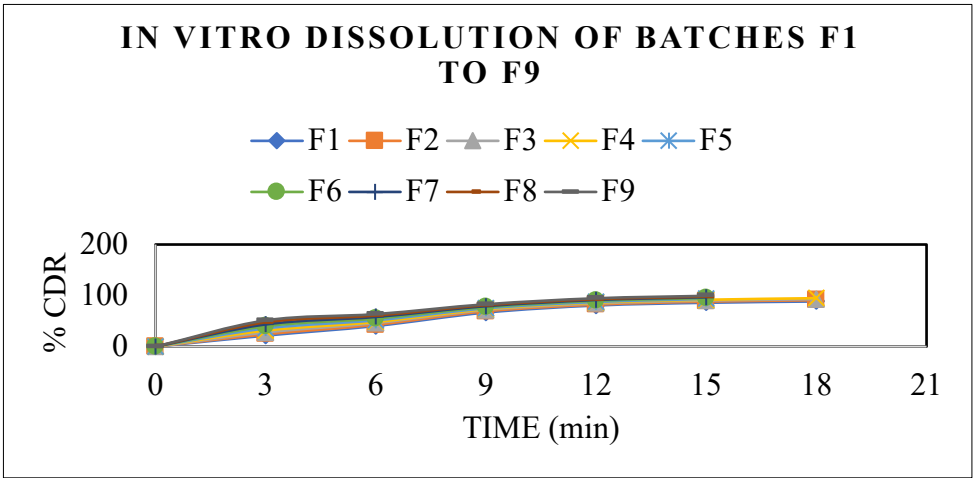

Figure 6: In vitro Dissolution of Batches F1 to F9

STATISTICAL ANALYSIS

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

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

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

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

A polynomial equation is used to draw the conclusion after considering the magnitude of coefficient and mathematical signs (positive or negative). A statistical analysis was adopted to optimize the variables in Design of experiment (D.O.E)11version.

R^2 value for Wetting time, *In vitro* Disintegration time (sec.) and % CDR indicated good correlation between dependent and independent variables. The terms with $p<0.05$ were considered statistically significant and retained in full model. (Table 9,10)

Table 9: Observed Dependent Variables for 3^2 Factorial Design

Batch	Wetting time (sec. ±S.D.)	*In vitro* disintegration time (sec. ±S.D.)	% Cumulative Drug Release at 15 min
F1	25.58 ±1.36	30.83 ±1.45	85.91
F2	23.85 ±1.31	29.34 ±1.07	88.12
F3	22.59 ±1.14	27.71 ±1.13	90.15
F4	21.51 ±1.34	26.64 ±1.33	91.76
F5	19.63 ±1.09	24.84 ±1.01	93.48
F6	17.95 ±1.53	22.77 ±1.09	95.11
F7	16.56 ± 1.07	21.68 ±1.40	96.78
F8	14.46 ±1.10	20.42 ±1.46	97.98
F9	13.21 ±1.17	18.82 ±1.14	99.43

Table 10: Summary of ANOVA Analysis

Source	Sum of Square	Degree of Freedom	Mean Square	F value	P value
Wetting time (Y1)					

Regression	145.42	5	29.08	1011.66	<0.0001
Residual	0.0862	3	0.0287	-	-
Total	145.50	8	-	-	-
***In vitro* disintegration Time (Y2)**					
Regression	137.36	5	27.47	315.09	0.0003
Residual	0.2616	3	0.0872	-	-
Total	137.63	8	-	-	-
% Cumulative Drug Release (Y3)					
Regression	168.51	5	33.70	5016.97	< 0.0001
Residual	0.0202	3	0.0067	-	-
Total	168.53	8	-	-	-

Statistical Analysis for Wetting time:

Polynomial equation for Wetting time**:**

$Y_1 = 19.53 - 1.65B_1 - 4.63B_2 - 0.0900B_{12} + 0.2533B_1^2 - 0.3217B_2^2$

The multiple linear regression analysis revealed that both coefficients B_1 and B_2 were negative. This negative sign suggests that as the quantity of Cross carmellose sodium and Crospovidone increases, there is a decrease in Wetting time.

Further examination of the equation showed that Variable B_1 had a p-value of 0.0002 ($p < 0.05$) 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 Wetting time in the formulation.(Figure 7)

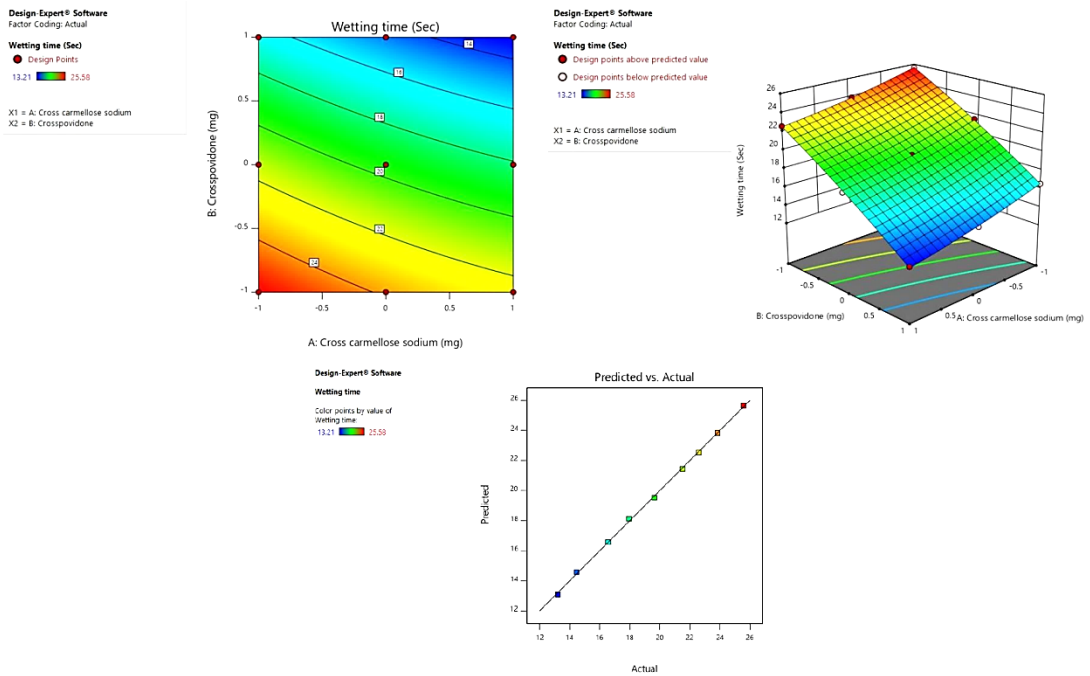

Figure 7: Contour plot, 3D surface plot, Actual value vs Predicted value graphs showing the effect of Cross carmellose sodium (X_1) and Crospovidone (X_2) of Wetting time.

Statistical Analysis for *In vitro* Disintegration time

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

$Y_2 = 24.83 - 1.64B_1 - 4.49B_2 + 0.0650B_{12} - 0.1250\ B_1^2 - 0.0500\ B_2^2$

The multiple linear regression analysis revealed that both coefficients B_1 and B_2 were negative. This negative sign suggests that as the quantity of Cross carmellose sodium and Crospovidone increases, there is a decrease in In vitro Disintegration time.

Further examination of the equation showed that Variable B_1 had a p-value of 0.0009 ($p < 0.05$) 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. (Figure 8)

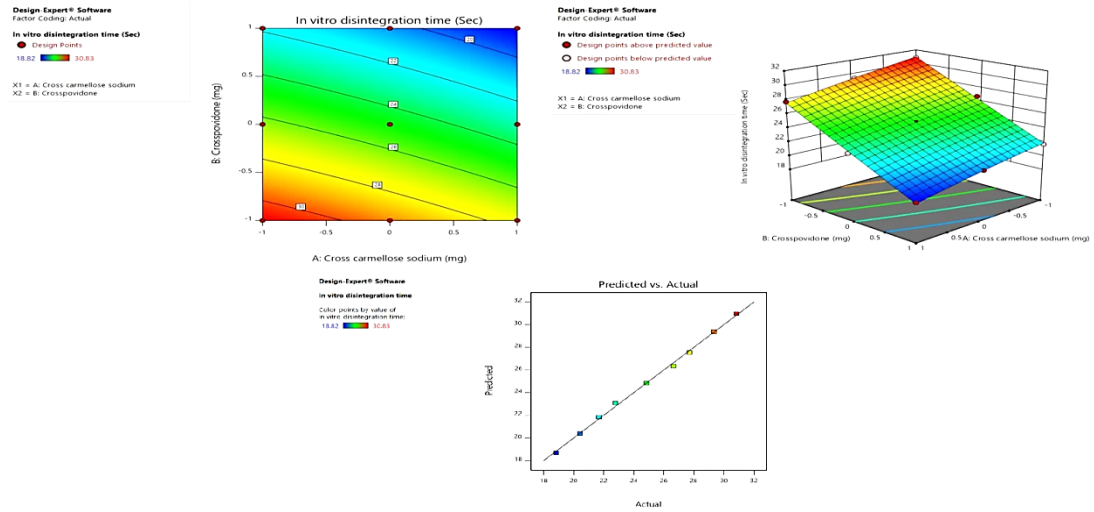

Figure 8: Contour plot, 3D surface plot, Actual value vs Predicted value graphs showing the effect of Cross carmellose sodium (X_1) and Crospovidone (X_2) of *In vitro* Disintegration time.

Statistical Analysis for % CDR

Polynomial equation for % CDR**:**

$$Y_3 = 93.45 + 1.71\ B_1 + 5.00\ B_2 - 0.3975\ B_{12} - 0.0033\ B_1^2 - 0.3883\ B_2^2$$

The multiple linear regression analysis showed that coefficient B_1 and B_2 both bear a positive sign. The positive coefficient indicates that as the quantity of Drug: Poloxamer 188 and Crospovidone increases, there is an increase in % CDR with respect to time.

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. (Figure 9)

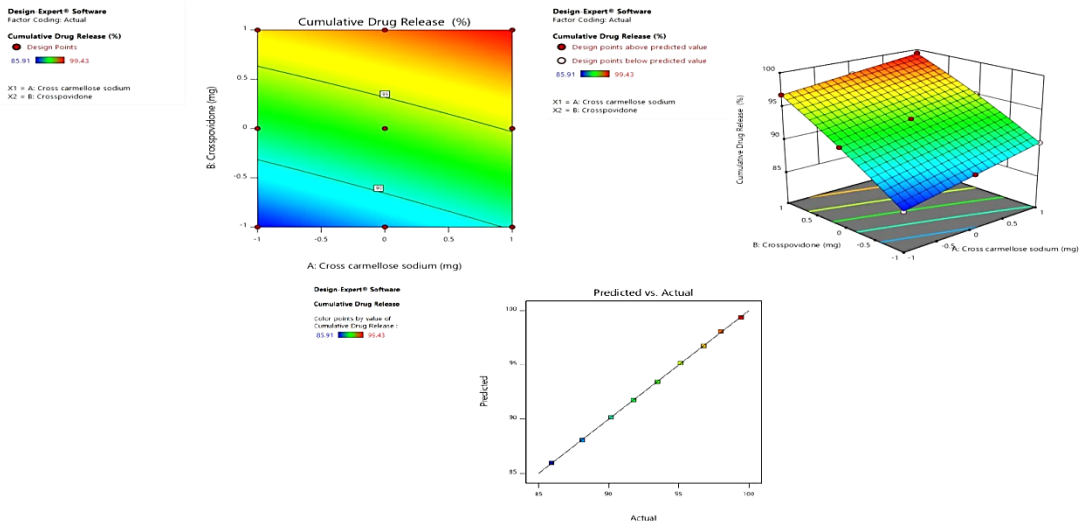

Figure 9: Contour plot, 3D surface plot, Actual value vs Predicted value graphs showing the effect of Cross carmellose sodium (X_1) and Crospovidone (X_2) of % CDR

RESULTS OF STABILITY STUDY

Based on the mentioned parameters of the Factorial Design batches, it was determined that batch F9 emerged as the optimized batch due to its favorable surface appearance, mechanical strength, and drug content.

Table 11: results of 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.)	2.45 ±0.05	2.41 ±0.03
Weight Variation (mg ± S.D.)	100.96 ±2.24	101.29 ±2.19
Friability (%)	0.68	0.71
Wetting Time (sec.± S.D.)	13.21 ±1.17	14.17 ±1.02
In vitro Disintegration Time (sec.± S.D.)	18.82 ±1.14	20.27 ±1.16
Drug Content (%)	98 ±0.81	97.12 ±0.64

Table 12: Cumulative Drug Release Study of Stability Batch

Time (Min.)	% CDR of Optimized Batch (%)	% CDR of batch After Time Period of 1 Month (%)
0	0	0
3	51.3	49.7
6	63.61	62.79
9	82.93	81.18
12	94.66	92.51
15	99.43	97.63

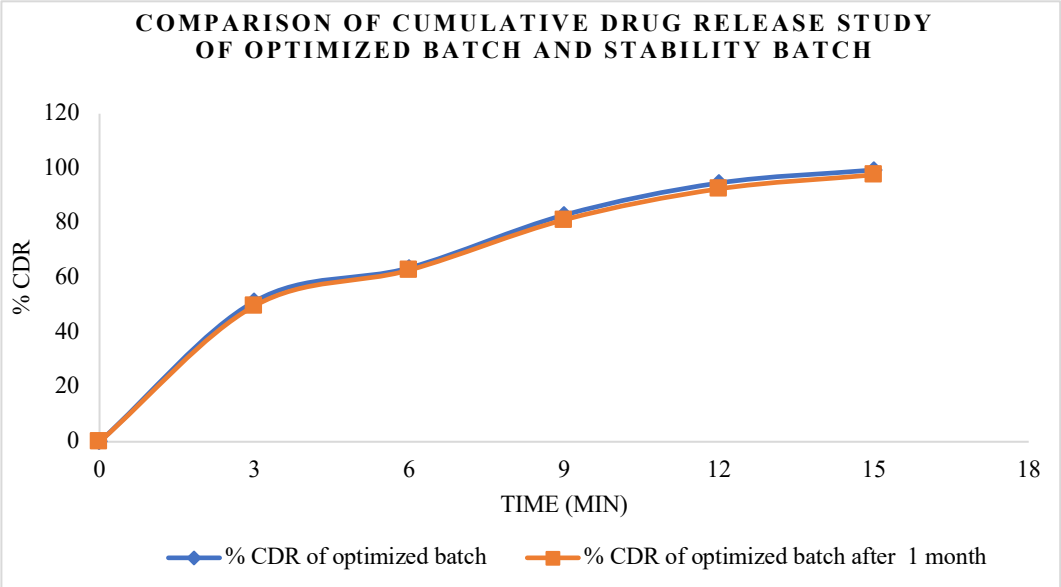

Figure 10: Comparison of Cumulative Drug Release study of Optimized batch and Stability batch

After evaluating the tablets placed for stability study, it was found that there were negligible changes in the before and after data for hardness, wetting time, *in vitro* disintegration time, % drug content and % CDR at the end of 1 month (Table 11,12) (Figure 10). Thus, it was concluded that the batch F9 was found to be stable.

CONCLUSION

Prasugrel hydrochloride is used in the treatment of Acute Coronary Syndrome. It was used for formulating Sublingual Tablets. Sublingual Tablets of Prasugrel hydrochloride were prepared by Direct compression method using Superdisintegrants. A 3^2 factorial design was applied to optimize the formulation where Cross carmellose sodium was selected as an independent variable (X_1) and Crospovidone was selected an independent variable (X_2) whereas Wetting time, *In Vitro* Disintegration time and % Cumulative Drug Release at 15 mins were selected as dependent variables Y_1, Y_2 and Y_3 respectively. All Precompression parameters met the standard values indicating good flow properties. The average weight, friability and hardness were within acceptable limits which showed that all formulations possessed good mechanical strength. Drug content uniformity was within acceptable limits, which indicated a homogeneous distribution of drug in tablets. Formulation F9 was optimized from the overlay contour plot which showed minimum wetting time of

13.21 ±1.17 secs, disintegration time of 18.82 ±1.14 secs and % cumulative drug release of 99.43 % in just 15 mins, the graphs and data obtained from Design Expert software showed that the batch F9 gave all the desired results as well as ANOVA analysis stated that the values of independent variables were in the acceptable limits. The result of stability study of the batch F9 showed that there was no significant change in post compression parameters for a period of one month when stored in stability chamber at 40 ± 2 °C/ 75 ± 5 % RH. From the study it was concluded that solid dispersions of Prasugrel HCl can be successfully formulated into Sublingual Tablets using Superdisintegrants by Direct compression method, which can provide rapid drug release within a short period of time. Thus, it will be an important factor in improving patient compliance which is prerequisite for the treatment of Acute Coronary Syndrome.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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