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GREEN SCALABLE APPROACH FOR DEVELOPMENT AND ASSESSMENT OF CUSTOMIZED TABLETS INVOLVING BOX BEHNKEN DESIGN

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ABSTRACT

One billion people worldwide suffer from hypertension, a condition that requires efficient and patient-friendly treatment options. In this work, propranolol hydrochloride, a beta-blocker often used to treat hypertension, is developed as a mucoadhesive bilayer tablet formulation. A mucoadhesive extended-release layer for prolonged medication administration and an immediate release layer for a quick therapeutic impact are both included into the suggested tablet form. A scalable and economical production technique, the direct compression method, was used to prepare both layers. Pre- and post-compressional characteristics were thoroughly evaluated to ensure the tablets fulfilled the necessary quality requirements. Additionally, a response surface approach called the Box-Behnken design was used in the study to improve the formulation. Desired results were shown by the optimized batch, MBT 16, which showed efficient drug release for both immediate and long-lasting effects. Propranolol hydrochloride's pharmacokinetic profile is improved by this innovative dual-layer technique, which may increase patient compliance by lowering dosage frequency while preserving steady blood pressure management all day. The formulation's affordability and safety are further demonstrated by the use of natural excipients. Through creative medication delivery methods that combine therapeutic efficacy with enhanced patient adherence, this study opens the door for more sophisticated hypertension therapy.

KEYWORDS: Customized Tablets, Green approach, Propranolol HCl, Design expert, Box Behnken Design, Chia Seed Mucilage, Aloevera Extract, Potato Starch.

INTRODUCTION

More than one billion people worldwide suffer with hypertension, commonly referred to as high blood pressure, which is a major cause of cardiovascular disease and death. It continues to be the leading cause of mortality globally. In 2019, cardiovascular diseases caused around 17.9 million deaths worldwide. Heart disease-related premature deaths in India increased from 23.02 million in 1990 to 37 million in 2010, a 59% increase in years of life lost. A chronic condition known as hypertension is defined by persistently high blood vessel pressure. Because it typically doesn't show any signs, high blood pressure is known as "the silent killer."[1-3]

Customized tablets are an innovative way to provide drugs with more advantages. The basic idea behind the customized tablet is to increase the bioavailability of the active component by either targeting organ or tissue locations or by using novel drug-delivery techniques that start certain processes. Modified-release tablets, which are distinguished by their drug-release pattern, and organ-specific tablets, which are distinguished by their drug targeting to an organ, are the two types of specialized tablets. One or two distinct kinds of medication are combined in varying degrees of compression to create bilayer pills. The dose type addresses a range of pharmacological and dosage form shortcomings. Often, a bilayer tablet has both an initial and a maintenance.[4-6]
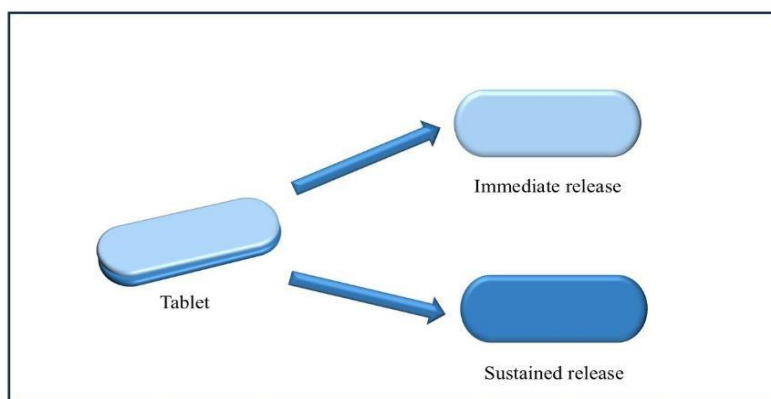
Figure 1: Bilayer tablet.

A nonselective beta-blocker, propranolol hydrochloride (Propranolol HCl) is frequently used to treat a variety of cardiovascular and other disorders. It lowers blood pressure by decreasing the heart's contraction force and tempo. Propranolol is a lipophilic (fat-soluble) medication that can enter the circulation by evading the gastrointestinal tract's lipid bilayer of cell membranes. It is not as well absorbed as other water-soluble drugs, and first-pass metabolism affects its bioavailability. Because of the liver's substantial first-pass digestion, only 25–35% of it is bioavailable. Food consumption, the medication's lipophilicity, and stomach pH all influence absorption. The beta-1 receptors in the heart quicken the pulse in reaction to norepinephrine and epinephrine. Because propranolol blocks these receptors, it has a negative chronotropic impact, lowering heart rate. Large amounts of it are present in the heart, kidneys, lungs, fat tissues, and brain.[7-9]

The purpose of this study was to develop a new drug delivery system for the efficient treatment of hypertension, a chronic heart condition. Propranolol hydrochloride, a beta-blocker frequently used to treat hypertension, is the focus of this study's bilayer tablet formulation and design. The proposed tablet design consisted of two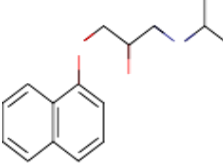 distinct layers: an immediate release layer and a mucoadhesive extended-release layer. Both layers were constructed using the direct compression technique.[10-11]

The Box-Behnken design is a stand-alone quadratic design devoid of fractional or embedded factorial designs. The treatment combinations in this design were located in the center and at the halfway points of the process space's edges. Box Behnken Optimization software is used in the research study, which makes use of natural disintegrant potato starch and natural mucoadhesive polymer chia seed mucilage. Although the agents have their own synergistic impact, using natural components is a biocompatible and environmentally friendly substitute for other synthetic agents of the same category. The study findings to increase the chosen active ingredient's potency and therapeutic effectiveness.[12-14]

MATERIALS AND METHODS MATERIALS
Propranolol Hydrochloride was obtained as a gift sample from Sun Pharma laboratories, HPMC K4M and HMPM K15 were purchased from LOBA Chemie. Other excipients used to prepare the bilayer tablets were of standard quality and all chemical reagents used were of analytical grade.

Table 1: Physical and chemical parameters of Propranolol HCl.

S. No.	Parameter	Predicted value
1.	Molecular formula	$C_{16}H_{21}NO_2$
2.	Molecular structure	
3.	IUPAC name	1-(naphthalen-1-yloxy)-3-[(propan-2 yl)amino]propan-2-ol
4.	Molecular weight	295.85 gm/mol
5.	BCS class	Class I
6.	pH and pKa	5-6 pH and 14.09
7.	Log P	3.03 or 2.58
8.	Crystallinity	white, crystalline solid
9.	Melting point	96°C
10.	Solubility	Highly soluble in water

Extraction of chia seed mucilage
The mucilage of chia seeds was extracted using the methods modified by Silveira Ramos et al. (2021). For almost three hours, the seeds were soaked in distilled water at a ratio of 1:30. The mixture was then constantly swirled for about an hour at a temperature of 70 to 80 °C using a magnetic stirrer. Following extraction, a muslin cloth was used to filter the mixture. Absolute ethanol was used to precipitate the extracted substance. The precipitated mucilage was dried for approximately twenty-four hours at 40°C in a hot air oven.[15-16]
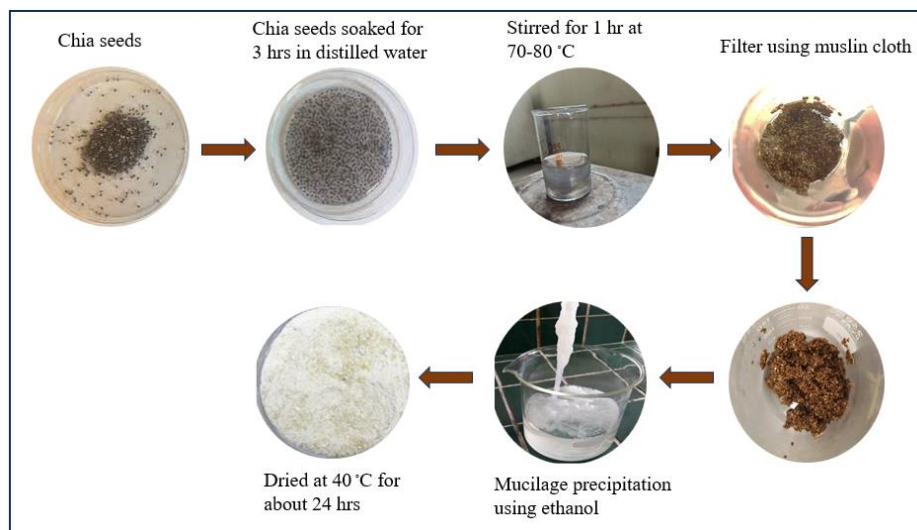

Figure 2: Extraction of chia seed mucilage.

Extraction of potato starch
After choosing a raw potato, it was cleaned, skinned, and then chopped into little pieces. Using distilled water, a slurry was created by crushing or blending. After that, the slurry was left to settle for around twenty-four hours. The starch was separated by decantation, and distilled water was used for washing. Ultimately, the starch was preserved in an airtight container after being dried for 48 hours at 40 °C.[17]
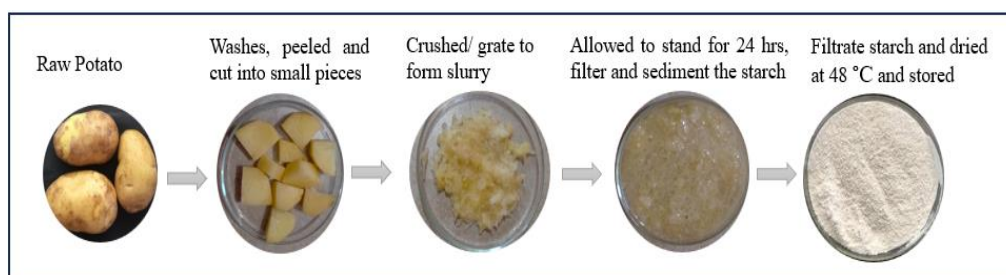
Figure 3: Extraction of potato starch.

Preparation of aloe vera mucilage powder
New leaves Mucilage from the inner leaves of Aloe vera (Aloe barbadensis) was collected and the plant was recognized. After removing extra water, the acetone was used to wash the slake. The final product was then steeped in ethyl acetate to cause precipitation. The resulting substance was spread out to let the ethyl acetate evaporate. After drying for almost four hours, it was finally passed through 250 μm mesh. Keep in an airtight container.[18]

Figure 4: Extraction of Aloe vera mucilage powder.

Table 2: Evaluation parameters of extracted material.

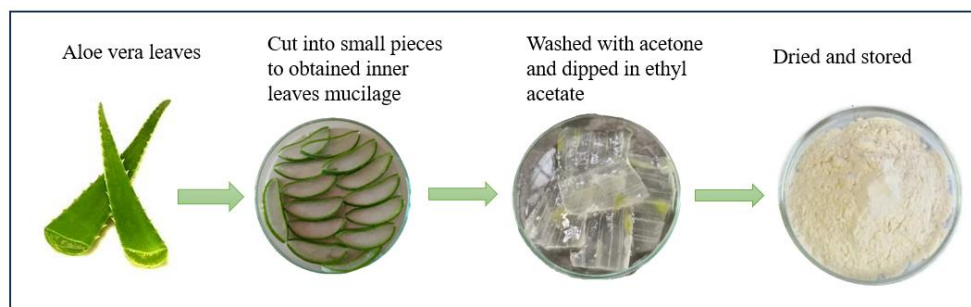| S. No.	Evaluation	Result		
		Chia seed mucilage	**Aloe vera mucilage powder**	**Potato starch**
1.	Colour	Light brown	Light beige	White
2.	Odour	Slightly earthy	Slightly herbaceous	Odourless
3.	Taste	Neutral taste	Slightly bitter	Tasteless
4.	Appearance	Fine and clumpy	Fine powdery	Fine powder
5.	Nature	Hydrophilic	Hydrophilic	Hydrophilic
6.	Melting point	-	38 °C	-
7.	pH	6-7	5-7	6-7
8.	Swelling Index	10ml/g	6.8ml/g	7.5 ml/g

Box-Behnken design (BBD)

The three levels of a factor 1 being the higher level, 0 being the intermediate level, and -1 being the lower level should be investigated in the box-Behnken design response surface technique. Three independent and three dependent variables were arranged in a polynomial model using BBD and design expert software. According to the table, the three independent variables X1, X2, and X3 are the intensity of the disintegrant (potato starch), the impact of the mucoadhesive polymer (chia seed mucilage), and the influence of the sustain release polymer.

Table 3: The table showing the independent variable and the levels that are selected.

S. No.	Independent variable	levels	
		-1(lower level)	+1(higher level)
1	Concentration of disintegrant (potato starch)	12	20
2	effect of mucoadhesive polymer (chia seed mucilage)	18	25
3	effect of sustain release polymer	16	20

The following table shows how the three independent factors disintegration time, mucoadhesive strength, and in-vitro drug release affect the three dependent variables (Y1, Y2, and Y3).

The design expert program recommends 15 formulation batches, as indicated in table no. 5, based on the chosen independent variables and their responses. We may formulate the tablets utilizing the recommended data from the software by employing an appropriate compression technique.

Table 4: Selected Dependent variables.

S. No.	Dependent variables	units
1	Disintegration time	Seconds
2	Mucoadhesive strength	Grams
3	In-vitro drug release	mg/ml

Table 5: Formulation Runs as per Box Behnken design.

Runs	Concentration of Disintegrant (potato starch)	Effect of mucoadhesive polymer (chia seed mucilage)	Effect of sustained release polymer
1	20	21.5	16
2	16	21.5	18
3	16	25	16
4	12	18	18
5	16	21.5	18
6	12	25	18
7	20	21.5	20
8	16	18	16
9	12	21.5	16
10	20	25	18
11	12	21.5	20
12	16	25	20
13	16	21.5	18
14	20	18	18
15	16	18	20

Preparation of Tablets

The Mucoadhesive bilayer tablets were prepared by using direct compression technique in which the powder blend after lubrication directly compressed using desired compression force and Diameter of die. To prepare a mucoadhesive bilayer tablet, the extended mucoadhesive layer was compressed followed by the compression of burst release layer using Karanavati Tablet punching machine.

Formulation of immediate release layer

The instant release layer's formulation composition is detailed in Table No. 6. To improve the biocompatibility and biodegradability, potato starch is utilized as a natural super dissolving agent. To provide the appropriate dose unit, lactose is added as a filler. Using a glass mortar and pestle, all the materials were precisely weighed and carefully combined. They were then greased with magnesium stearate and stirred for ten more minutes. An 11 mm die was used to compress the powder mixture.

Table 6: Formulation Batches for immediate release layer.

Formulation	Propranolol Hcl (mg)	Potato starch (mg)	Lactose (mg)	Magnesium Stearate (mg)
MBT 1	30	20	145	5
MBT 2	30	16	149	5
MBT 3	30	16	149	5
MBT 4	30	12	153	5
MBT 5	30	16	149	5
MBT 6	30	12	153	5
MBT 7	30	20	145	5
MBT 8	30	16	149	5
MBT 9	30	12	153	5
MBT 10	30	20	145	5
MBT 11	30	12	153	5
MBT 12	30	16	149	5
MBT 13	30	16	149	5
MBT 14	30	20	145	5
MBT 15	30	16	149	5

Formulation of Mucoadhesive layer

The formulation composition of mucoadhesive extended-release layer described in the table no. 7 Chia seed mucilage is used as a mucoadhesive polymer and aloevera mucilage is used as a binding agent. While the HPMC K4 M and HPMC K15 is used as a Matrix former to sustain the drug release. Microcrystalline cellulose is used as diluent. All the ingredients were properly mixed thoroughly and lubricated with Talc. Mucoadhesive layer was compressed in 11 mm die followed by compression of immediate release layer.[19-23]

Table 7: Formulation batches for mucoadhesive layer.

Formulation	Propranolol Hcl (mg)	Chia seed mucilage (mg)	HPMC K4M (mg)	HPMC K15 (mg)	MCC (mg)	Aloe-vera (mg)	Talc (mg)
MBT 1	50	21.5	16	10	137.5	10	5
MBT 2	50	21.5	18	10	135.5	10	5
MBT 3	50	25	16	10	134	10	5
MBT 4	50	18	18	10	139	10	5
MBT 5	50	21.5	18	10	135.5	10	5
MBT 6	50	25	18	10	132	10	5
MBT 7	50	21.5	20	10	133.5	10	5
MBT 8	50	18	16	10	141	10	5
MBT 9	50	21.5	16	10	137.5	10	5
MBT 10	50	25	18	10	132	10	5
MBT 11	50	21.5	20	10	133.5	10	5
MBT 12	50	25	20	10	130	10	5
MBT 13	50	21.5	18	10	135.5	10	5
MBT 14	50	18	18	10	139	10	5
MBT 15	50	18	20	10	137	10	5

Pre-compressional Parameter

Pre compressional parameters involve the bulk characterization, powder flow property, solubility, melting point etc.[24-26]

Angle of repose
It is the angle at which the granular pile can rest on the horizontal surface without fall. The technique measures the resistance between the material particles and critical parameter to measure the flowability and granular packing. Pile forming method was used to identify angle of repose in which a funnel was positioned to hold and release the material slowly onto a smooth flat surface. The height and radius of pile formed by material was notes and the θ was measured using the given equation.

Formula: - $Tan\theta = \frac{h}{r}$

Table 8: Angle of repose.

S. No.	Flow Property	Angle of Repose
1.	Excellent	25-30
2.	Good	31-35
3.	Fair	36-40
4.	Passable	41-45
5.	Poor	46-55
6.	Very poor	56-65
7.	Very, very poor	>66

Bulk Density
Bulk density is an important physical parameter of powder flow property. It is the density of powder in its natural state and can be calculated by the mass to volume ratio expressed in gm/ml or gm/cm^3. It was measured using cylindrical container method in which measuring cylinder was poured with pre-weighed powder material and the volume was directly observed, finally the bulk density was calculated using the formula.
Formula: - Bulk density = Mass of substance / Volume of substance

Tapped density
It is the density of powder after the particular number of mechanically tapping the powder material and calculated by dividing the mass of powder mass by its final volume after tapping. It helps to measure the powder compressibility and flowability expressed in gm/cm^3.
Formula: - Tapped density = Mass of substance / Final volume after tapping

Compressibility Index
Carr's index measures the powder compressibility which defines the tablet strength and stability. If it is less than 15 indicates the good flowability and if it is more than 25 indicates the poor flowability.
Formula: - Carr's Index = Tapped Density – Bulk Density / Tapped Density $\times$ 100

Table 9: Flow properties as per Carr's Index.

S. No.	Carr's Index	Flowability
1.	5-15	Excellent
2.	12-16	Good
3.	18-21	Fair possible
4.	23-35	Poor
5.	33-38	Very poor
6.	>40	Very, very poor

Hausner's Ratio
It is a critical parameter of powder flow property and measures the flowability or granular material. Low Hausner's ratio indicates the less interaction between the granular particles and material is more easily flowable.
Formula: - Hausner's ratio = Tapped density / Bulk density

Table 10: Flow properties as per Hausner's Ratio.

S. No.	Hausner' ratio	Flowability
1.	1.05 - 1.18	Excellent
2.	1.14 - 1.20	Good
3.	1.22 - 1.26	Fair possible
4.	1.30 – 1.54	Poor
5.	1.50 – 1.61	Very poor
6.	>1.67	Very, very poor

Particle size analysis
Particle size determination of powders is a critical parameter which directly affect the quality, flowability, stability and performance of the substances. Smaller particle size shows higher surface area and have greater absorbance. Sieve method was used to define the particle size of the mixture.

Table 11: Methods for determining particle size of solids.

S. No.	Techniques	Particle size (mm)
1.	Microscopic	1-100
2.	Sieve	>5
3.	Sedimentation	>1
4.	Elutriation	1-50
5.	Centrifugal	<50
6.	Permeability	>1
7.	Light Scattering	0.5-50

Solubility Studies
The amount of material that dissolves in a solution to form a saturated solution at a certain temperature and pressure is known as solubility. The greatest volume or mass of the solute that dissolves in a certain volume or mass of a solvent is how solubility is stated. The shake-flask method was used to determine the solubility: -
➢ The method involves addition of compound to a medium and shaking it to achieve saturation after giving particular temperature.
➢ After formation of supersaturated solution, filtration was done followed by slow cooling and shaking.
➢ Sample was then analysed (diluted if needed) to determine the solute content using appropriate method.

Table 12: Characterization of solubility.

Descriptive Term	Parts of Solvent Required for 1 part of Solute	g/L in water	M=400 mol/L in water	M=40000 mol/L in water
Very soluble	≤1	≥1000	≥2,5	≥0,025
Freely soluble	1 to 10	1000 to 100	2,5 to 0,25	0,025 to 0,0025
Soluble	10 to 30	100 to 33	0,25 to 0,08	0,0025 to 0,0008
Sparingly soluble	30 to 100	33 to 10	0,08 to 0,025	0,0008 to 0,00025
Slightly soluble	100 to 1000	10 to 1	0,025 to 0,0025	0,00025 to 0,0000025
Very slightly soluble	1000 to 10,000	1 to 0,1	0,0025 to 0,00025	0,000025 to 0,0000025
Practically insoluble, or Insoluble	≥10,000	≤0,1	≤0,00025	≤0,0000025

Melting point Determination
It is the temperature at which the substance starts to melt or changes its state from solid to liquid. It was determined by using electrically heated melting point apparatus.

Loss on drying
LOD is the resultant weight of the compound expressed in percentage (w/w) to determine the moisture content in the sample compound. Following steps were used to determine the LOD: -
➢ Sample was accurately weighed
➢ Sample was heated till it gets completely dry
➢ Dried sample was again weighed and difference was calculated.

$$\% \text{ of Loss on drying} = \frac{\text{weight loss}}{\text{weight of sample}} \times 100$$

Standard Calibration Curve
A calibration curve is used to compute the limit of detection, the limit of quantitation, and the concentration of an unknown material. Using a series of standard samples at various concentrations, the instrumental response is used to build the curve. Unknown concentrations can then be predicted by fitting the data with a function.
➢ Stock solution of known (1000 µg/ml) concentration was prepared by dissolving 100mg into 100ml of 0.1 N hydrochloric acid.
➢ Second stock solution (100 µg/ml) prepared by pipetting 10 ml of above solution and diluted up to 100ml with the same solvent.
➢ Dilutions of different strength was prepared and analysed using UV spectrophotometer.

Post Compressional Parameters
Organoleptic Characters
The organoleptic parameters were studied by visually evaluating tablets properties like colour and odour.

Thickness
To assess the tablet's homogeneity in size and shape, its thickness was examined.
Methods: A Vernier calliper was used to measure the tablet's thickness.

Hardness
A Monsanto hardness tester was used to measure the tablets' hardness. On the testing platform, each tablet was positioned separately, and pressure was applied until the tablets broke. The hardness value was determined by measuring the force needed to break each tablet. This technique made it possible to assess the tablets' resistance to mechanical stress precisely.

Friability
The Roche Friabilator was used to assess the produced formulations' friability. After a pre-weighed sample of tablets was put in the friability testing and rotated for 100 revolutions, the tablets were cleaned and weighed again. The following formula was used to determine the tablets' friability:

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight Variation
Twenty tablets were weighed separately, the average weight was determined, and the weight of each tablet was compared to the average weight to perform the weight variation test.

Table 13: Uniformity of Weight and Percentage Deviation.

S. No.	USP	Max % difference allowed	IP / BP
1.	130mg > or less	±10%	80mg > or less
2.	130mg > 324 mg	±7.5%	80mg-250mg
3.	324 mg < or more	±5%	250mg < or more

Content uniformity test
A content/potency assay was used in content uniformity testing to ascertain the amount of active substance present in several samples taken during the batch. The UV was used to measure the amount of drug and the consistency of the material. Ten tablets were selected

randomly and assay was performed to check individual content of active ingredient in each tablet. The potency of nine out of ten pills must be within 1% to 15% of the drug's stated content. There can only be one tablet within a quarter.

Swelling index study

The swelling index of a tablet measures how much its volume increases over a specific amount of time as a result of absorbing a liquid, often a dissolving medium. The swelling state of the polymer is a key factor affecting the tablet's bio adhesion. Until the glue hits a threshold where too much hydration causes the adhesive quality to suddenly drop owing to unwinding at the polymer/tissue interface, the degree of hydration will strengthen the binding.

Mucoadhesive strength and time

The force that holds a mucoadhesive substance like a gel or polymer to the mucosal surface like the mucosa of the mouth, nose, or stomach is known as mucoadhesive strength. The mucoadhesive strength was determined by using ex vivo test. Goat intestine was cut cut to obtain a small piece and pasted on a petri dish using adhesive. The intestine membrane was moistened with 2-3 drops of 0.01 N HCl and the tablet was tied with a thread with physical balance on one side. The total weight required to detach the tablet from the intestine membrane was noted as mucoadhesive strength.

Disintegration test of tablets

The disintegration test shows how quickly and effectively a tablet disintegrates into smaller pieces in a liquid. The disintegration test is performed to confirm that the body is absorbing the medicine as intended. the process for figuring out how long pills take to dissolve. Initially, the disintegration apparatus was filled with distilled water and kept at 37°C± 2°C. The six tablets from each formulation are then chosen at random and put one at a time in each of the six cylinders of a disintegration test device. After that, the device was activated, which caused the basket to move up and down. The time it takes for each pill to completely dissolve is then recorded. The average amount of time it took for the pills to dissolve.

In vitro dissolution test

The medication release profile is ascertained using the in-vitro dissolution test. This is how the mucoadhesive bilayer tablets are tested for in-vitro dissolution. The USP type II paddle-type equipment was used to conduct the in-vitro dissolving test for the bilayer tablets. The paddle's speed was set at 50 rpm, and the water bath's temperature was kept at 37°C +/- 0.5°C. The tank that serves as a dissolving media was filled with 900 millilitres of 0.1 N HCL. A tablet chosen at random is put in the dissolving test apparatus's vessel. The sink state was maintained while a 10-milliliter sample was taken out of the vessel at various prearranged intervals. After the samples were filtered, they were analysed at

λmax 290nm using a UV-visible spectrophotometer. The absorbance was recorded, and the percentage of drug release and cumulative drug release was computed.

Stability studies

Stability studies are a crucial assessment metric that aids in figuring out a product's shelf life or how external factors may impact the final product's quality over time. ICH quick study criteria were used to examine the stability of all salbutamol sulphate tablet formulations for a period of one month. Each sample was securely wrapped in aluminium foil and placed in airtight glass containers. These tablets were exposed to three different temperature settings. Tablets were removed from storage at 10-, 20-, and 30-day intervals for examination, with a focus on physical attributes, drug concentration, and segregation patterns.[27-30]

RESULT AND DISCUSSION

Organoleptic properties of Propranolol HCl

Table 14: Organoleptic properties of Propranolol HCl.

S. No.	Organoleptic Characteristics	Result
1.	Colour	White
2.	Odour	Odourless
3.	Taste	Slightly bitter
4.	Nature	Lipophilic
5.	Crystallinity	Crystalline solid

Melting points

While studied done on the Propranolol hcl, the melting point was determined using melting point apparatus was found to be 148.2°C.

Calibration curve

Table 15: Calibration curve of Propranolol hcl in 0.1 N HCL at λmax 290nm.

S. No.	Concentration (µg/ml)	Absorbance (λmax 290 nm)
1.	0	0
2.	2	0.218
3.	4	0.339
4.	6	0.472
5.	8	0.591
6.	10	0.711

Calibration curve of Propranolol HCl in 0.1 N HCl at λmax 290nm

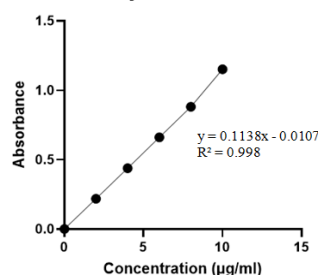$y = 0.1138x - 0.0107$
$R^2 = 0.998$

Figure 5: Calibration curve of Propranolol HCL in 0.1 N HCL.

Pre-compressional evaluation

The prepared powder blend for mucoadhesive bilayer tablets were characterized for Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio for both immediate and mucoadhesive layer which are shown in table. Angle of repose of all batches was within 30°-36°, Carr's index of all batches was within 7.40-13.20 and Hausner's ratio of all batches was found within 1.08-1.15 which indicate good flow property of granules.

Table 16: Pre-compressional data of the formulation batches of powder blend.

Formulation batch	Angle of Repose(θ)	Bulk Density (gm/ cm3)	Tapped Density (gm/ cm3)	Hausner's Ratio (HR)	Carr's Index (CI)
MBT 1	34.56	0.49	0.56	1.14	12.5
MBT 2	33.19	0.50	0.54	1.08	7.40
MBT 3	31.62	0.48	0.53	1.10	9.43
MBT 4	34.17	0.49	0.56	1.14	12.5
MBT 5	32.87	0.46	0.53	1.15	12.5
MBT 6	33.51	0.46	0.53	1.15	13.20
MBT 7	31.38	0.51	0.57	1.11	10.52
MBT 8	36.43	0.47	0.54	1.14	12.9
MBT 9	36.15	0.46	0.53	1.15	13.20
MBT 10	30.71	0.51	0.57	1.11	10.52
MBT 11	34.56	0.49	0.54	1.10	9.25
MBT 12	30.96	0.47	0.53	1.12	11.32
MBT 13	35.81	0.50	0.57	1.14	12.28
MBT 14	32.87	0.46	0.52	1.13	11.53
MBT 15	30.10	0.51	0.56	1.09	8.92

Post-compressional evaluation
Shape and size
On the evaluation of the Propranolol hcl formulated bilayer tablets have the circular in shape and the size of the tablets was found to be 0.65 ± 0.05 cm.

Table 17: Post-compressional data of the formulation batches.

Formulation batch	Weight Variation (mg)	Thickness (mm)	Hardness (kg/ cm^2)	Swelling Index (ml/g)	Mucoadhesive Strength (gm)	Disintegration time (sec)	Friability (%)
MBT 1	451.1	4.50	6.21	8.9	29	14.7	0.13
MBT 2	447.6	4.51	5.78	8.3	31	12.9	0.17
MBT 3	460.4	4.54	5.23	9.1	24	12.7	0.19
MBT 4	445.9	4.11	5.21	7.8	27	17	0.11
MBT 5	454.3	4.21	5.10	9.1	33	12.2	0.14
MBT 6	443.8	4.24	6.55	8.8	29	19.6	0.19
MBT 7	447.7	4.55	5.32	8.6	24	15	0.12
MBT 8	446.3	4.53	4.85	8.9	30	12.9	0.12
MBT 9	461.1	4.10	6.11	8.7	26	17.2	0.11
MBT 10	454.7	4.41	5.61	9.2	24	19	0.14
MBT 11	447.5	4.48	5.91	8.3	23	15.6	0.15
MBT 12	462.9	4.46	6.12	8.5	28	13.7	0.13
MBT 13	447.4	4.32	4.55	9.1	35	13.2	0.12
MBT 14	460.7	4.27	4.91	9.1	27	14	0.11
MBT 15	447.9	4.27	5.74	8.6	30.5	12.6	0.21

All the prepared tablet batches (MBT 1 – MBT 15) were evaluated for post compression parameters and results obtained in the range are sufficient for mucoadhesive bilayer tablets shown in the table no. 17. Hardness ranged between 4.5-6.5kg/cm^2, thickness of all tablet batches results from 4.27-4.55mm, friability was found to be in range of 0.11-0.19% which is less than 1% showed good mechanical strength, weight variation test results in between 445.9-462.9mg, swelling index found in 8.3-9.1 ml/gm, mucoadhesive strength results from 14-18.2gm, mucoadhesive time, disintegration time for immediate release layer ranged between 12.2-19.6 seconds. The content uniformity test results ranged between 1.9-2.5% for all the prepared batches.

In-vitro dissolution studies
The amount drug release was analysed at a pre-determined time intervals using a USP type II dissolution

test apparatus. The obtained results for cumulative   amount of drug release are shown in the table no. 18.

Table 18: In vitro dissolution test data of the Propranolol hcl Mucoadhesive bilayer tablets.

| Formulation batch	5 min	10 min	20 min	30 min	40 min	60 min	120 min	180 min	240 min	480 min	720 min
MBT 1	4.458	9.364	18.273	25.582	34.546	41.164	46.564	51.220	56.342	73.348	91.924
MBT 2	5.478	8.345	17.992	25.188	37.984	40.376	45.498	50.047	55.057	71.574	96.756
MBT 3	4.795	8.487	17.774	24.886	35.488	43.761	49.318	54.249	58.674	76.276	89.245
MBT 4	5.134	6.697	16.581	23.213	37.162	44.826	48.697	53.863	59.761	77.689	96.524
MBT 5	3.420	7.985	18.068	25.295	37.702	40.588	45.651	51.216	57.754	75.802	96.752
MBT 6	5.324	8.681	18.193	25.472	36.664	41.944	47.841	52.625	57.932	76.215	95.156
MBT 7	4.951	9.645	19.437	27.211	38.874	44.488	49.366	54.302	60.871	79.135	91.102
MBT 8	6.358	8.125	16.345	22.953	32.687	45.906	50.921	56.013	61.897	80.465	90.561
MBT 9	5.753	9.126	17.679	26.756	37.314	43.512	48.357	53.192	59.754	77.684	89.442
MBT 10	5.951	8.644	19.549	27.268	39.786	43.525	49.987	54.985	60.175	78.442	97.779
MBT 11	4.158	9.146	16.993	24.792	35.907	44.284	48.684	53.549	59.121	76.781	94.304
MBT 12	6.147	8.464	18.715	26.201	37.431	42.435	49.952	55.942	61.248	80.121	94.353
MBT 13	3.963	6.846	17.395	24.353	34.617	40.705	43.68	51.048	57.874	75.156	95.979
MBT 4	4.846	9.866	19.372	27.128	38.546	42.256	46.314	50.944	55.357	71.653	92.104
MBT 15	4.782	7.891	16.227	22.717	37.524	45.435	50.462	54.508	59.849	77.837	92.856
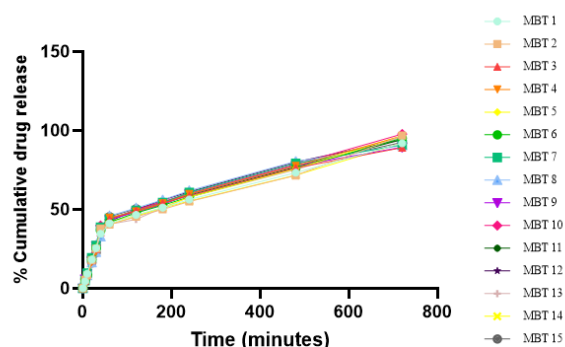
Figure 6: Percent drug release for all the batches MBT 1-MBT 15.

Preparation of Propranolol hcl Mucoadhesive bilayer tablets with responses

Table 19: The BBD composition of Propranolol hcl Mucoadhesive bilayer tablets formulations and their measured responses.

Formulation batch	Independent Variables			Dependent Variables		
	Concentration of disintegrant	Effect of mucoadhesive polymer	Effect of sustain release polymer	Disintegration time (Seconds)	Mucoadhesive strength (grams)	In-vitro dissolution time (%)
MBT 1	20	21.5	16	14.7	18.2	91.924
MBT 2	16	21.5	18	12.9	17.9	96.756
MBT 3	16	25	16	12.7	14	89.245
MBT 4	12	18	18	17	12.7	96.524
MBT 5	16	21.5	18	12.2	18.3	96.752
MBT 6	12	25	18	19.6	15.1	95.156
MBT 7	20	21.5	20	15	18.2	91.102
MBT 8	16	18	16	12.9	11.9	90.561
MBT 9	12	21.5	16	17.2	18.6	89.442
MBT 10	20	25	18	19	11.9	97.792
MBT 11	12	21.5	20	15.6	16.6	94.304
MBT 12	16	25	20	13.7	14.1	94.353
MBT 13	16	21.5	18	13.2	17.4	95.979
MBT 14	20	18	18	14	12.9	92.104
MBT 15	16	18	20	12.6	16.3	92.856

Response 1: Disintegration time for immediate release layer
3D and 2D contour plot images show that an increase in the concentration of Disintegrant leads to decrease disintegration time but only at optimum value. Increase in the mucoadhesive polymer also increases the disintegration time for the tablet which is a significant factor but ideally it should not have any kind of interaction. It could be because of any noise. Sustain release polymer doesn't have any significant effect on the disintegration time.
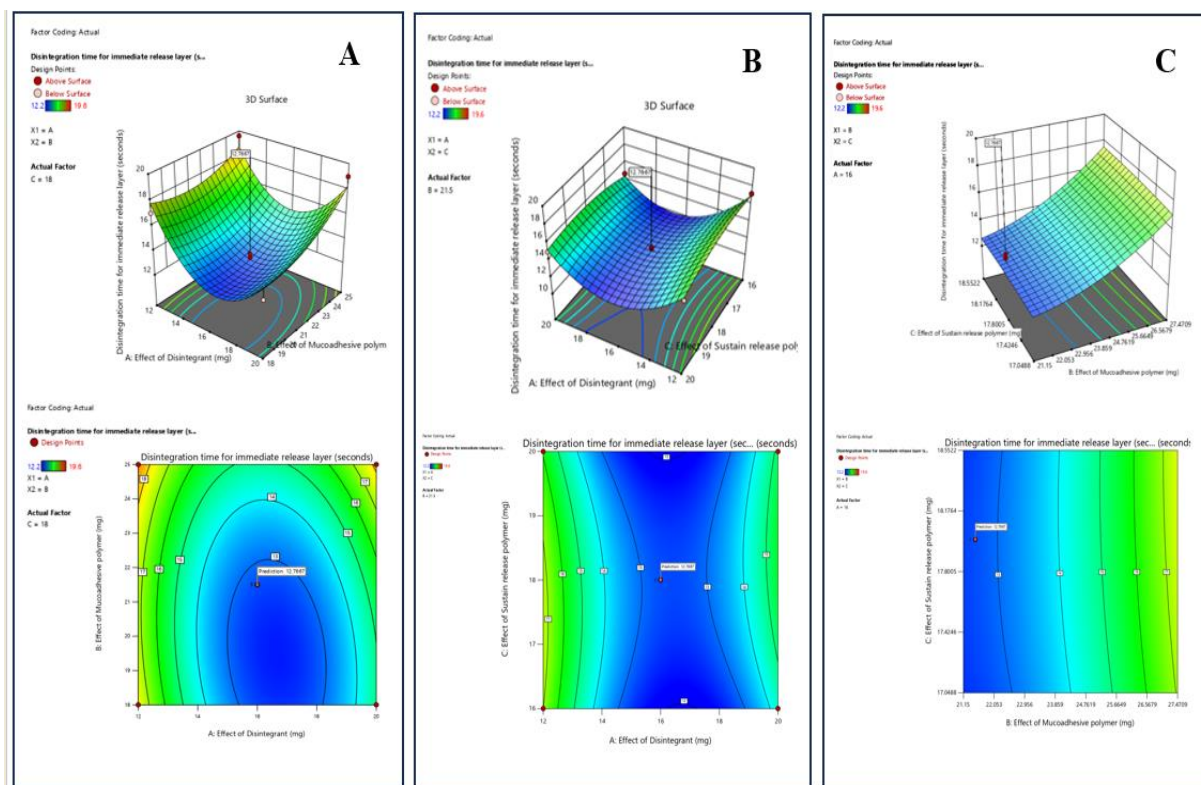

Figure 7: The 2D contour plot and 3D surface graph show that how disintegration time for immediate release layer is affected by factors X_1 (effect of disintegrant), X_2, (effect of mucoadhesive polymer), X_3 (effect of sustained release polymer).

ANOVA for Quadratic model Response 1: Disintegration time for immediate release layer
The obtained model for ANOVA is significant and lack of fit is non-significant which represent good model alignment. The ANOVA for Disintegration time is shown in the table no. There is only a 3.05% chance that an F-value this large could occur due to noise. In this case B, A² are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

Table 20: ANOVA for Disintegration time for immediate release layer (Response 1).

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	72.93	9	8.10	6.08	0.0305	significant
A-Effect of Disintegrant	5.61	1	5.61	4.21	0.0955	
B-Effect of Mucoadhesive polymer	9.03	1	9.03	6.77	0.0481	
C-Effect of Sustain release polymer	0.0450	1	0.0450	0.0337	0.8615	
AB	1.44	1	1.44	1.08	0.3464	
AC	0.9025	1	0.9025	0.6766	0.4482	
BC	0.4225	1	0.4225	0.3168	0.5979	
A²	48.97	1	48.97	36.71	0.0018	
B²	3.63	1	3.63	2.72	0.1599	
C²	2.27	1	2.27	1.70	0.2493	
Residual	6.67	5	1.33			
Lack of Fit	6.14	3	2.05	7.78	0.1161	not

						significant
Pure Error	0.5267	2	0.2633			
Cor Total	79.60	14				

Response 2: Mucoadhesive strength

The 3D and 2D Surface plot studies shows how the mucoadhesive polymer, disintegrant and sustain release polymer affect the mucoadhesive strength of tablet.

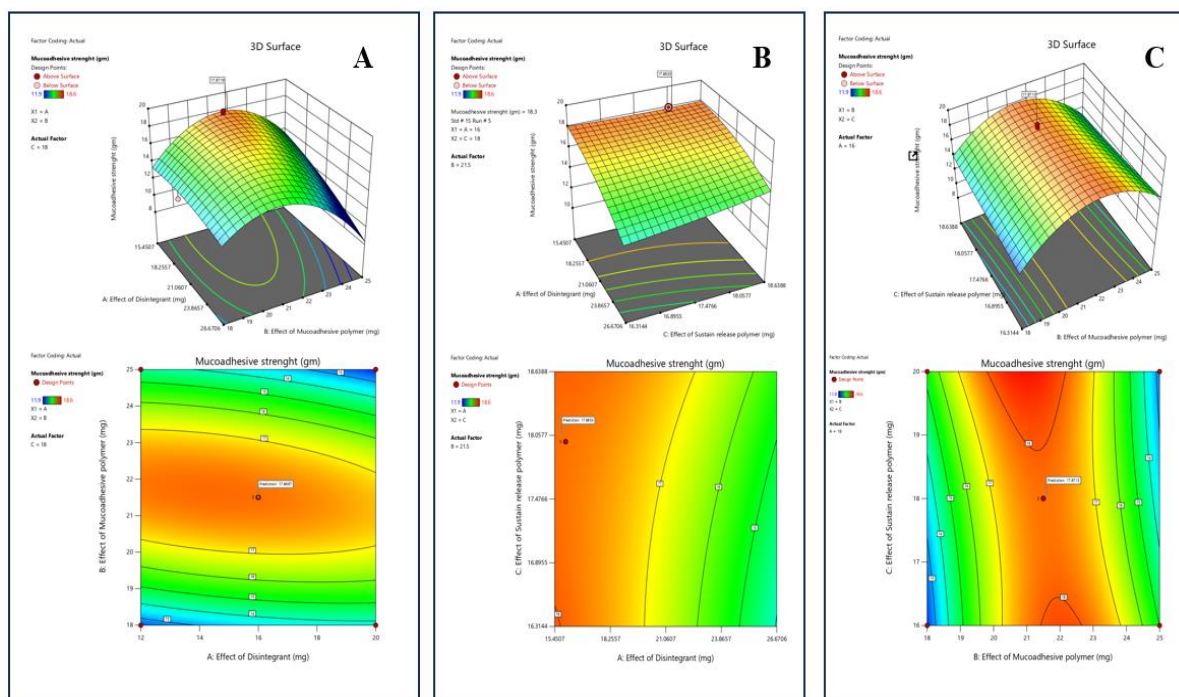Higher mucoadhesive polymer represent higher strength, while disintegrant has minimum effect. Red and orange colour shows higher mucoadhesive strength.

Figure 8: The 2D contour plot and 3D surface graph shows that how Mucoadhesive strength is affected by factors X_1, X_2, X_3.

ANOVA for Quadratic model Response 2: Mucoadhesive strength

The model appears significant with F-value 6.56 and there is only 2.60% chance that F value this large occur due to noise. In this case B² is a significant model term.

Means increasing the mucoadhesive polymer leads to increase in mucoadhesive strength while the increasing the mucoadhesive polymer leads to increase in disintegration time. Sustain release polymer have negligible effect on mucoadhesive strength.

Table 21: ANOVA for Mucoadhesive strength (Response 2).

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	84.74	9	9.42	6.56	0.0260	significant
A-Effect of Disintegrant	0.4050	1	0.4050	0.2823	0.6180	
B-Effect of Mucoadhesive polymer	0.0113	1	0.0113	0.0078	0.9329	
sC-Effect of Sustain release polymer	0.2813	1	0.2813	0.1960	0.6765	
AB	2.89	1	2.89	2.01	0.2151	
AC	1.0000	1	1.0000	0.6969	0.4419	
BC	7.02	1	7.02	4.89	0.0779	
A²	0.3801	1	0.3801	0.2649	0.6287	
B²	71.35	1	71.35	49.73	0.0009	
C²	0.4631	1	0.4631	0.3228	0.5945	
Residual	7.17	5	1.43			
Lack of Fit	6.77	3	2.26	11.09	0.0838	not significant
Pure Error	0.4067	2	0.2033			
Cor Total	91.92	14				

Response 3: In vitro drug release

The sustain release polymer greatly affect the in vitro

drug release rate, higher sustained release polymer promote slow release of drug from dosage unit but

decreases the in vitro drug release for desired period while the mucoadhesive polymer also affect the drug release but at the optimum. Orange region indicates the balanced level of both sustained release polymer as well as mucoadhesive polymer. Sustained release polymer help to improve strength and extend the release but can negatively impact disintegration of tablet.
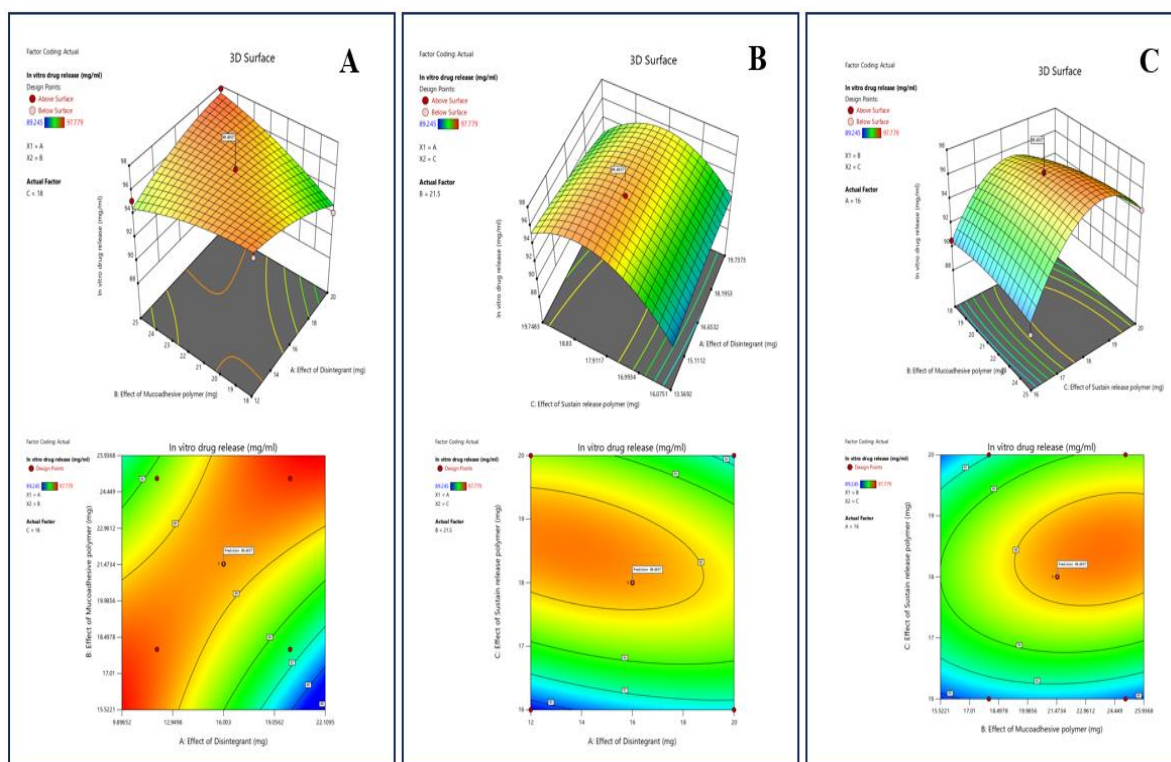

Figure 9: The 2D contour plot and 3D surface graph shows that how In vitro drug release is affected by factors X_1, X_2, X_3.

ANOVA for Quadratic model Response 3: In vitro drug release

P-values less than 0.0500 indicate model terms are significant. In this case C, AB, AC, C^2 are significant model terms. There is non-significant lack of fit which represent model is aligned. And is there is only a 0.43% chance that an F-value this large could occur due to noise.

Table 22: ANOVA for in vitro drug release (Response 3).

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	108.25	9	12.03	14.71	0.0043	significant
A-Effect of Disintegrant	0.7919	1	0.7919	0.9688	0.3702	
B-Effect of Mucoadhesive polymer	2.52	1	2.52	3.08	0.1396	
C-Effect of Sustain release polymer	16.37	1	16.37	20.02	0.0066	
AB	12.40	1	12.40	15.17	0.0115	
AC	8.08	1	8.08	9.88	0.0256	
BC	1.98	1	1.98	2.42	0.1805	
A²	1.25	1	1.25	1.53	0.2704	
B²	1.01	1	1.01	1.23	0.3177	
C²	65.75	1	65.75	80.43	0.0003	
Residual	4.09	5	0.8174			
Lack of Fit	3.69	3	1.23	6.14	0.1433	not significant
Pure Error	0.4004	2	0.2002			
Cor Total	112.34	14				

As we studied the box behnken design we put the responses that we analysed from the evaluation studies as shown in the table no. 19. then the box behnken design optimized the responses and give the optimized batch of formulation and the optimized batch responses and the formulation are shown in table.

Table 23: Formulation of optimized batch from BBD (MBT 16).

S. No.	Ingredient	Quantities (in mg)
Immediate release layer (200mg)		
1.	Propranolol HCl	30
2.	Potato starch	12.35
3.	Lactose	152.65
4.	Magnesium stearate	5
Mucoadhesive extended-release layer (250mg)		
1.	Propranolol HCl	50
2.	Chia seed	21.03
3.	HPMC K4 M	16.34
4.	HPMC K15	10
5.	Aloe vera	10
6.	Microcrystalline cellulose	137.63
7.	Talc	5

Table 24: Pre compressional data of optimized batch (MBT 16).

S. No.	Pre-compressional evaluation parameter	Results
1	Bulk density	0.45
2	Tapped density	0.49
3	Hausner's ratio	1.08
4	Carss index	8.163
5	Angle of repose	32

Table 25: Post compressional data of optimized batch (MBT 16).

S. No.	Post-compression evaluation parameter	Results
1	Weight variation	445.9
2	Thickness	4.32 mm
3	Hardness	3.357 kg/cm^2
4	Swelling Index	8.4 ml/gm
5	Mucoadhesive strength	18.2 gm
6	Disintegration time	15.8 seconds
7	Friability	0.11 %
8	% Drug release	95.981 %

Table 26: In vitro drug release for optimized batch (MBT 16).

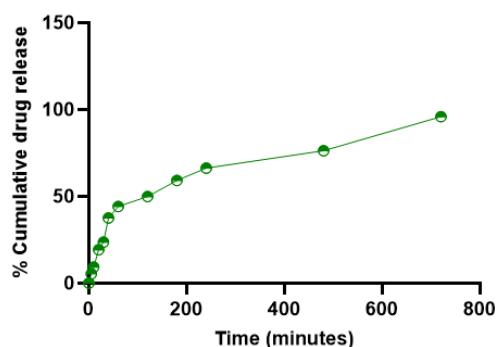| Formulation batch	5 min	10 min	20 min	30 min	40 min	60 min	120 min	180 min	240 min	480 min	720 min
MBT 1	5.458	9.304	19.273	23.672	37.586	44.194	49.964	59.220	66.342	76.348	95.981

Figure 10: Percent drug release of batch MBT 16 (optimised batch).

The obtained Percent drug release of batch MBT 16 (optimised batch) has 95.981 % of drug release in12 hrs (720 minutes), and the optimized batch was evaluated for all the pre and post compressional parameters required for quality control of dosage form and the obtained results was found between satisfied range.

CONCLUSION
The studies that are being presented show that propranolol hydrochloride tablets may be made into mucoadhesive bilayer tablets, which are desirable for the treatment of hypertension. Every before and post compressional parameter was assessed for the tablets. The produced tablets satisfy every fundamental need and criterion for a high-quality dosage form. More research can be done on specialized tablets to improve patient compliance and scale-up procedures. The study also decides whether to use natural components for safe and affordable research. In order to improve illness

treatment, the study investigates the necessity of a drug's quick release into the systemic circulation combined with a supportive maintenance dosage given over a longer period of time. The goal of the study was to determine the optimal batch utilizing Box Behnken design and the appropriate response surface methods. Three independent criteria were chosen for each respondent's response. The optimized batch MBT 16 that was produced the intended result.

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