RESEARCH PAPER

Design and Optimization of Nadolol sublingual tablet

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ABSTRACT

Objective: The objective of the present investigation is to develop a formulation of sublingual tablets of Nadolol. **Materials and Method**: For the preparation of sublingual tablets various super disintegrants were used like Kyron T-314, and SSG. A 3^2 factorial design was employed to optimize the formulation by systematically evaluating the effects of two independent variables. Kyron T-314 (X_1) and sodium starch glycolate (SSG) (X_2) were selected as the formulation factors. The study aimed to investigate their influence on key performance responses, namely in vitro disintegration time (Y_1) and percentage cumulative drug release at 12 minutes (Y_2). **Results and Discussion**: All precompression parameters like Carr's Index, Hausner's Ratio and Angle of Repose meets the standard values of powder indicating good flow properties. FTIR was performed to check compatibility between drug and excipients and no major changes were found. The average weight, friability and hardness were within compendial limits which showed that all formulations possessed good mechanical strength. The optimized formulation N9 showed minimum disintegration time of 17.41 ± 1.64 secs, and drug release of 99.48 % in 12 mins among all other batches of tablets. The result of stability study of the batch N9 showed that there was no significant change in hardness, in-vitro disintegration time, drug content, and in vitro dissolution profile for a period of one month when stored at 40° ± 2°C / 75 ± 5% RH for period of one month. From the study it was concluded that sublingual tablets of Nadolol is an acceptable dosage form which suggests that it is likely to become one of the choices of Nadolol preparations for the treatment of hypertension.

Keywords: Nadolol, 3^2 factorial design, In Vitro Disintegration time, Drug release

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INTRODUCTION

A chronic medical disease known as hypertension, or high blood pressure, is characterized by a consistently high force of blood against the artery walls. One of the most prevalent and important risk factors for a number of cardiovascular conditions, such as aortic aneurysms, heart failure, stroke, and renal failure, is hypertension. According to World health organization (WHO). The relative risks of stroke as well as heart disease strongly associated with blood pressure. The people that aged 80 to 90 had a lower risk of 33 %. The People that aged 50 to59 had the risk of stroke (62%). [1-3]

It takes a lot of study and testing to develop a formulation that yields the optimum outcomes. Nadolol is used once day at a dose of 20 mg and has a 30-35% oral bioavailability. It takes about 3-4 hours to reach T-max. Nadolol goes in hepatic First pass metabolism in liver. [4,5] Currently Nadolol available as s Conventional tablet(20,40,80mg).

Recently, there has been growing interest in utilizing the oral cavity as a route for drug delivery into the systemic circulation. In comparison to conventional oral tablets, sublingual administration allows the drug to be absorbed directly through the blood vessels beneath the tongue, thereby bypassing hepatic first-pass metabolism and providing a more rapid onset of action. Although traditional oral tablets are widely used, they may not be suitable in certain situations, such as during travel when water is not readily available. In such cases, sublingual tablets offer a convenient alternative, as they can be administered without water and minimize the risk of choking. These formulations generally require only a small amount of saliva to dissolve within the oral cavity. While sublingual absorption is typically rapid, it is often associated with a relatively short duration of action.[6-8] So to avoid these problems regarding conventional dosage forms the objective of the study was to develop a formulation of sublingual tablets of Nadolol.

MATERIALS AND METHODS

Materials

Nadolol was supplied by Zydus life Science, Ahmedabad, Gujarat, India. Croscarmellose sodium (CCS), Sodium starch glycolate (SSG), Talc, Magnesium stearate Mannitol and Aspartame, Sodium Lauryl Sulfate (SLS) were provided by Chemdyes corporation, Rajkot, Gujarat, India. Kyron T 314 was supplied by Corel Pharma Chem, Ahmedabad, Gujarat, India.

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Fabrication of Sublingual tablets by direct compression method

Direct compression is used for sublingual tablets because it produces rapidly disintegrating tablets, ensuring quick drug release and fast onset of action. It also avoids heat and moisture, thereby maintaining the stability of sensitive drugs. [9]

The sublingual Tablets were prepared using the direct compression method. Following passage through filter #60, geometric dilution was used to combine the exact amount of the active component and all additions evenly. The blend was directly compressed using a multi-rotatory tableting machine (Cronimach, Ahmedabad, Gujrat, India) equipped with a die set and an 8 mm flat-faced punch. The mass and compression force of each Tablet did not change. Each tablet contained 20 milligrams of Nadolol. [10]

3^2 Full Factorial Design

A 3^2 full factorial design was adopted to optimize the variables in Design of experiment (D.O.E)11version. In this design 2 factors were evaluated, each at 3 levels (-1, 0, +1) and experimental trials were performed at all 9 possible combinations. The amounts of super Disintegrants Kyron T-314 (X_1) and the amount of SSG (X_2), were selected as independent variables. The disintegration time and % cumulative drug release was selected as dependent variables Y_1 and Y_2 respectively.[11,12,13] Batches of factorial design are shown in Table 1.

Table 1. Composition of formulations of Nadolol Sublingual tablets Factorial batches

Materials(mg)	Formulation Batches								
	N1	N2	N3	N4	N5	N6	N7	N8	N9
Nadolol	20	20	20	20	20	20	20	20	20
Kyron T-314	2	2	2	3	3	3	4	4	4
SSG	2	2.5	3	2	2.5	3	2	2.5	3
D-Mannitol	70	69.5	69	69	68.5	68	68	67.5	67
Aspartame	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1
SLS	1	1	1	1	1	1	1	1	1
Total Weight	100	100	100	100	100	100	100	100	100

Determination of melting point of Nadolol

Nadolol's melting point was determined using a capillary device (Bhawana, India). A capillary tube with narrow walls, sealed at one end, was filled with the least amount of medication. After mounting this capillary in a thermometer-equipped melting point device, the temperature range across which Nadolol melts was measured. The measurements were obtained in triplicate.[14]

Identification by UV Spectroscopy

UV–Visible spectrophotometry is used for estimation as it offers a simple, fast, and reliable method to determine drug concentration based on its absorbance and use for Identification of pure drug.

Calibration curve of Nadolol in Phosphate buffer pH 6.8

10 milligrams of Nadolol were dissolved in 100 milliliters of phosphate buffer (pH 6.8) to create a standard stock solution with a concentration of 100 µg/ml. By pipetting out 2, 4, 6, 8, and 10 ml of the stock solution of 100 µg/ml and diluting it up to 10 ml in a volumetric flask, working solutions with concentrations of 20, 40, 60, 80, and 100 µg/ml were created. Working solutions' absorbance was measured three times at λ max 269 nm using phosphate buffer pH 6.8 as a blank. The above performed using UV spectroscopy is Shimadzu UV-1900, Japan and the Software was used UVprob-2.[15]

Compatibility study of drug and excipients

Drug–excipient compatibility studies are performed to ensure that no interactions occur that could negatively influence the stability, performance, or safety of the final formulation.

To determine whether the drug and excipients were compatible, FTIR spectroscopy was performed By Shimadzu IRAffinity-1S, Japan. on both pure drugs and physical mixtures of drugs and excipients. [16,17]

Determination of precompression parameters

The flow properties of powders are critical for an efficient tableting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. If a drug is identified at the Preformulation stage to be "poorly flowable," the problem can be solved by selecting appropriate excipients.

Hausner's ratio, bulk density, tapered density, compressibility index, and angle of repose were all measured. Good flow qualities were indicated by the powder mixture's minimum Carr's index, Hausner's ratio, and angle of repose. [18-19]

Determination of post compression parameters

Thickness and diameter

Tablet thickness and diameter are measured to ensure uniform size and shape, which is important for proper

packaging, handling, and appearance. They also help maintain consistent drug dose and quality across all tablets.

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.[20]

Hardness

Tablet hardness is evaluated to confirm adequate mechanical strength for handling, while still permitting proper disintegration and effective drug release. "Hardness is defined as the resistance of the tablet against the applied force till it breaks"

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. [20]

Weight Variation

Weight variation testing is performed to ensure uniformity of tablet weight, which reflects consistent drug content in each tablet. it helps maintain dose accuracy and quality control during tablet manufacturing. Weighing of the tablets in Scale-Tec Gujrat, India.

From each batch, twenty tablets were removed and weighed separately. Then, using the Indian Pharmacopoeia's parameters, the average weight and standard deviation of the tablets were calculated. [21]

% Friability

The friability test is carried out to evaluate a tablet's ability to withstand abrasion and mechanical stress during handling, packaging, and transportation.

The Roche friabilator (Bhawana, India) was used to assess the tablets' friability. First, ten pills were put into a friabilator and weighed (W Initial). The friabilator was operated at 25 rotations per minute for 4 minutes and 100 revolutions. After then, the tablets were taken out, cleaned, and weighed once more (W Final). The % friability was calculated by using formula:

$\%F = 100\ (1 - W_{Final} / W_{Initial})$ [22]

***In Vitro* Disintegration test**

The in vitro disintegration test is performed in to verify that sublingual tablets disintegrate quickly under the tongue, ensuring efficient drug release and absorption for rapid therapeutic effect.

Using a digital tablet disintegration test device Bhawana, India, this test was conducted on six tablets. As a disintegration medium, phosphate buffer pH 6.8 at 37°±0.5 °C was utilized, and the amount of time in seconds it took for the tablet to completely dissolve and leave no residue in the device was noted. [23]

Drug content

Drug content is measured to confirm that each tablet contains the appropriate amount of active ingredient, ensuring accurate dosing and therapeutic effectiveness.

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 269 nm.

***In Vitro* Drug release study**

The in vitro dissolution test is conducted to evaluate the rate and extent of drug release from the tablet, ensuring adequate bioavailability.

In vitro drug release from sublingual tablets was assessed using a USP type II (paddle type) dissolution device (DKB Instruments, India). 900 milliliters of phosphate buffer pH 6.8 at 37° ± 0.5 °C and 50 rpm were used for this test. At regular intervals, 5 ml of the sample solution was taken out of the dissolution equipment and replaced with the same amount of new dissolution medium. A 0.45µm membrane filter was used to filter the sample. These samples' absorbance was measured at 269 nm using a UV spectrophotometer. [24]

Stability study

Stability studies are performed to confirm that sublingual tablets maintain quality, safety, and performance over time.

In the current investigation, the optimized batch's stability was investigated for one month at 40° ± 2°C / 75 ± 5% relative humidity in stability chamber (Patel Scientific Instruments Pvt. Ltd Ahmedabad, Gujrat, India). The formulation was shielded from light by being wrapped in aluminum foil. Tablets were assessed for hardness, friability, weight fluctuation, drug content, in vitro disintegration time, and in vitro drug release study after a 30-day period. [24]

RESULTS AND DISCUSSION

Melting point of Nadolol

One common method for identifying drugs is melting point determination, which uses melting point apparatus. The melting point of Nadolol was determined to be between 119 and 133°C. The melting temperature of Nadolol is comparable to the reported melting point of 124–130°C.

Identification of drug by FTIR

FTIR was used to identify the medication. The FTIR spectra verified that it was Nadolol and conformed with the original medication. The FTIR of Nadolol shows band at 1581 cm-1, 2904 cm-1, 1180 cm-1, 3574 cm-1, 3336 cm-1, corresponding to the functional groups C=C Aromatic, C-H Strech, C-O Strech, O-H Strech, N-H Strech.

The FTIR of Nadolol With excipients shows band at 1462 cm-1, 2904 cm-1, 1170 cm-1, 3574 cm-1, 3336 cm-1, corresponding to the functional groups C=C Aromatic, C-H Strech, C-O Strech, O-H Strech, N-H Strech. When Nadolol was mixed with polymers, no changes in IR peaks were observed. These results imply that excipients and Nadolol are compatible. (Figure 1 and 2).

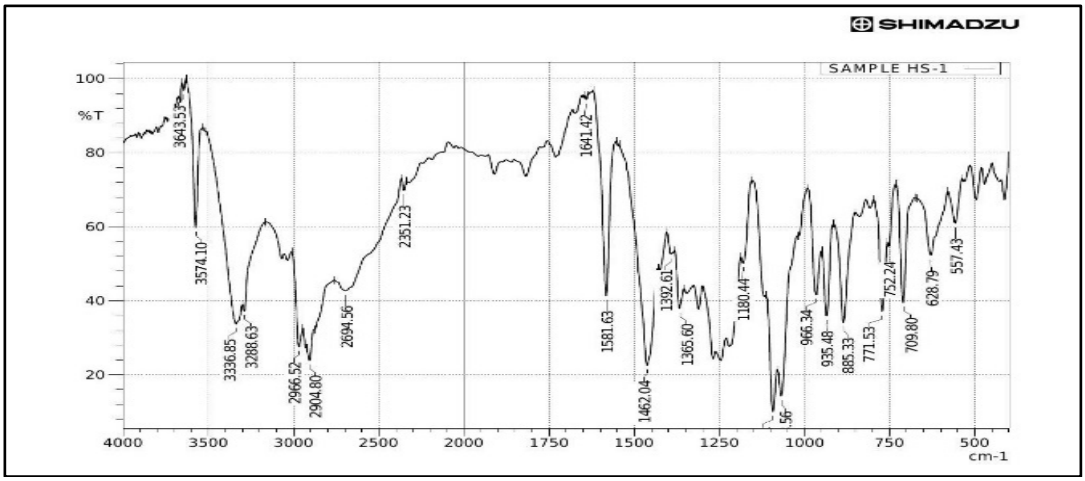

Figure 1 FTIR Spectra of Nadolol

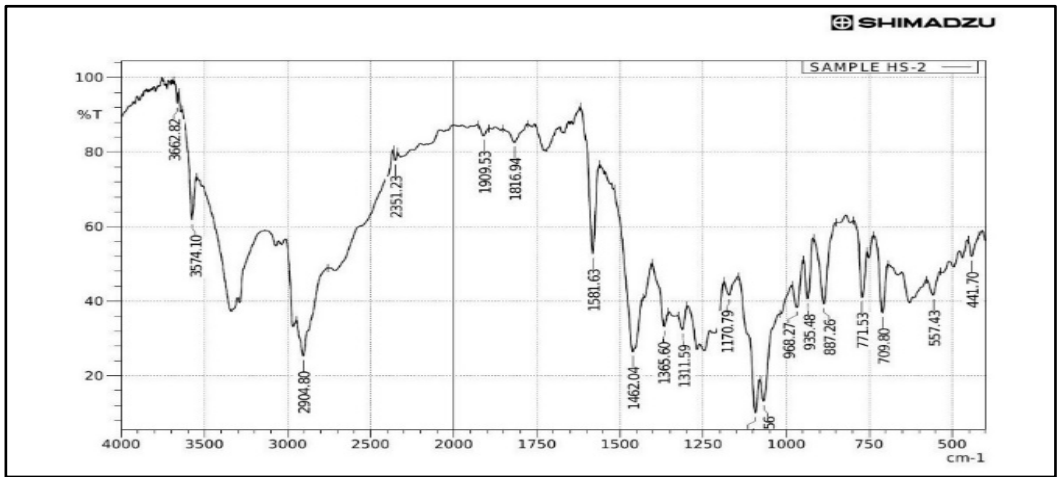

Figure 2 FTIR Spectra of Nadolol with excipients

Identification of drug by UV Spectroscopy Method

Drug overlay spectra were acquired by scanning solutions with varying concentrations (20, 40, 60, 80, and 100 µg/ml) at 269 nm. Figure 3 displays the Nadolol Overlay Spectra. UV Absorbance data for calibration curve of Nadolol in phosphate buffer pH 6.8 is mentioned in Table 2 and figure 4.

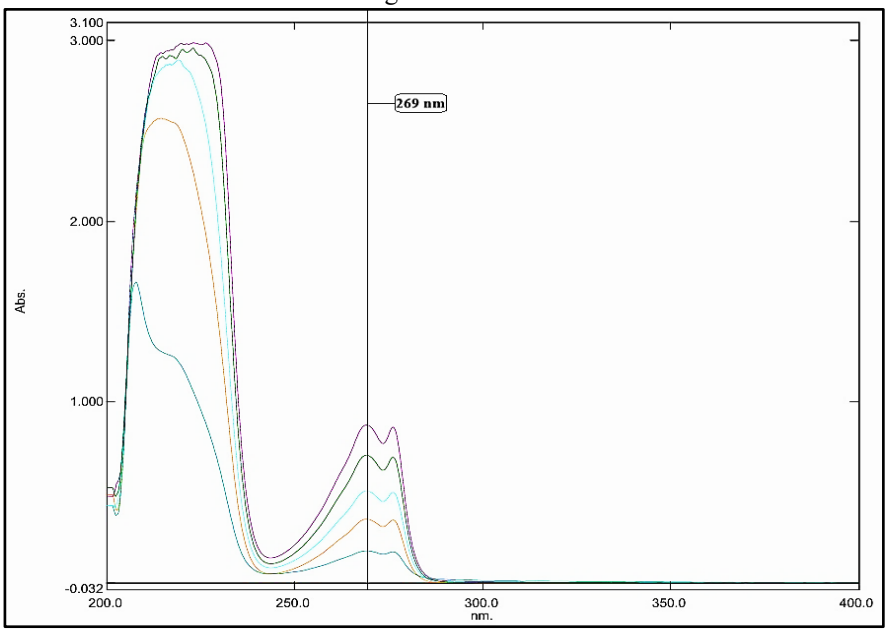

Figure 3: Overlay Spectra of Nadolol in phosphate buffer pH 6.8

Table 2. UV Absorbance data for calibration curve of Nadolol in phosphate buffer pH 6.8

Sr. No.	Concentration (µg/ml)	Absorbance			Mean Absorbance ± SD
		I	II	III	
1	20	0.176	0.177	0.178	0.177±0.001
2	40	0.354	0.352	0.350	0.352±0.002
3	60	0.506	0.508	0.510	0.508±0.002
4	80	0.705	0.706	0.709	0.706±0.002
5	100	0.875	0.873	0.872	0.873±0.001

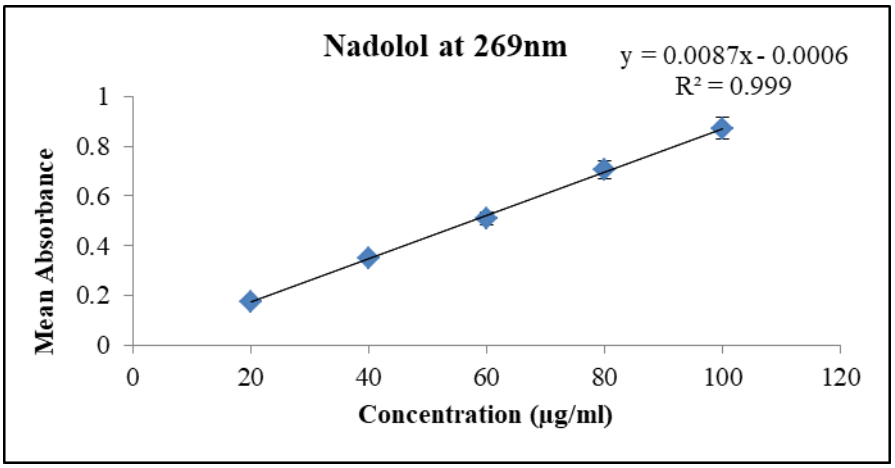

Figure 4: Calibration curve of Nadolol in phosphate buffer pH 6.8

RESULTS OF SUBLINGUAL TABLETS FORMULATED BY 3^2-FACTORIAL DESIGN

PRECOMPRESSION PARAMETERS

The powder blend's bulk density, taped density, Hausner's ratio, Carr's index, and angle of repose were all measured. It was discovered that every parameter had acceptable flow characteristics. Blend's flow characteristics have been tested and documented. The tapped density ranged from 0.61 to 0.67 gm/ml, while the bulk density was found to be between 0.50 and 0.57 gm/ml. Carr's compressibility index was computed using the two data points mentioned above. The range of the compressibility index was 15.08 to 17.91 percent. Data on compressibility and flow ability showed that all powder mixes had adequate flow characteristics. Angle of repose also demonstrated the superior flow characteristics of all powder blends. The angle of repose was range of 23.7º to 30.1° so it indicates good flow property (Table 3).

Table 3. Precompression Parameters

Batch	Bulk density (gm/ml ± S.D)	Tapped density (gm/ml ± S.D)	Carr's index (%± S.D)	Hausner's Ratio (± S.D)	Angle of repose (°θ ± S.D)
N1	0.55 ± 0.01	0.66 ± 0.01	16.65 ±1.44	1.20 ±0.01	26.5 ± 1.01
N2	0.53 ± 0.02	0.64 ± 0.03	17.77 ±0.80	1.21 ±0.01	29.3 ± 1.03
N3	0.57 ± 0.01	0.67 ± 0.01	15.08 ±1.59	1.17 ±0.02	25.8 ± 1.30
N4	0.56 ± 0.01	0.67 ± 0.01	16.32 ±1.17	1.19 ±0.01	23.7 ± 2.11
N5	0.54 ± 0.01	0.66 ± 0.01	17.63 ±1.23	1.21 ±0.01	28.7 ± 2.02
N6	0.52 ± 0.01	0.64 ± 0.02	17.91 ±0.55	1.21±0.007	26.4 ± 1.28
N7	0.54 ± 0.02	0.66 ± 0.02	17.68 ±0.76	1.21 ±0.01	30.1 ± 1.57
N8	0.56 ± 0.01	0.67 ± 0.01	16.31 ±1.62	1.19 ±0.02	27.3 ± 1.65
N9	0.50 ± 0.01	0.61 ± 0.02	17.59 ±1.04	1.21 ±0.01	25.5 ± 1.79

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

Physical parameters Sublingual tablets of Nadolol

Physical characteristics such as hardness, friability, weight fluctuation, thickness, were measured. Thickness was found that batches N1 through N9 ranged between 2.75 ± 0.02 mm and 2.85 ± 0.02 mm. It was discovered that the improved batch's friability was 0.78%, meeting Pharmacopeia standards. The optimal batch's hardness was 2.36 ± 0.28. This was enough to keep the tablet from shattering while being transported. The weight variation was 104.09 ± 1.03, in accordance with the US Pharmacopeia. The prepared batches' in vitro disintegration time ranged from 17.41 ± 1.64 to 40.01 ± 1.74 seconds. The drug content of the tablets, which were made using the direct compression

method, was determined to be between 94.32± 0.96 and 99.23± 0.67 percent. These drug content results showed that the active component was evenly distributed and at the right dosage in the sublingual tablet (Table 4).

Table 4. Post compression parameters of Nadolol Sublingual tablets

Batch	Thickness (mm ± S.D.)	Weight Variation (mg ± S.D.)	Hardness (Kg/cm^2 ± S.D.)	Friability (%)	*In vitro* disintegrating time (sec. ± S.D.)	Drug content (%)
N1	2.83 ± 0.02	100.84 ± 2.40	2.65 ± 0.18	0.40	40.01 ± 1.74	98.02 ± 0.54
N2	2.79 ± 0.01	101.40 ± 2.51	2.58 ± 0.14	0.49	37.11 ± 2.71	96.47 ± 0.73
N3	2.80 ± 0.01	98.83 ± 1.68	2.42 ± 0.25	0.69	27.86 ± 2.27	97.77 ± 0.99
N4	2.75 ± 0.02	99.75 ± 2.86	2.55 ±. 018	0.54	33.68 ± 1.71	98.57 ± 0.87
N5	2.77 ± 0.01	102.54 ± 1.76	2.49 ± 0.11	0.58	28.81 ± 1.42	97.12 ± 0.82
N6	2.85 ± 0.02	104.09 ± 1.03	2.38 ± 0.23	0.71	22.58 ± 1.21	94.32 ± 0.96
N7	2.81 ± 0.02	99.77 ± 1.86	2.51 ± 0.14	0.41	26.50 ± 1.79	98.08 ± 0.99
N8	2.78 ± 0.01	97.17 ± 1.38	2.45 ± 0.18	0.62	23.77 ± 2.94	98.66 ± 0.97
N9	2.76 ± 0.02	101.93 ± 2.06	2.36 ± 0.28	0.78	17.41 ± 1.64	99.23 ± 0.67

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

Percentage Cumulative Drug Release

Results showed that increasing the concentration of a super disintegrant in the tablet led to higher drug release. For formulations N1 to N3, the drug release started at 15.92 %, 18.84% and 23.22 % after 2 minutes, reaching 89.67 %, 92.16% and 95.22 % by the end of 12 minutes. Formulations N4 to N6 displayed initial drug release percentages of 21.95 %, 24.84% and 28.16 % at 2 minutes, which increased to 93.27 %, 94.11% and 98.61 % by 12 minutes. In formulations N7 to N9, the drug release ranged from 26.61 %, 28.42% and 30.24 % at 2 minutes, escalating to 94.87 %, 96.94% and 99.48 % by 12 minutes, respectively. The super Disintegrants concentration increase to 4% (Kyron T-314) and 3% (SSG) the %CDR was increase Simultaneously. And the batch contain this mixture that batch is N9. (Table 5 and figure 5).

Table 5. Percentage Cumulative Drug Release of Batches N1 To N9

Time (Min)	N1	N2	N3	N4	N5	N6	N7	N8	N9
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
2	15.92	18.84	23.22	21.95	24.84	28.16	26.61	28.42	30.24
4	33.23	35.45	41.03	37.49	39.24	43.10	41.94	45.86	48.66
6	53.37	55.41	60.11	57.95	59.73	61.45	62.88	64.91	67.14
8	68.78	71.08	73.66	72.35	75.48	78.68	77.11	79.22	81.12
10	78.21	80.27	83.61	82.12	84.78	86.03	85.96	87.95	90.24
12	89.67	92.16	95.22	93.27	94.11	98.61	94.87	96.94	99.48

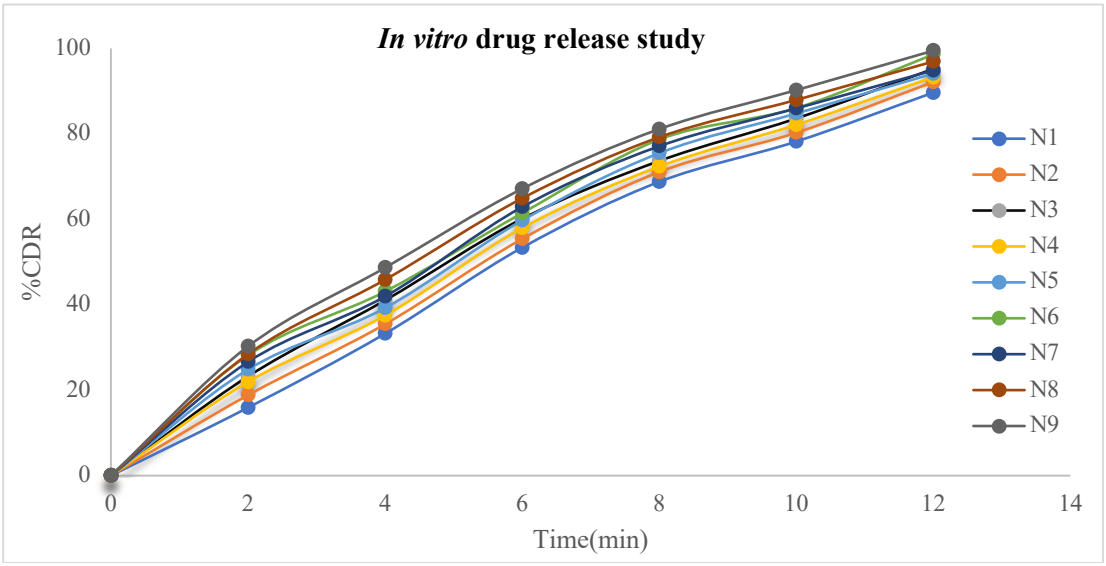

Figure 5: *In vitro* drug release study of batches N1 To N9

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 and % CDR at 12 min were 0.9948 and 0.9855, 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. Formulation batches N1 to N9 underwent evaluation for In vitro Disintegration test and % CDR. Summary of ANOVA Analysis is mentioned in table 6.

Table 6. Summary of ANOVA Analysis

Source	Sum of Square	Degree of Freedom	Mean Square	F Value	P Value
In vitro Disintegration time (Y_1)					
Regression	416.03	5	83.21	115.70	0.0013
Residual	2.16	3	0.7191	-	-
Total	418.19	8	-	-	-
% CDR (Y_2)					
Regression	76.02	5	15.20	40.77	0.0059
Residual	1.12	3	0.3730	-	-
Total	77.14	8	-	-	-

Statistical Analysis for *In vitro* Disintegration Time

Polynomial equation for *In vitro* Disintegration time(Y_1)**:**

$$Y_1 = 29.62 - 6.22\ B_1 - 5.39\ B_2 + 0.7650\ B_{12} + 0.4200\ B_1^2 - 1.89\ B_2^2$$

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 Kyron T-314 and SSG increases, there is a decrease in In vitro Disintegration time. Further examination of the equation showed that 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 6).

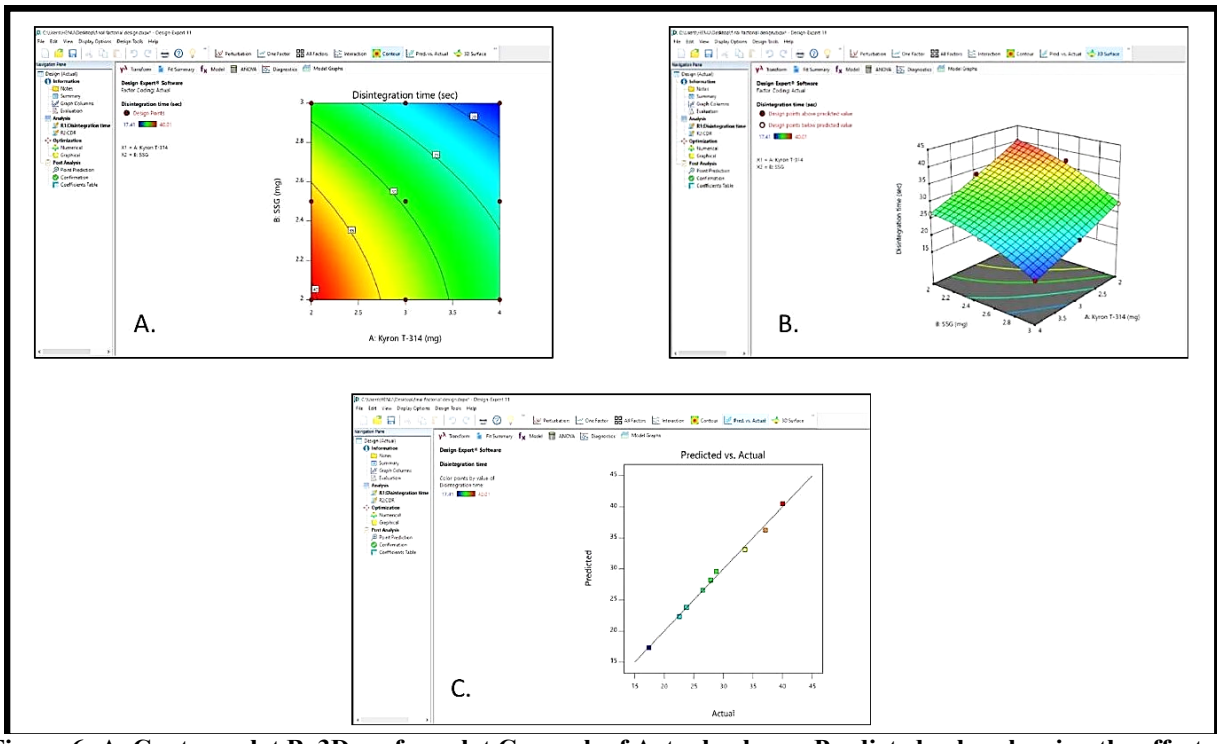

Figure 6: A. Contour plot B. 3D surface plot C. graph of Actual value vs Predicted value showing the effect of KyronT-314 (X1) and SSG(X2) on *In vitro* Disintegration Time

Statistical Analysis for % CDR

Polynomial equation for % CDR**:**

$$Y_3 = 94.81 + 2.37\ B_1 + 2.58\ B_2 - 0.2350\ B_{12} + 0.6067\ B_1^2 + 0.7833\ B_2^2$$

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 Kyron T-314 and SSG increases, there is an increase in % CDR with respect to time. from the above equation it was found that 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 7)

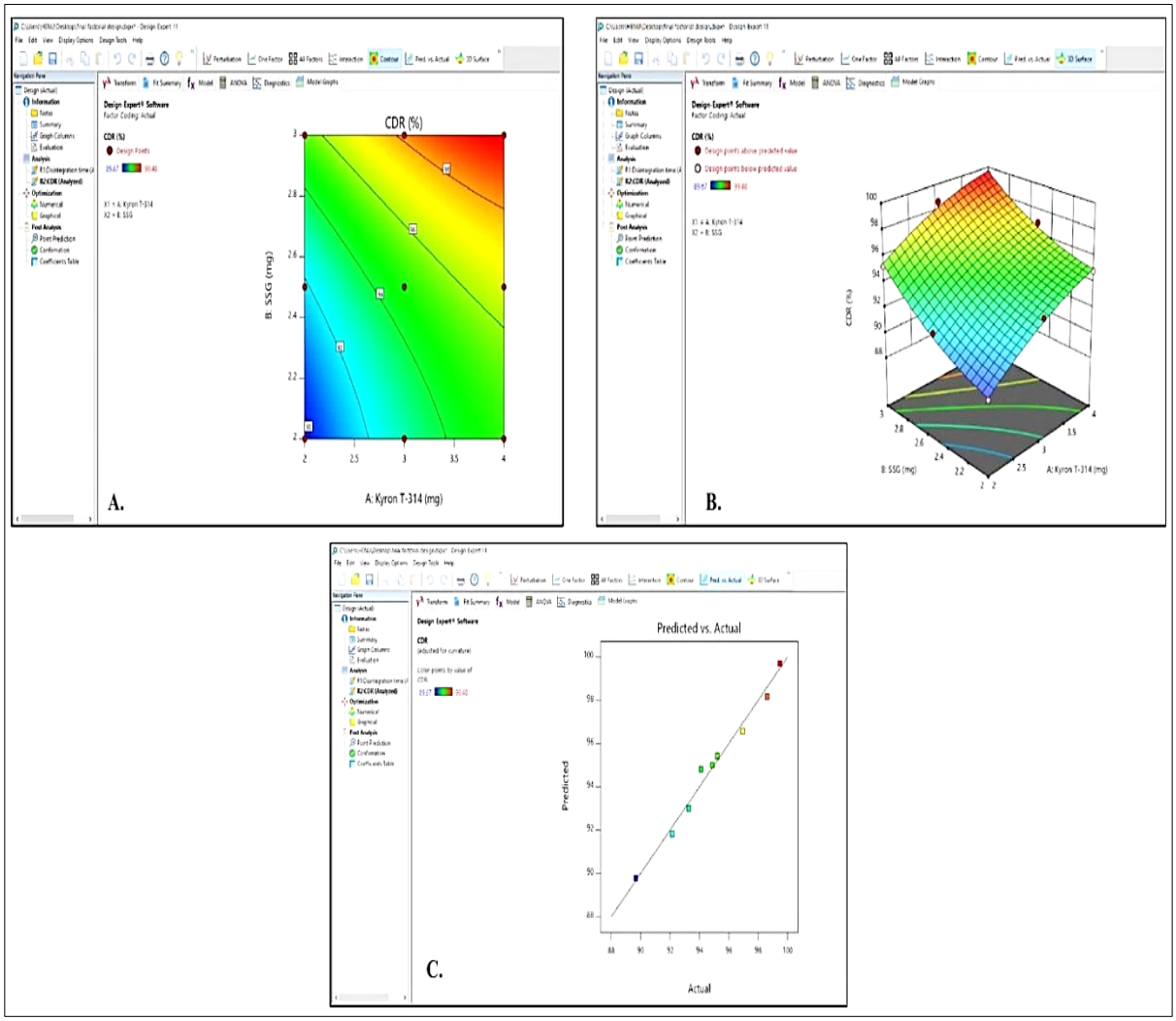

Figure 7: A. Contour plot B. 3D surface plot C. graph of Actual value vs Predicted value showing the effect of KyronT-314 (X1) and SSG(X2) on %CDR

Based on the evaluation of all parameters of the factorial design batches, batch N9 was identified as the optimized formulation due to its acceptable surface characteristics, adequate mechanical strength, and uniform drug content. It also exhibited rapid drug release of 99.48% within 12 minutes and an in vitro disintegration time of 17.41 seconds, which was the shortest among all batches.

Stability studies

Batch N9 was selected as the optimized batch. Further, stability studies of the optimized batch were carried out at 40 ± 2°C and 75 ± 5% RH for a period of one month. After completion of the study, the tablets were evaluated for hardness, wetting time, in vitro disintegration time, drug content, and percentage cumulative drug release.

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, in vitro disintegration time, drug content and % CDR at the end of 1 month. Thus, it was concluded that the batch N9 was found to be stable (Table 7, 8 and figure 8).

Table 7. 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.)	2.36 ± 0.28	2.35 ± 0.18
Friability (%)	0.78	0.80
Weight variation (mg ± SD)	101.93 ± 2.066	102.03 ± 1.86
In vitro Disintegration Time (sec. ± S.D.)	17.41 ± 1.64	19.40 ± 1.57
Drug Content (%)	99.32	98.46

Table 8. *In Vitro* Drug Release study of Stability batch

Time (Min.)	% CDR of Optimized Batch (%)	% CDR of batch After Time Period of 1 Month (%)
0	0.0	0.0
2	30.24	29.12
4	48.66	46.21
6	67.14	66.89
8	81.12	80.91
10	90.24	88.36
12	99.48	98.93

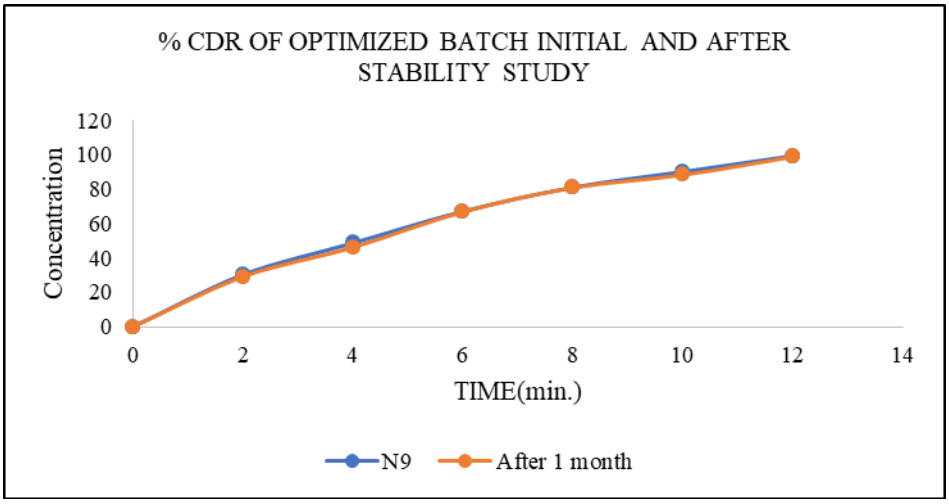

Figure 8: Comparison of *in Vitro* Drug Release study of Optimized batch and Stability batch

CONCLUSION

Nadolol, utilized for treating Hypertension, falls under BCS Class 3 and go through hepatic first-pass metabolism, resulting in a limited bioavailability of just 30-35%. Compatibility assessments, conducted via FT-IR, were carried out on Nadolol and the carriers utilized in the formulations, confirming their compatibility. Sublingual tablets containing Nadolol were produced via the direct compression method utilizing super disintegrants. A 3^2 factorial design was employed to optimize the formulation, with the Kyron T-314 designated as an independent variable (X_1) and SSG selected as another independent variable (X_2). Meanwhile, *In Vitro* Disintegration time and % Cumulative Drug Release at 12 minutes were chosen as dependent variables Y_1 and Y_2 respectively. Formulation N9 was optimized based on the overlay contour plot, revealing a minimum disintegration time of 17.41 ± 1.64 seconds, and a cumulative drug release percentage of 99.48% within just 12 minutes and this batch containing KyronT-314 (4%) and SSG (3%). Thus, batch N9 of sublingual tablets was determined as the optimal batch utilizing the desirability function. The comparison between predicted responses and actual outcomes revealed excellent agreement and was further assessed for additional parameters such as stability study. Further, ANOVA analysis confirmed that the values of independent variables fit within acceptable limits, and examination of the graphs and data generated by Design Expert software showed that batch N9 produced all the desired outcomes. Additionally, batch N9 was determined to be the optimal batch by the contour and overlay plots. The stability study of batch N9 showed that, when kept in a stability chamber at 40 ± 2 °C/75 ± 5% RH for a month, there was no noticeable variation in hardness, weight variation, friability, in vitro disintegration time, drug content, and in vitro dissolution profile. According to the study's results, it is conceivable to successfully construct Nadolol sublingual tablets. These tablets are made with super disintegrants using the direct compression method, which allows for quick

drug release. As a result, it will have an important impact in increasing patient compliance, which is necessary for the treatment of acute hypertension.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

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