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Formulation and Optimization of Propranolol Hydrochloride Oro-dispersable Tablets by Central Composite Design

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Abstract

The present work aimed to formulate and optimize propranolol HCL mouth tablets through experiment design. The scientific knowledge of input and output factors was assessed using the central composite design tool to create a design space for regulatory flexibility. The natural super disintegrant concentrations were chosen as the independent variables. The dependent variables were in vitro dispersion time and drug release %. FTIR tests showed drug and excipient compatibility. Precompression parameters showed that the flow characteristics were generally good. The direct compression method was used to manufacture the tablets, and all of the tablets made in the tests above met the predetermined limitations for pharmacotechnical characteristics. Dehydrated banana powder concentration increases led to a reduction in in vitro dispersion time and an increase in drug release percentage. According to kinetic studies, drug release from all formulations followed the first-order release. The outcomes proved that the suggested concept for creating Propranolol Hcl Mouth Melt Tablets with optimal qualities worked well.

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INTRODUCTION

The most popular method of medicine administration is oral. The most widely used oral dose type is a tablet. It is not novel to manufacture a solid dosage form using powder compression. A tablet comprises various chemicals used in manufacturing a comprehensive preparation and one or more pharmaceuticals, often active ingredients. The GI tract and hepatic portal systems are circumvented by orodispersible tablets, enhancing oral medications' bioavailability that would otherwise undergo

Table 1 Formulation of Propranolol HCL mouth melt tablets

Ingredients in (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Propranolol HCL	25	25	25	25	25	25	25	25	25
Dehydrated Banana powder	8.5	10	8.5	10	7	5.5	13	7	7
Orange peel pectin powder	7.63	7.63	11.32	11.32	9.47	9.47	9.47	5.78	13.16
Mannitol	175.5	175.5	175.5	175.5	175.5	175.5	175.5	175.5	175.5
Microcrystalline cellulose	77.87	71.87	74.18	68.10	73.03	79.03	67.03	76.72	69.34
Aspartame	8	8	8	8	8	8	8	8	8
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Talc	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Total weight(mg)	300	300	300	300	300	300	300	300	300

hepatic first-pass metabolism. In addition, the pH and GIT enzymes prevent the medication from being broken down [1]. Due to the lack of discomfort associated with injections, the ability to provide drugs to unconscious or disabled patients, the ease of administration compared to injectables or oral medications, and the quick release of drugs from dosage forms, it promotes patient compliance. When opposed to the oral route, this method can produce a comparatively quick beginning of the effect, and the formulation can be withdrawn after therapy is stopped. Taking drugs through the buccal mucosa is simple. The buccal mucosa has a robust blood supply, is less porous than the sublingual area, and allows for the quick absorption of medications into the circulatory system beneath the mouth mucosa [2]. Additives called disintegrants, or mixtures of chemicals, are used in drug formulations to help break up and disperse tablet and capsule contents into tiny pieces for faster dissolving. Using appropriate super disintegrants allows for the development of tablets that dissolve quickly. Several more advanced substances dubbed "Superdisintegrants" have been created recently. Compared to disintegrants, these compounds promote a faster disintegration with less quantity. The combined impact of swelling and water absorption by the formulation causes super disintegrants to disintegrate quickly. The super disintegrants' swelling causes the carrier's wetted surface to grow, which raises the system's wettability and dispersibility and accelerates the disintegration and dissolving process [3].

METHODOLOGY:

Compatibility Studies:

The drug's compatibility with the excipients was determined using FT-IR spectroscopy (FT IR-8400-S, Shimadzu, Japan). Six tonnes of pressure were used to create pellets after about two milligrams of pure medication and formulation were mixed with potassium bromide powder. Using FT-IR mapping of pharmaceuticals with formulation, the locations of FT-IR bands of significant functional groups were found. The single drug and the finished formulation with the excipients were chosen and scanned individually. To validate that the two spectra had familiar peaks, they were compared.

Preparation of Dehydrated Banana Powder:

Bananas were bought at the local market in Ananthapuramu. Fruits were chopped, and their peels removed. To remove the water-soluble material, sliced pulp was cleaned with distilled water. [4] As a preservative, 0.2% w/w methylparaben was added. The chopped pulp was ground in a home mixer to get a consistent weight, dried for 24 hours at 45°C, and then sieved through Sieve No. 80.

Preparation of Orange peel powder:

The ripped orange peel was acquired from the local market in Anantapuramu. The peel was thoroughly cleaned, dried for 24 hours in the shade, and then dried again in a hot air oven at 60 °C. Dried fruit peel was chopped into pieces and powdered using an electric grater. Sieve No. 20 was used to pass the powdered peel further. To maintain an acidic pH of 2, 200 g of peel powder was dissolved in 1 L of water, and 1 g of citric acid was added. This solution was reflux-condensed for six hours at 70ºC to extract the pectin. The extract, or thimble, was a Whatman cellulose thimble, measuring 80 mm outside and 33 mm inside [5]. The concentrated juice was chilled to 4 ºC after the hot acid extract was pressed in a cheesecloth bag. Pectin was precipitated by

treating ethanol with water (2:1 v/v) and continuously stirring for 15 minutes, then letting it stand for two hours. After filtering through cheesecloth and washing with 95% alcohol, the pectin coagulate was pressed. At 35 to 45 C, the pressed pectin was dried to a consistent weight. After being powdered and going through sieve No. 60, the hard pectin cake was kept in desiccators for later use [6].

Characterization of Orange Peel Pectin Powder and Dehydrated Banana Powder

For dehydrated banana powder and orange peel pectin powder, physiochemical analyses were performed, including solubility, viscosity, swelling index, Bulk density, tapped density, and angle of repose [7]. The model turned out to be nonlinear. Thus, the Central Composite Design was included in the design.

Formulation of Propranolol Hcl blend by dry mixing

The direct compression method was used to make propranolol mouth melt tablets using the formula shown in **Table 1**. Fifteen formulations (F1 to F9) of mouth melt propranolol Hcl were made with natural super disintegrants, such as powdered orange peel pectin and dehydrated banana powder.

Each ingredient was individually passed through mesh number 60 before being gathered. The drug, mannitol, and microcrystalline cellulose were combined gently using a mortar and pestle to create a homogenous mixture. Aspartame and super disintegrants in the appropriate amounts were taken for each formulation and combined with the mixture above. Talc and magnesium stearate were subsequently added and thoroughly blended [8].

Evaluation of Precompression parameters [9]

Bulk density (BD)

The Bulk density was ascertained after carefully weighing the combined sample and placing it in the 100 ml graduated cylinder with a slight inclination. Notable were the initial weight and volume. A calculation was made to determine the sample's weight-to-volume ratio.

Tapped density (TD)

By carefully weighing the blend sample and transferring it to a 100 ml measuring cylinder, the Electro lab Tapped Density Apparatus (method USP-I) could estimate the taped density. The cylinder was tapped ten times to determine its initial volume (V0), after which the volume was measured. There were 500 more tapings made, and the loudness was recorded. If the volume measured after 10 and 500 tapings differed by more than 2 milliliters, continue until 1250 tapings.

Compressibility index (CI)

The Compressibility Index (CI) quantifies a powder's probability of being compressed. It measures the strength and stability of the bridge directly or the potential powder arch. It was computed using the equation (**Table 8**) provided below.

Hausner ratio: The Hausner ratio measures powder flow simplicity that is not direct. The following formula was used to calculate : **Table 8**

Hausner ratio =Tapped density/ Bulk density

A lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Compression of propranolol Hcl Mouth melt tablets

The drug and excipient mixture was squeezed using a 7 mm punch on a ten-station "B" Tooling Rotatory Tablet Punching Machine to create convex-facing tablets.

Evaluation of physical parameters of tablets [10]

Average weight

From each formulation, ten pills were chosen randomly and weighed separately and collectively to look for weight variations. The weighted average was recorded, and the standard deviation was computed. The tablet weight variation is permitted to be within ± 5% in all formulations.

Thickness

The thickness was determined using a Vernier caliper scale. The tablet thickness was kept within a five percent range of the reference value.

Hardness

Using an Erweka tablet hardness tester, the

hardness of tablets chosen randomly was determined. Five tablets of each formulation were examined. It is stated as kg/cm^2.

Friability

The Roche friability was filled with ten weighted pills and operated at 25 rpm for four minutes. After dedusting, these tablets were weighed once more. The following formula was used to calculate the % friability:

$\%F = \{1-(W_t/W)\} * 100$

Compressed tablets with a loss of less than 0.5–1.0% are considered suitable.

Drug content

Each mixture was given three separate weights before being ground into a powder. A pH 6.8 buffer was used to adjust the volume to 100 milliliters after the powder equivalent to 20 milligrams of propranolol Hcl was weighed and dissolved in 10 milliliters of methanol. The solution was measured at 217 nm by UV-visible spectrophotometer using a pH 6.8 buffer as the blank. From this solution, 10 ml was extracted and built up to 100 ml using a pH 6.8 buffer.

In-vitro disintegration time

The test was conducted at 370C ± 0.50C with distilled water as the disintegration medium in a disintegration apparatus. The system was set up with six tubes, one disc put into each tube, and a tablet placed within each. The duration required for the tablet to completely dissolve and retain no mass inside the device was calculated in terms of seconds.

Wetting time

A quick and easy method can be used to determine the tablets' wetting time. In a 10 cm diameter Petri dish, five circular tissue papers are arranged in a circle. The Petri plate is filled with 10 milliliters of water diluted with the water-soluble dye Eosin. The surface of the tissue paper is gently touched with a tablet. One measure of wetting time is the time it takes for water to reach the tablet's upper surface.

Water absorption ratio

A Petri plate with six milliliters of distilled water was filled with double-folded tissue paper. The time for a pre-weighed tablet to completely wet was measured seconds after the tablet was placed on the paper. We next weighed the moist pill. Equation (1) was used to calculate the water absorption ratio.

R= (Wa-Wb) / WaX 100

Using Sigma Tech Software, evaluate the effect of crucial formulation factors such as DBP and OP levels on in-vitro dispersion time and in-vitro drug release.

In-vitro dispersion time

The tablet was mixed with 10ml phosphate buffer (pH 6.8) at 37±0.5°C. The time it takes for the tablet to disperse completely was measured.

In-vitro drug release [11]

USP dissolving test apparatus II (Paddle type) was used to measure the in-vitro drug release of propranolol HCl from mouth melt tablets. At 37 ±0.5°C, 900 *ccs* of PBS (pH 6.8) was used for the dissolution test. Fifty revolutions per minute was the paddle's rotational speed. Five milliliters of the sample were taken at predefined intervals (five minutes) and filtered using Whatman filter paper. A UV spectrophotometer measured the solution's absorption at 217 nm, and a standard curve was used to calculate the drug's release.

Kinetic analysis of In-vitro release data

The in vitro release data were fitted to zero-order, first-order Higuchi matrix model and Korsmeyer-Peppas model using PCP Disso v2.08 software to identify the release mechanism that best describes the drug release pattern. The best-fitting model was defined as the one with the highest correlation coefficient values, also known as the determination coefficient (R2). The Korsmeyer-Peppas model was utilized to analyze the release data kinetically. The release exponent (n), which describes the drug release mechanism from the matrices, was determined by regression analysis utilizing the subsequent equation:

$Mt/M\infty = k\ tn$

Statistical analysis and optimization

Using Sigma Tech software, data from every formulation of mouth melt tablets were examined and utilized to create the study design. Sigma Tech software was used to compare multiple statistical factors and determine which model best fits the

data. ANOVA, or analysis of variance, was also employed to determine which factors significantly impacted response regression coefficients. Using the software, the F test and P values were also computed. Contour plots provided more insight into the relationship between the independent and dependent variables. Afterward, new formulations with the intended answers were produced using a graphical optimization technique that employed contour plots [12].

RESULTS AND DISCUSSION

To guarantee a certain level of product quality, Critical Quality Attributes (CQAs) were considered for the design of experimentation based on their significant association with the Total Quality Product Profile (TQPP). The essential formulation variables (independent variables) and the responses able to gauge the quality of the product were defined based on previous research and exploratory studies to construct the "design space." The concentration of DBP and the amount of OPP were the independent factors considered for mouth melt tablet formulations because they were thought to be important in determining the responses in vitro dispersion time and drug release percentage. To optimize the propranolol Hcl mouth melt tablets, a 22-factorial design with four replicates was chosen based on the number of parameters or variables and their levels; however, it was discovered that the curvature impact was nonlinear, so the design was extended for the central composite design. The direct compression method was used to prepare the mouth melt tablets.

Compatibility studies

FT-IR Spectroscopy

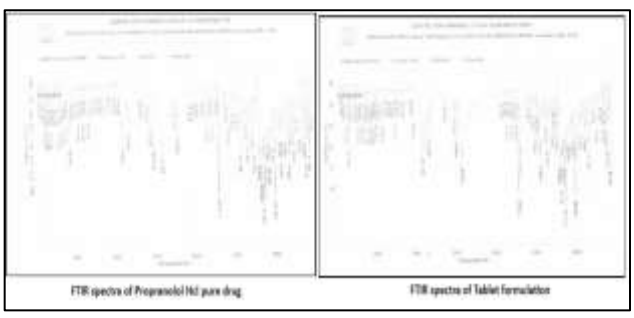

Figure 1 FT-IR Spectrums

Table 2 Interpretation of IR spectra of Optimised Formulation

IR PEAKS (cm^{-1})	GROUPS PRESENT
1712.08	C=O(stretching)
1181.79	-C-O (stretching)
2922.95	-C-H(stretching)CH_2
1485.56	-C-H(bending)CH_2
1440.76	-C-H(bending)CH_3
1358.66	-C-N(stretching)

ANOVA was utilized to determine the significant effect, with a coefficient of determination of R2 = 0.995. Since the obtained value of F is more than the critical F-value, the outcome was considered significant at that probability level ($p<0.05$). As the acquired F value (i.e., 6.59) is greater than the critical value of 4.95, which is the essential value of F, it may be argued that the obtained F value is likely to occur by chance with ap<0.05, indicating significance at that level of probability (**Table 16**). Since the R2 model was shown to be necessary, predictions have been made using this model. Since Sigma Tech software indicates that the relationship between Y1 Vs X, X is nonlinear, the Central composite design has been used; the observed results can be seen in **Table 12**.

A statistical quadratic model was obtained by entering the values in Sigma Tech in two variable optimization modules.

A final equation in terms of coded factors

$Y1 = 82.25 - 16.0\ X_1 + 1.6667\ X_2 - 24.5 X_1X_2 - 3.15\ X_1^2 + 2.6\ X^2$

The final equation in terms of actual factors

$Y1 = 82.25 - 16.0\ DBP + 1.6667\ OPP - 24.5\ DBP\ OPP - 3.15\ DBP^2 + 2.6 OPP^2$

After considering the coefficient amount and the mathematical sign (positive or negative), the polynomial equations were utilized to form conclusions. The multiple linear regression analysis findings showed that while dispersion time increased with an increase in orange peel powder, it decreased with an increase in banana powder. This quadratic model's R2 score, which is 0.9128 and found to be greater than 0.70, indicates that it is a dependable model for formal CQAs.

As a result, forecasts and contours/design space are established to construct a robust technique.

Table 3 Orange peel pectin powder with dehydrated banana powder characteristics

Parameter	Dehydrated banana powder	Orange peel pectin powder
Appearance	Colourless Powder(white)	Browncolour
Taste	Mucilaginous	Mucilaginous
Odor	Characteristic	Characteristic
Solubility	Soluble in water, Slightly Insoluble in acetone, methanol, ether	Soluble in water, Insoluble in acetone, methanol, ether
Swelling index	5.98	6.14
Bulk density(g/ml)	0.50 + 0.125	0.47 + 0.214
Tapped density(g/ml)	0.56+ 0.098	0.59 + 0.107
Angle of repose(Θ)	35.12 + 0.147	34.48 + 0.128
Melting point(°C)	82	79

Table 4 Evaluation of Pre compression parameters

Formulation Code	Bulk density (g/cm3)	Tapped Density (g/cm3)	Compressibility Index (%)	Hausner's ratio	Angle of repose
F1	0.322+0.042	0.409+0.0.36	22.57	1.28	29°.33+0.042
F2	0.334+0.021	0.391+0.038	15.11	1.17	28°.52+0.021
F3	0.315+0.022	0.405+0.027	23.28	1.29	36°.64+0.022
F4	0.343+0.044	0.428+0.061	21.28	1.26	35°.04+0.044
F5	0.336+0.027	0.407+0.024	18.74	1.22	31°.96+0.027
F6	0.328+0.023	0.402+0.015	21.95	1.27	32°.38+0.036
F7	0.343+0.025	0.434+0.076	22.02	1.27	29°.26+0.048
F8	0.345+0.045	0.404+0.014	15.65	1.18	30°.22+0.027
F9	0.357+0.028	0.428+0.029	17.63	1.21	34°.02+0.032

Table 5 Evaluation of propranolol Mouth melt tablets-1

Batch code	Average weight (mg)*	Thickness (mm)*	Hardness (kg/cm²)**	Friability (%)*
F1	298+2.6	4.11+0.032	2.4+0.111	0.55+0.055
F2	302+1.6	4.19+0.028	2.2+0.109	0.24+0.113
F3	302+1.8	4.18+0.519	2.5+0.649	0.45+0.199
F4	302+1.3	4.22+0.604	2.4+0.752	0.22+1.164
F5	302+1.1	4.17+0.264	2.6+0.254	0.47+0.683
F6	303+0.8	4.14+0.649	2.8+0.613	0.34+0.264
F7	302+0.7	4.17+0.734	2.7+0.116	0.25+0.377
F8	302+2.6	4.19+0.757	2.4+0.131	0.42+0.359
F9	299+1.2	4.11+0.759	2.6+0.787	0.44+0.422

The mean + standard deviation is used to express all values (n=10*, n=5**)

Table 6 Evaluation of propranolol Hcl Mouth melt tablets-2

Drug content (%)*	Disintegration time (sec)*	Wetting time (sec)*	Water absorption ratio (%)*
99.37+0.24	40+0.31	46+0.78	92.48+0.19
99.03+0.77	28+0.65	35+0.25	96.3+0.132
97.31+0.31	48+0.28	62+0.55	85.25+1.05
97.45+0.22	48+0.37	37+0.12	81.12+2.63
98.90+0.63	40+0.60	51+0.33	93.41+3.12
99.30+0.34	60+0.63	72+1.11	86.1+0.516
98.36+0.67	25+0.68	29+1.28	98.1+0.662
98.66+0.23	90+0.15	57+0.87	80.2+0.343
97.40+0.71	47+1.32	49+0.77	94.23+3.82

The mean + standard deviation is used to express all values (n=3*)

Table 7 In-vitro Dispersion time of tablets

Batch code	Dispersion time (sec) (n=3)
F1	61+0.318
F2	39+0.206
F3	125+0.44
F4	45+0.88
F5	93+0.11
F6	130+028
F7	34+1.120
F8	77+0.991
F9	72+1.24
F10 (optimized formulation)	33+1.56

Table 8 Statistical Design of Experiments for Response (Y1)

Combination	Dehydrated Banana Powder	Orange peel pectin Powder	Y1
I	9	12.63	61+0.318
X1	15	12.63	39+0.206
X2	9	16.32	125+0.44
X1X2	15	16.32	45+0.88
Midpoint	12.0	14.475	93+0.11
Midpoint	12.0	14.475	92+0.12
Midpoint	12.0	14.475	93+0.25
Midpoint	12.0	14.475	90+0.22

Table 9 DoE experimental observations with two variables statistically analyzed

S. No	Co-efficient	Name of Variable	Co-efficient values	SS% (% of sum of squares)
1	b0	-	77.5	-
2	b1	DBP	-24.5	66.93
3	b2	OP	7.5	6.272
4	b12	DBP, OP	-15.5	26.79

Table 10 ANOVA results for response Y1, or the in-vitro dispersion time

S. No	Sr of Vari	SS	DF	MS	F-value	Fstdat 0.1p	Fstdat 0.05p	Fstdat 0.01p
1	Model	3587.0	3	1195.6667	9.2233720	4.19	6.59	16.7
2	Error	0.0	4	0.0				
3	Total	3587.0	7					
Curvature Effect		15.35to17.17						
95% Confident Level of Curvature effect Nonlinear								

Table 11 CCD experiments for two variables

S. No	Combination redesigned	X1	X2	Y1
1	I	9	12.63	61+0.318
2	X1	15	12.63	39+0.206
3	X2	9	16.32	125+0.44
4	X1X2	15	16.32	45+0.88
5	Midpoint	12.0	14.475	93+0.11
6	X1At-2L	6	14.475	130+028
7	X1At+2L	18	14.475	34+1.120
8	X1At-2L	12	10.785	77+0.991
9	X1At+2L	12	18.165	72+1.24

Table 12 Drug release of formulations (F1-F5 n=3)

Time (min)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	59.8+0.12	60.5+0.33	47.8+0.51	61.4+0.89	44.7+0.14
10	88.7+0.09	74.8+0.14	57.9+0.37	81.9+0.16	60.8+0.18
15	98.6+0.62	99.5+0.18	87.5+0.28	103.3+0.67	83.5+0.68

Table 13 Drug release of formulations (F6-F10 n=3)

Time (min)	F6	F7	F8	F9	F10 (optimized formulation)
0	0	0	0	0	0
5	39.9+0.56	69.4+1.48	66.5+0.38	67.9+0.14	70.5+1.58
10	56.4+0.68	88.9+1.59	88.4+1.29	80.7+0.65	84.9+0.97
15	85.9+0.34	99.8+0.53	96.6+0.87	94.2+0.38	99.7+2.57

Table 14 Kinetics of in vitro drug release data (F1-F5)

ReleaseModel		Formulation code				
		F1	F2	F3	F4	F5
Zeroorder	R^2	0.226	0.4144	0.3210	0.2654	0.1485
First order	R^2	0.9598	0.9817	0.9844	0.9758	0.9984
Peppas		0.9115	0.9214	0.9096	0.9365	0.9040
	n	0.1918	0.2028	0.1728	0.1585	0.1709
Higuchi	R^2	0.6481	0.5558	0.4860	0.6388	0.6650
Hixson	R^2	0.3479	0.2564	0.4532	0.2421	0.5127

Table 15 Kinetics of in-vitro drug release data (F6-F10)

Release Model		Formulation code				
		F6	F7	F8	F9	F10
Zero-order	R2	0.2246	0.5144	0.3310	0.3674	0.3458
First order	R2	0.9898	0.9889	0.9844	0.9858	0.9978
Peppas	n	0.7115	0.8214	0.8096	0.7365	0.7547
		0.1618	0.2028	0.1728	0.1585	0.1289
Higuchi	R2	0.5481	0.6558	0.4760	0.6478	0.5874
Hixson	R2	0.2479	0.3564	0.4235	0.3421	0.3376

Table 16 Statistical Design of Experiments for Response (Y2)

Combination	Dehydrated Banana Powder	Orange peel Powder	Y2
I	9	12.63	98.6+0.62
X1	15	12.63	99.5+0.18
X2	9	16.32	87.5+0.28
X1X2	15	16.32	103.3+0.67
Midpoint	12.0	14.475	83.5+0.68
Midpoint	12.0	14.475	84.7+0.68
Midpoint	12.0	14.475	84.2+0.68
Midpoint	12.0	14.475	83.8+0.68

In-vitro Dispersion time

All formulations' in-vitro dispersion times ranged from 33 to 130 seconds.

In-vitro dispersion time: (Y1)

After these numbers had been entered into Sigma Tech software, the following statistical analysis was produced.

In-vitro drug release(Y2)

83.5% to 103.3% was found to be the drug release for all formulations (**Table 12** , **Table 13**).

Table 17 Two-variable statistical analysis of DoE experimental observations

S. No	Co-efficient	Name of Variable	Coefficient values	SS%(% of Sum of squares)
1	b0	-	97.45	-
2	b1	DBP	4.425	54.44
3	b2	OP	-2.075	11.97
4	b12	DBP,OPP	3.475	33.57

Table 18 ANOVA results for response Y2 (in vitro drug release)

S. No	Srcof Vari	SS	DF	MS	F-value	Fstdat 0.1p	Fstdat 0.05p	Fstdat 0.01p
1	Model	143.8475	3	47.9492	9.2233720	4.19	6.59	16.7
2	Error	0.0	4	0.0				
3	Total	143.8475	7					
Curvature Effect		9.635to1.685						
95% Confident Level of Curvature effect Nonlinear								

Table 19 CCD experiments for two variables

S. No	Combination redesigned	X1	X2	Y2
1	I	9	12.63	98.6+0.62
2	X1	15	12.63	99.5+0.18
3	X2	9	16.32	87.5+0.28
4	X1X2	15	16.32	103.3+0.67
5	Midpoint	12.0	14.475	83.5+0.68
6	X1At-2L	6	14.475	85.9+0.34
7	X1At+2L	18	14.475	99.8+0.53
8	X1At-2L	12	10.785	96.6+0.87
9	X1At+2L	12	18.165	94.2+0.38

Table 20 Absolute values of the Contour Diagram

S.No.	X-axis = Dehydrated Banana Powder	Yaxis = Orange peel powder	Invitro dispersion time	Invitro drug release
1	15	10.785	56	91.6
2	6	12.63	75	84.7
3	12	14.475	40	98.4
4	9	10.785	63	85.3
5	18	16.32	45	97.4
6	18	12.63	35	100.2
7	15	18.165	55	90.1

Table 21 Comparison of the formulation's expected reactions to the experimental findings for propranolol HCl mouth melt tablets

Ingredient	Composition (mg/tab)	Response	Predicted value	Experimental value	Standard error
DBP	18	Y1(DT) (sec)	35	33	1.49%
OP	12.63	Y2(DR) (%)	100.2	99.7	1.10%

Drug release kinetics:

The values of k, n, and R2 (coefficient of determination) have been determined from the mathematical treatment of the mouth melt tablet in-vitro release data, and they are shown in **Table 14**, **Table 15**.

After analyzing in-vitro drug release data, it was discovered that X had the most vital interaction with the SS ratio (54.44%) and a positive coefficient (4.425). It suggested that the medication released more when the level of X1 rose. (**Table 18**)

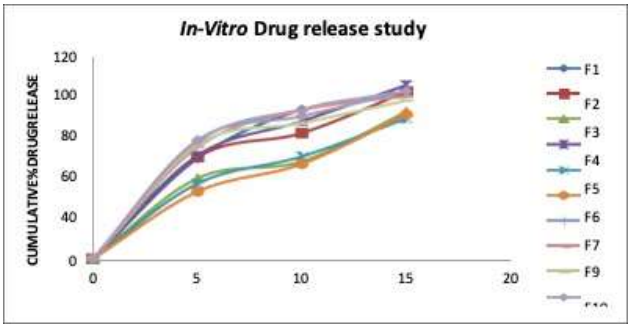

Figure 2 In-vitro drug release of propranolol HCl from formulations (F1-F10)

The significant effect was found using ANOVA, with a coefficient of determination of R2 = 0.9023. The obtained value of F is greater than the crucial F-value, indicating statistical significance at that probability level ($p<0.05$). The obtained F value of 6.59, which is bigger than the essential value of 4.95, suggests significance at that probability level and is thus likely to occur by chance with a p-value of less than 0.05. Since the R2 model was shown to be necessary, predictions have been made using this model. The Central composite design was used because the Sigma Tech program indicates that the relationship between Y2 and X is nonlinear. The observed results are displayed in **Table 19**.

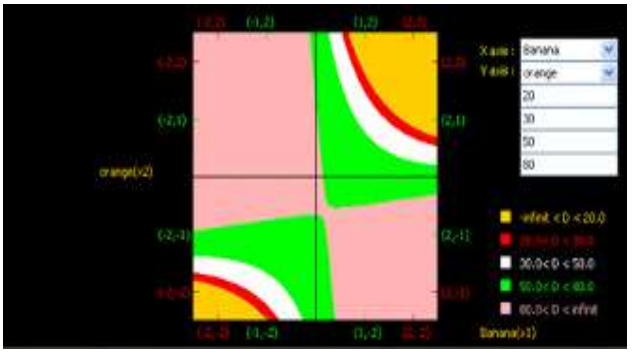

Figure 3 Contour plots for Dicyclomine Hcl tablets (In-vitro dispersion time)

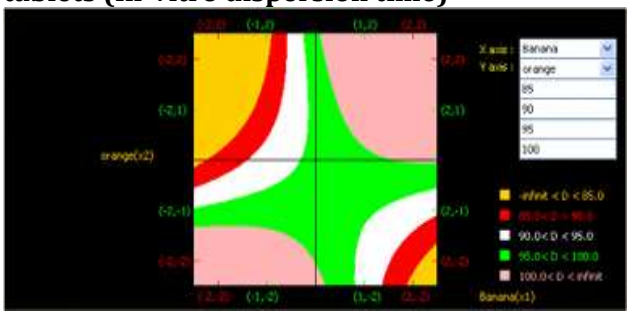

Figure 4 Contour plots for Dicyclomine Hcl tablets (In-vitro drug release)

The following statistical quadratic model was created by entering the data in Sigma Tech at two variable optimization modules.

Final equation with factors coded

Drug release (Y2) = 78.05 +2.85 X_1-2.65 X_2+4.425 X_1X_2+2.775 X^2-4.075X_2^2

The final equation in terms of actual factors

Y2=78.05 +2.85DBP-2.65OPP+4.425DBP OPP+2.775 DBP^2 -4.075OPP^2

Central composite design – Contour plot analysis

Based on a multidimensional combination of DBP and OPP, the study produced a design space that led to the permissible operating ranges for the formulation of mouth melt tablets about the target product profile. Design space, also known as a contour plot, is the area of a successful operating range shaded with white (**Figure 3**) for in vitro dispersion time and green (**Figure 4**) for in-vitro drug release.

Based on the polynomial equations produced by Sigma Tech Software for every response, an intense grid search was conducted across the experimental domain. All of the physicochemical requirements were satisfied by the statistically optimized formulation. To confirm the theoretical prediction, in vitro dispersion time and dissolution investigations were performed on the developed optimized formulation. The relative errors (%) between the experimental and anticipated values were computed for every answer.

CONCLUSION

The formulation of Propranolol Hcl Mouth melt tablets utilizing natural super disintegrants has reduced the disadvantages associated with the traditional dosage forms of the drug. As demonstrated by the model created using a central composite design, the concentration of different superdisintegrants was found to have a significant and interactive impact on the dispersion time and drug release in this investigation. The experiment results demonstrated that the concentration of different super disintegrants may be optimized to create mouth melt tablets with the desired characteristics of high drug release and short

dispersion time. We may conclude that using a central composite design, it would be possible to develop Propranolol Hcl Mouth melt tablets with superior quality attributes and fewer trials.

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