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Development And Characterization Of Sustained Release Tablets Using Tamarind Seed Gum

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Abstract
A sustained-release tablet of Aprepitant was made using TG which was utilized as a binder. Box Behkhen design (BBD) was used for optimization. Three independent variables as Microcrystalline cellulose (X1), Tamarind gum extract (X2), and Dicalcium phosphate (X3), and dependent variables as Percentage Drug release at 1 hour (Q1), Percentage Drug release at 12 hr (Q12) and Time required for 50% drug release (t50%). Granules made using the wet granulation process were found to be free-flowing since pre-compression characteristics such as bulk density, tapped density, angle of repose, and Hauser's ratio were within the range specified in the official standard. The produced tablets were tested for hardness, friability, weight fluctuation, disintegration time, and drug content after compression. The results were found to be within the permitted official limits. The FT-IR spectrum did not show the presence of any additional peaks for new functional groups indicating no chemical interaction between the drug and TG. The cumulative proportion of drug release was shown to be much lower as the concentration of natural TG increased. Formulation AF4 was chosen as the best formulation after an in-vitro release research, and it was tested for stability for 90 days. The stability investigations confirmed that the created tablet formulation remained unchanged in terms of its physical appearance, drug content, and in-vitro drug release properties, thereby confirming that the tablet was stable.

Keywords: Aprepitant, Sustained-release tablet, Granules, free-flowing, drug release, kinetics, Stability.

Introduction

Hydrophilic matrices are an interesting option when developing an oral sustained-release formulation. The drug release from such matrices can be controlled through their physical properties [1]. Polysaccharides are the choice of materials among the hydrophilic polymers used because they are non-toxic and acceptable to the regulating authorities [2]. The various polysaccharides used in drug delivery applications are cellulose ethers[3], xanthan gum[4], locust bean gum[5], and guar gum[6]. Another natural polysaccharide, Tamarind seed polysaccharide obtained from the seed kernel of Tamarindus indica, possesses properties like high viscosity, broad pH tolerance,[7] noncarcinogenicity [8], mucoadhesive nature, and biocompatibility[9]. It is used as a stabilizer, thickener, gelling agent, and binder in the food and pharmaceutical industries. The tamarind seed polysaccharide constitutes about 65% of the tamarind seed components[10]. It is a branched polysaccharide with a main chain of β -d-(1,4)- linked glucopyranosyl units, and a side chain consisting of a single d-xylopyranosyl unit attached to every second, third, and fourth d-glucopyrnosyl unit through an α-d-(1,6) linkage. One d-galatopyranosyl unit is attached to one of the xylopyranosyl units through a β - d-(1,2) linkage.

Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in the

development of a sustained release system. For sustained release systems, the oral route of drug administration has received the most interest as it is a natural, uncomplicated, convenient, and safer route. The Aprepitant sustained-release pills were made using the obtained TG powder as a binder in varying concentrations [11].

Materials and Methods

Materials

Aprepitant was obtained as a gift sample from MSN Laboratories, Hyderabad. Tamarind kernel powder was obtained as a gift sample from Chhaya Industries of Barshi, Maharashtra, India. Hydroxy Propyl Methyl Cellulose (HPMC) was purchased from Colorcon Asia Pvt Ltd, Goa, India. Polyvinyl pyrrolidine (PVP-K-30) was purchased from Anshul Agencies, Mumbai, India. Dicalcium phosphate and Microcrystalline cellulose were purchased from S.D. Fine Chemical Ltd, Mumbai, India. All the chemicals used were of A.R grade.

Extraction and modification of tamarind gum (TG)

TG was isolated from commercially available TKP. A mixture of 50 grams of defatted powder and 200 milliliters of cold water was made into a slurry. Then, the dispersion was heated in 800 cc of water that also contained 0.2% citric acid. After settling the proteins and fibers in the solution for 12 hours, it was centrifuged at 5000 rpm for 20 minutes. The thick mixture was poured into the surplus of ethyl alcohol while being constantly stirred (1:1). We rinsed the product with 200 ml of ethyl alcohol, diethyl ether, petroleum ether, and/or acetone before drying it at 400C for 12 hours. The 54,162 units of dried product were ground, screened, and kept. Furthermore, TG was isolated from tamarind seeds. The percentage of yield was determined and noted down.

Characterization of TG

Organoleptic evaluation of TG: We looked assessed the gum's color, smell, taste, texture, and fracture [13].

Shape of TG particles: The Motic microscope was used to observe TG particles at a resolution of 10X.

Identification tests: The usual protocols were followed to conduct the TG identification tests.

Determination of solubility

After the TG dispersion of one percent was made, it was mixed for three minutes. After a 15-minute centrifugation run, the resulting suspension had its supernatant removed. After transferring 50 ml of the supernatant to a Petri dish, it was dried at 105 ℃ until its weight remained constant. Next, the solubility percentage in cold water was determined and noted [14].

Determination of pH

After dissolving 1 gram of TG in 100 milliliters of distilled water, the pH was measured using a pH meter.

Determination of Swelling

A precisely measured one milligram of powder was used to make measurements of 25 milliliters. We measured the effects of increasing the volume of TG by adjusting the solvent volume of each cylinder and recording our findings. A consistent volume was achieved in each of the cylinders by taking readings at predefined intervals. The research was carried out three times [15].

Determination of viscosity

Distilled water was used to create a 1% TG solution. We measured the viscosity after one hour. The viscosity was measured using a small sample adapter and Spindle No. 21, which was revolved at 100 RPM. The research was carried out three times [16].

Powder Characteristics of TG

The density of the polymer was measured in both its bulk and its tap form.

Hausner's ratio and Carr's index: The parameters in question were determined by utilizing bulk and tap densities [17].

Solid state 13C NMR spectroscopy

13C CP-MAS, solid-state cross-polarization-magic angle spinning The TG's NMR spectra were captured using a JEOL-ECX400 spectrometer set to 400 MHz, with the following parameters: a relaxation delay of 5 s, a 35 kHz sweep width,

and a 10 KHz rotating speed. An external methyl resonance standard of hexamethylbenzene at 17.3 ppm was used to calibrate the chemical shifts [18].

Formulation Design

Table 1: Selected Ingredients for formulation with function

S. No	Drug/Excipient	Function
1	Aprepitant	Model Drug
2	Microcrystalline cellulose	Diluent
3	Dicalcium phosphate	Diluent
4	Magnesium Stearate	Lubricant
5	Talc	Glidant
6	Bentonite	Adsorbent
7	Tamarind Seed Extract	Binder
8	Starch paste	Binder

Flow Properties

Angle of Repose

There is a maximum value for a particular powder when the static heap is left to stand with only gravity acting on it. This value is determined by the angle between the free surface of the heap and the horizontal plane [19].

Tan ɵ = h/r

where h and r are the height and radius of the powder cone

Tapped density (Td)

Obtaining the tapped density or poured density from a container holding the powder sample by mechanical tapping is the standard procedure [20].

$$T_d = M/V_p$$

Where, M = weight of samples in grams and Vp = final tapped volume of powder in cm^3

Bulk Density

The mass densities of the material were measured, both in its loose and tapped states. After each formula's granules were gently shaken to break any agglomerates that may have formed, a certain amount was added to a graduated measuring cylinder. Following the measurement of the initial volume, the cylinder was released from a height of 2.5 cm onto a hard surface at 2-second intervals, allowing it to fall under its weight. The tapping was kept up till the volume didn't alter any further. The following formulas were used to calculate LBD and TBD [21].

$$\text{LBD} = \frac{\text{Mass of the powder}}{\text{Volume of the packing}}$$

$$TBD = \frac{\text{Mass of the powder}}{\text{Tapped Volume of the packing}}$$

Compressibility Index

With a low Carr's index, the initial packing arrangement is good and there are fewer voids in the volume. Powder flow reduces when these indices' values rise [22].

% Carrs index $\frac{\text{TBD}-\text{LBD}}{\text{TBD}}$x100

Hausner's Factor

The relative significance of interparticulate interactions can be evaluated using Hausner's ratio, which assesses the

powder's capacity to settle [23].

$$\text{Hausner ratio} = \frac{D_F}{D_0}$$

where D_F is Tapped bulk density and D_0 is Loose bulk density.

Design of the Experiment (DOE)

Full Factorial Design

This research endeavor utilized a full factorial design with three levels of factors to produce a tablet. To find out how different doses of medication and TG affected the percentage drop in blood glucose level, researchers also employed a full factorial design with three levels for each element. Nine trials were carried out, simultaneously altering both variables, by the model. X and Y are the independent and dependent variables in this factorial design [24].

Table 2: The optimization of aprepitant tablets using the Full Factorial Design

Parameter	Low (-1)	Medium (0)	High (+1)
Independent Variables			
MCC (X1)	50	100	150
TG (X2)	30	60	90
Dicalcium phosphate (X3)	20	30	40
Dependent variables			
Percentage Drug release at 1 hour (Q1)	Maximize		
Percentage Drug release at 12 hr (Q12)	Maximize		
Time required for 50% drug release (t50%)	Maximize		

Preparation of Aprepitant Tablets

To make the Aprepitant tablets, the following ingredients were taken: 125 mg of the drug, 2 mg of magnesium stearate, distilled water, talc, and TG and MCC [25].

Preparation of glipizide tablets using Tamarind seed extract

Wet granulation was used to generate nine distinct formulations (AF1–AF17) with varying proportions of tricalcium phosphate (TG), dicalcium phosphide (DCP), and microcrystalline cellulose (MCC). Before mixing with glipizide and MCC, the TG powder was individually sieved via sieve no. 22. After adding enough distilled water, the mixture was ground into granules. In a tray drier set at 40°C, the grains were evaporated [26]. The granules were lubricated by passing them through filter no. 20, followed by the addition of talc and magnesium stearate (1:1). With the help of appropriate punches, the granules were crushed using a 10-station tablet compression machine (Shakti Machineries, India). To find out how each independent variable affected each dependent variable, researchers used a 3^2-way full factorial design.

Post Compression

Appearance:

Color and smell, among other organoleptic qualities, were assessed. Ten tablets were chosen at random from each batch; their colors were compared visually, and their odors were evaluated [30].

Dimensions:

A digital vernier caliper was used to measure the tablet's thickness and diameter. Five tablets of the mixture were selected at random and measured one by one [27].

Hardness:

The Pfizer hardness tester was used to measure the hardness. There were five pills used for every batch [28].

Friability:

After weighing twenty pills, the device was spun at 25 rpm for four minutes in the Roche friability. After being powdered, the pills were weighed once again [29]. To determine the percentage of friability, the following formula was used:

$F = \{1-(Wt/W)\} \times 100$

Where, F = Friability in percentage; W = Initial weight of tablets; W_t = Weight of tablets after friabiation.

Drug content estimation

Weigh 150 mg of Verapamil HCl sustained-release tablets, dissolve in a small quantity of methanol in a 100 ml volumetric flask, sonicate for 5 minutes, and then add 100 ml of 0.1N HCl to get the volume up to 100 ml. Finally, the mixture is through a membrane filter [30]. The drug concentration is determined by utilizing a standard curve and subsequent dilutions are performed by measuring absorbance at 278 nm against a blank solution of 0.1N HCl.

$$\%\ \text{drug content} = \frac{\text{actual drug content in tablet}}{\text{theoretical amount of drug in tablet}} \times 100$$

Weight variation test: We took 20 pills at random from the batch, weighed them separately, and averaged their weights. Each tablet's weight was compared to the average weight and the percentage variation was determined [31]. If there are no more than two cases where the individual weights differ from the average weight by no more than 5%, then the test is considered passed.

$$\text{weight variation} = \frac{\text{Average weight} - \text{tablet weight}}{\text{tablet weight}} \times 100$$

Disintegration test

Following USP guidelines, the disintegration test apparatus was used to measure the disintegration time. Each tube in the basket contained one tablet [32]. The basket, which had a stainless-steel screen (mesh no.10) on the bottom, was submerged in water at a temperature of 37± 2°C. The duration needed for the tablet to fully dissolve in each tube was calculated

In-vitro dissolution studies:

Using a paddle, the tablets were dissolved using USP XXIII dissolving type II equipment. The pH 1.2 buffer (0.1N HCl) made up 900 ml of the dissolution medium for the first two hours, while the pH 6.8 phosphate buffer was maintained for the next three to twelve hours. The temperature of the medium was kept at 37±0.5 ºC. 50 rpm was the pace at which the paddle could spin [33]. 5 milliliters of the sample were removed at intervals of 1 to 10 hours according to the protocol, and the same volume of fresh medium was added at each interval. The samples that were taken out were mixed with 10 milliliters of pH 6.8, filtered, and then tested on a UV spectrophotometer at 278 nanometers with pH 6.8 set as a blank. The cumulative percentage release of the medication was determined.

Stability Studies

The capacity of a given formulation under a given set of circumstances to maintain conformity with its physical, chemical, therapeutical, and toxicological criteria is the definition of drug Stability. The testing is done to show how the medication formulation's quality changes over time in response to several environmental factors like light, humidity, and temperature [34].

Statistical Analysis

Design Expert version 12.0.3.0 (Stat-Ease, USA) and Microsoft Excel 2022 (Microsoft, USA) were used for factorial design and statistical optimization. The PCP Disso program was used to analyze in vitro drug release trials. Using a

samples t-test, we looked for statistically significant changes in the in vivo data.

Results & Discussion

Preformulation tests

Solubility studies:

For each addition, the mixture is forcefully mixed and visually checked for any particles of solute that have not dissolved. The solubility was measured by comparing the solute-to-solvent ratio.

Table 3: Solubility study ofAprepitant

S. No	Solvents/Medium	Solubility (mg/mL)
1	Water	0.395
2	0.1 N HCl	10.475
3	Phsophate Buffer pH 6.8	85.69
4	Phsophate Buffer pH 6.8 + 1% SLS	99.74
5	Acetone	52.43
6	Methanol	75.94
7	Ethanol	62.18

Melting point

The drug's melting point was determined to be close to 253.33 °C, which agrees with the results of the DSC and the literature (251-255 °C).

Table 4: Melting point of the ingredients

S. No	Ingredients	Average Observed Melting point (°C)	Reference Melting point (°C)
1.	Aprepitant	253.33 ± 0.24	251-255

Extraction of TG

Using TKP for extraction resulted in a TG yield of more than 50% (58.46 ± 3.75). We screened the obtained TG via sieve no. 80 and then placed it in a desiccator for storage.

Table 5: Extraction of TG

Parameter	Tamarind Seeds	Tamarind Kernel powder
Weight of Raw materials (g)	50	50
Yield (g)	10.24	19.75
Yield (%)	20.48	39.5

Characterization of TG:

Organoleptic properties:

Table 6: Organoleptic characteristics of TG extract

Parameters	Observations
Color	Brown in color
Odorless	Odorless
Taste	Tasteless

Shape	Irregular
Touch & Texture	Rough & Hard

Identification tests

The TG powder was found to include carbohydrates, according to the identification tests. The presence of carbohydrates was confirmed by the positive result of Molisch's test for TG. Tests for alkaloids, tannins, proteins, lipids, and TG all came back negative for TG powder. The separated TG was found to be pure and devoid of proteins and lipids according to the results of the identification test.

Table 7: Phytochemical identification tests for TG extract

Phytochemical Test	Present (+) /Absent (-)
Carbohydrate	+
Hexose sugar	+
Monosaccharides	-
Alkaloid	-
Tannins	-
Fats and oils	-
Proteins	-
Amino acids	-
Mucilages	-

Determination of solubility

It was determined that the TG sample had a cold water solubility of 1.85 ± 0.27 mg/ml. Swelling of TG in water causes the sample to develop a thick solution when heated. It shows that TG can gel. No amount of ethanol, methanol, benzene, ether, or acetone could dissolve the TG powder.

Determination of pH

The results showed that the pH of distilled water with 1% TG was 6.58 ± 0.11. That the TG has a slightly acidic tendency is what it says.

Swelling of TG

The amount of TG that swelled was determined to be 1.72 times the gum's dry volume. It suggests that TG has the potential to be utilized for controlled or sustained medication delivery.

Determination of viscosity

The measured viscosity of 1% TG was 41.23±0.85 cP. This data suggests that a high TG concentration is necessary for gel formation.

Powder characteristics of TG

The table below lists the powder characteristics of TG powder. The particle form determines how the powder material flows. If the right glidant is added to the produced TG, it could be useful for the production of solid dosage forms.

Table 8: Micromeretic properties of TG

Parameters	Observed Value
Bulk density (g/mL)	0.534± 0.038
Tapped density (g/mL)	0.492±0.012
Carrs index (%)	7.865±0.11
Hausners ratio	1.08±0.05

Angle of repose	32.51±2.47
Loss on drying (%)	6.95±0.42
Swelling index (%)	18.54±2.67
Total ash (%)	1.76±0.35
Acid insoluble ash (%)	0.16±0.23
Water soluble ash (%)	0.85±0.14

Solid state 13C NMR spectroscopy

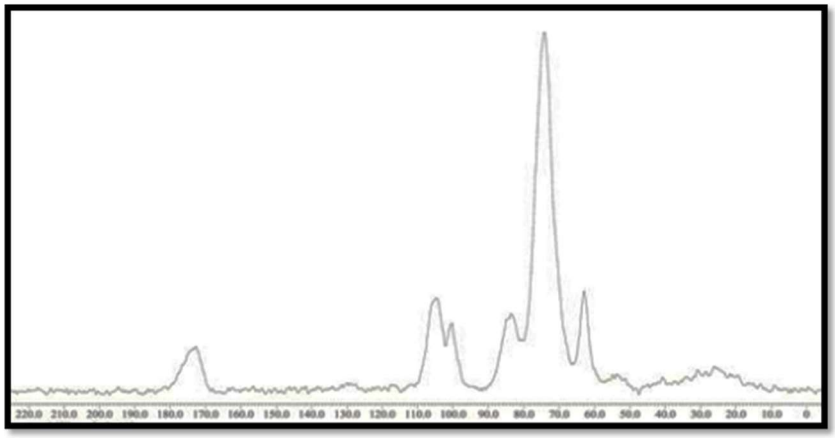

Figure 5: Solid-state ^{13}C NMR of TG

Three separate peaks were seen in the solid-state 13C NMR spectra of TG (Figure 5). Carbon atoms (C2–C5) linked by -OH groups are responsible for the resonance peak at 74 ppm, while an anomeric carbon atom (C1) is attributed to the resonance peak at 105 ppm. The C6 carbon atom of the alcohol group is responsible for the presence of a peak at 63 ppm.

Drug - Excipient Compatibility

In the FTIR analysis of TG, the stretching of the -OH groups in the polysaccharide was identified by a broad peak at 3500-300 cm^{-1}. The stretching of the C-O bond in the alcoholic group is responsible for the peaks observed at 1039 cm^{-1} and 1143 cm^{-1}. At 2920 cm^{-1}, the medium peak was associated with the CH asymmetric stretch. Due to carbonyl stretching, the peaks at 1747 cm^{-1} and 1689 cm^{-1} were observed.

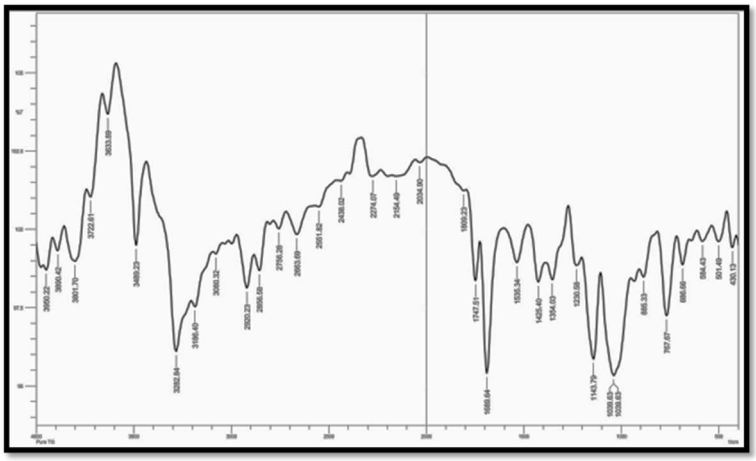

Figure 6: ATR-FTIR spectrum of TG

For these samples, the storage conditions were 40 ºC with 75% relative humidity, and they were examined after 1, 2, and 4 weeks. The table displayed the outcomes of the physical examination. The alcohol group O-H, amines N-H, alkanes C-H, ketones C=O, alcohol C-O, and alkenes C=C have respective important peaks at 3866.38 cm^{-1}, 3449.51 cm^{-1}, 2894.11 cm^{-1}, 1709.08 cm^{-1}, 1114.38 cm^{-1}, and 770.93 cm^{-1} in Aprepitant. solid bands in the FT-IR spectra were detected with minor shifting, indicating that the formulation is stable and can maintain the drug's functional ability.

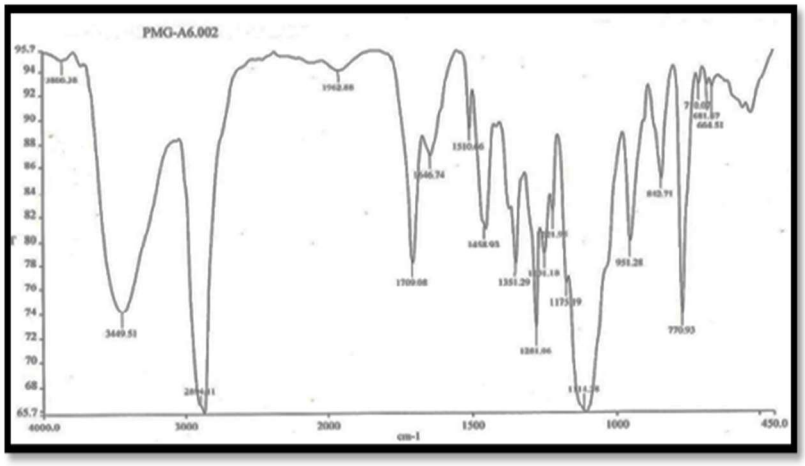

Figure 7: FTIR spectrum of Pure drug (Aprepitant)

Aprepitant displayed several distinct and noticeable peaks. O-H bond stretching vibrations at 3305 cm^{-1} and C-O bond stretching vibrations at 1120 cm^{-1} were caused by secondary alcohols, respectively. The asymmetric C-H stretching of the CH3 group, the symmetric C-H stretching of the CH2 group, and the C=N stretching might be shown by the peaks at 2967, 2856, and 1707 cm^{-1}, respectively. There was no drug-excipient interaction in the optimized formulation since all of Aprepitant's distinctive peaks were present.

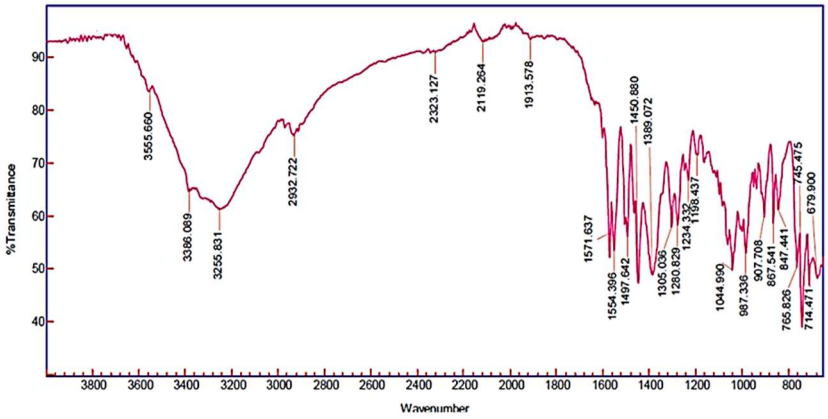

Figure 8: FTIR spectrum of Optimized formulation

DSC

Figure 9 shows the DSC of TG. The thermal decomposition curve of TG exhibited two primary phases of degradation. Starting at 35 °C and ending at 100 °C is the first stage. The extraction of bound and free water from the polymer could be the cause of this. Stage two of weight loss occurred between 2280 and 3000 degrees Celsius, and it involved a 35% reduction in body mass. Thermogravimetric analysis of TG revealed an endotherm at 238.560 °C. As shown in the TGA curve, the DSC curve corroborates the weight reduction.

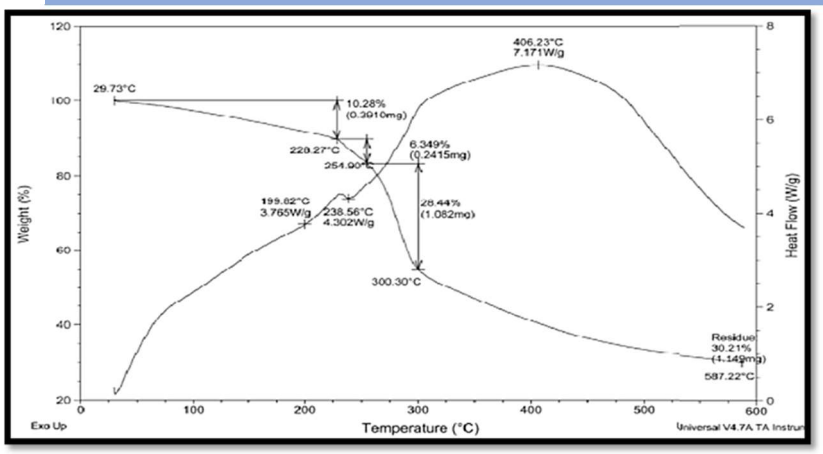

Figure 9: DSC of TG

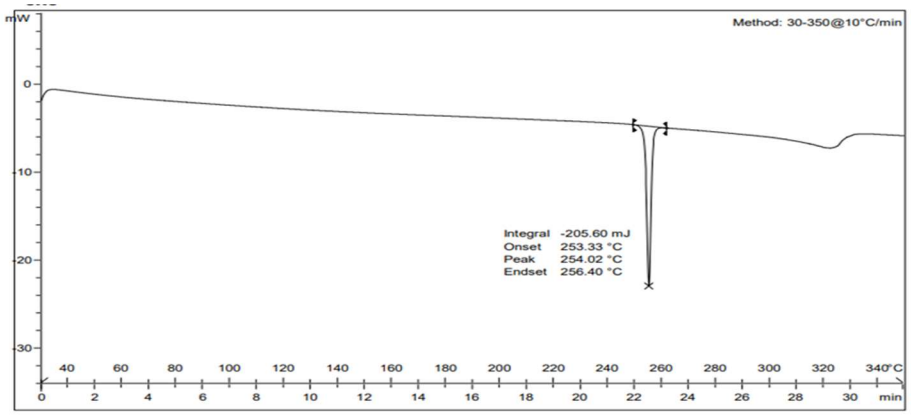

Figure 10: DSC thermogram of Pure drug (Aprepitant)

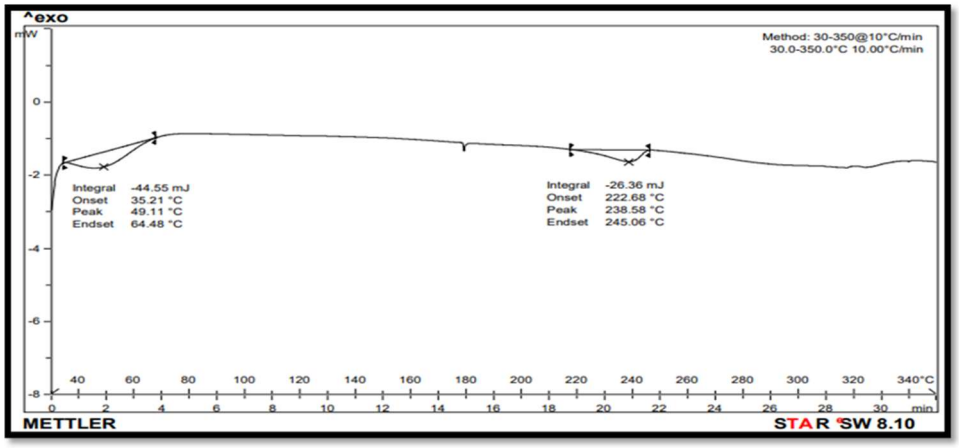

Figure 11: DSC thermogram of Optimized formulation

X-ray powder diffraction

Figure 6 displays the XRD pattern of TG. Since TG showed no peak, we can assume that the structure is entirely amorphous.

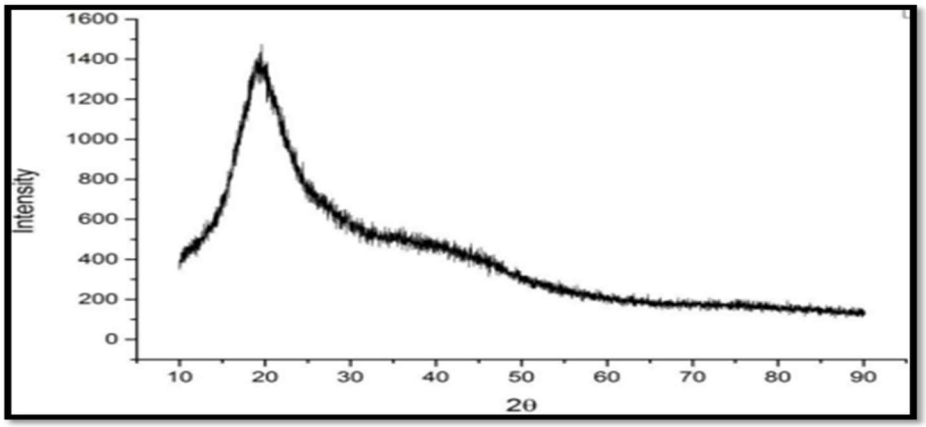

Figure 12: Powdered X-ray diffractogram of TG

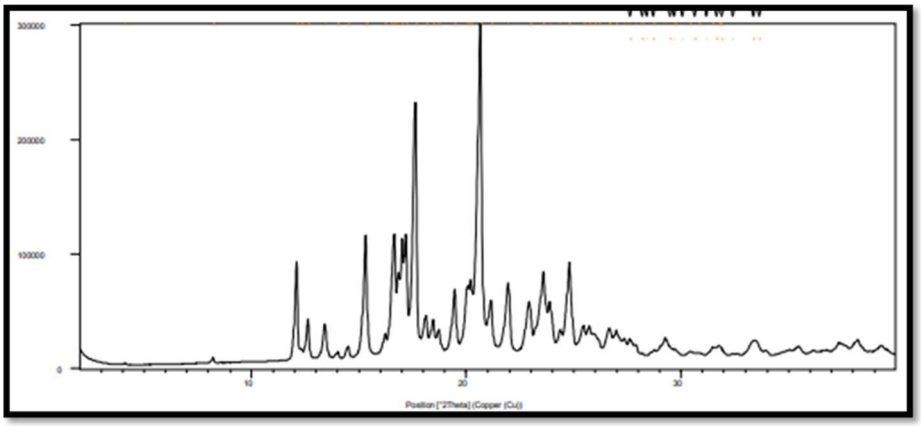

Figure 13: Powdered X-ray diffractogram of Pure drug (Aprepitant)

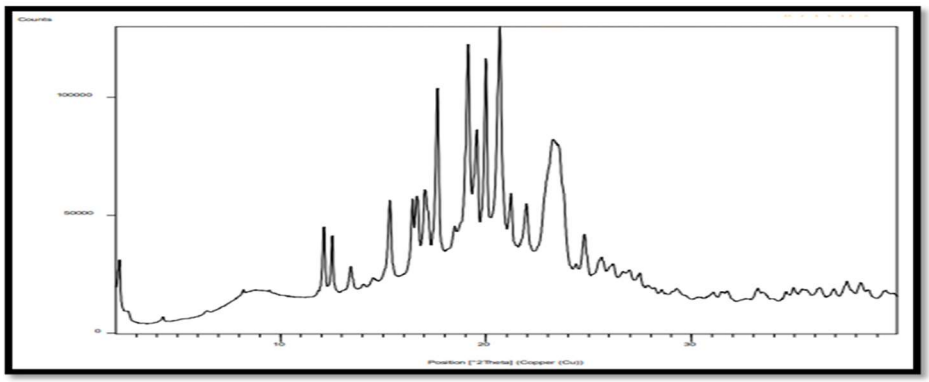

Figure 14: Powdered X-ray diffractogram optimized formulation

Pre-compression Parameters

Table 9: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped densit (gm/ml)	Carr's index (%)	Hausner's Ratio
AF1	26.35	0.482	0.573	15.88	1.188
AF2	28.49	0.493	0.594	17.01	1.204
AF3	32.51	0.514	0.612	16.01	1.190
AF4	26.59	0.531	0.614	13.51	1.156
AF5	29.35	0.465	0.559	16.81	1.202
AF6	30.42	0.532	0.641	12.79	1.204
AF7	26.51	0.496	0.586	15.35	1.181
AF8	23.48	0.483	0.573	15.70	1.186
AF9	24.57	0.467	0.571	18.21	1.222
AF10	26.95	0.515	0.612	15.84	1.188
AF11	28.64	0.546	0.631	13.47	1.155
AF12	30.12	0.533	0.627	14.99	1.176
AF13	31.42	0.524	0.619	15.34	1.181
AF14	30.26	0.422	0.519	18.68	1.229
AF15	28.76	0.465	0.559	16.81	1.202
AF16	29.81	0.512	0.611	16.20	1.193
AF17	30.64	0.534	0.621	14.00	1.162

The powder blend's outstanding flow characteristics are supported by the data on the angle of repose. The bulk densities of all the formulations ranged from 0.48 ± 0.04 to 0.546 (gm/cm3), suggesting that the powder has adequate flow characteristics. The powder showed adequate flow characteristics, with tapped densities ranging from 0.519 to 0.641 across all formulations. With compressibility indices ranging from 12.79 to 18.68 across all formulations, the powder seems to have great flow properties. According to Hausner's ratio, which falls between 1.155 and 1.229, the powder has great flow properties. Indeed, this is the case with every formulation.

Design of formulation

Table 10: Formulation design

Std	Run	X1	X2	X3	Y1	Y2	Y3
1	7	50	30	30	14.36	86.93	8.96
2	2	150	30	30	18.36	97.42	9.84
3	10	50	90	30	19.03	98.46	10.42
4	14	150	90	30	9.56	56.43	22.54
5	8	50	60	20	16.32	84.15	13.54
6	3	150	60	20	8.79	62.48	23.45
7	5	50	60	40	15.43	89.75	10.42
8	9	150	60	40	16.45	93.51	7.53
9	6	100	30	20	5.69	40.21	25.43
10	4	100	90	20	10.49	46.51	28.96
11	16	100	30	40	13.62	80.15	13.45
12	17	100	90	40	5.26	42.13	25.89
13	12	100	60	30	12.43	69.82	18.65
14	15	100	60	30	15.43	72.41	19.82
15	1	100	60	30	13.64	70.43	20.75
16	11	100	60	30	14.82	74.15	19.53
17	13	100	60	30	15.03	73.49	20.43

Response 1: Response 1: Percentage Drug release at 1 hour (Q1)

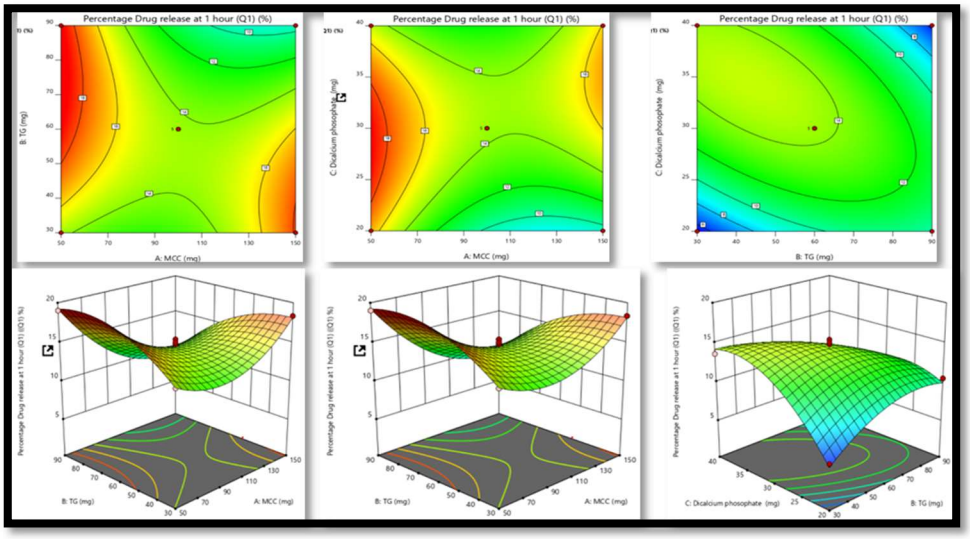

Figure 15: Effect of independent variables on dependent variables of Percentage Drug release at 1 hour (Q1)

A significant model is indicated by an F-value of 23.59. The likelihood of a noise-induced F-value this large is a meager 0.02%. Significant model terms are indicated by p-values that are less than 0.0500. Here, important model terms are A, B, C, AB, AC, BC, A^2, B^2, and C^2. With an F-value of 0.50 for Lack of Fit, it is clear that the absence of Fit is not statistically significant when compared to the pure error. A Lack of Fit F-value of this magnitude could be the result of random chance with a probability of 70.30 percent.

Percentage Drug release at 1 hour (Q1) = +14.27 -1.50A -0.9612B +1.18C -3.37AB +2.14AC -3.29BC +3.27A2 -2.21B2

-3.29C2

Response 2: Percentage Drug release at 12 hr

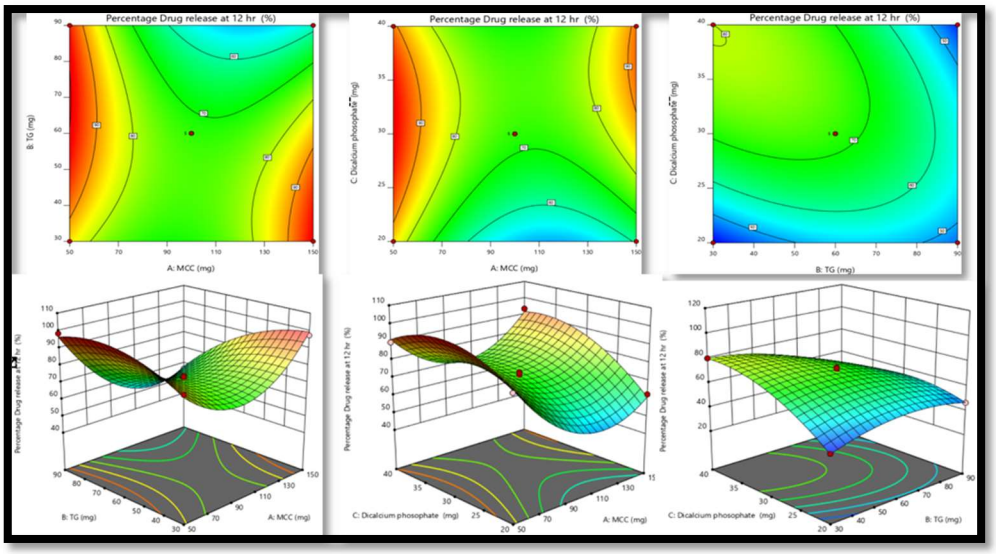

Figure 16: Effect of independent variables on dependent variables of Percentage Drug release at 12 hr

A significant model is indicated by an F-value of 110.12. An F-value this high could only happen by accident (with a probability of only 0.01%). Significant model terms are indicated by p-values that are less than 0.0500. Here, important model terms are A, B, C, AB, AC, BC, A^2, B^2, and C^2. A 2.25 for the Lack of Fit F-value means that it is not significantly different from the pure error. A Lack of Fit F-value of this magnitude could be the result of random chance, which accounts for 22.45% of the cases.

Percentage Drug release at 12 hr (Q12) = +72.06 -6.18A -7.65B +9.02C -13.13AB +6.36AC -11.08BC +21.49A2 -8.74B2 -11.07C2

Response 3: Time required for 50% drug release (t50)

With an F-value of 57.69, the model is statistically significant. An F-value this high could only happen by accident (with a probability of only 0.01%). Significant model terms are indicated by p-values that are less than 0.0500. Here, important model terms are A, B, C, AB, AC, BC, A^2, B^2, and C^2. The model terms are not considered significant if the values are more than 0.1000. Reducing the number of irrelevant model words (not including those needed to maintain hierarchy) will help your model perform better. An F-value of 3.41 for Lack of Fit indicates that, as compared to pure mistake, the Lack of Fit does not warrant substantial consideration. The likelihood of noise producing a Lack of Fit F-value of this magnitude is 13.36%.

Time required for 50% drug release (t50%) = +19.84 +2.50A +3.77B -4.26C +2.81AB -3.20AC +2.23BC -8.30A2 +1.40B2 +2.20C2

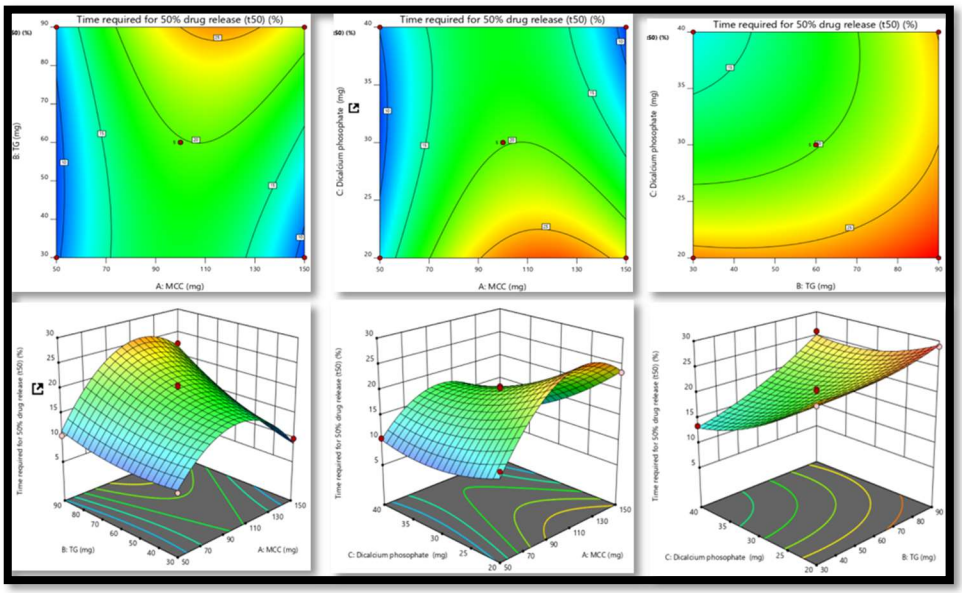

Figure 17: Effect of independent variables on dependent variables of Time required for 50% drug release (t50)

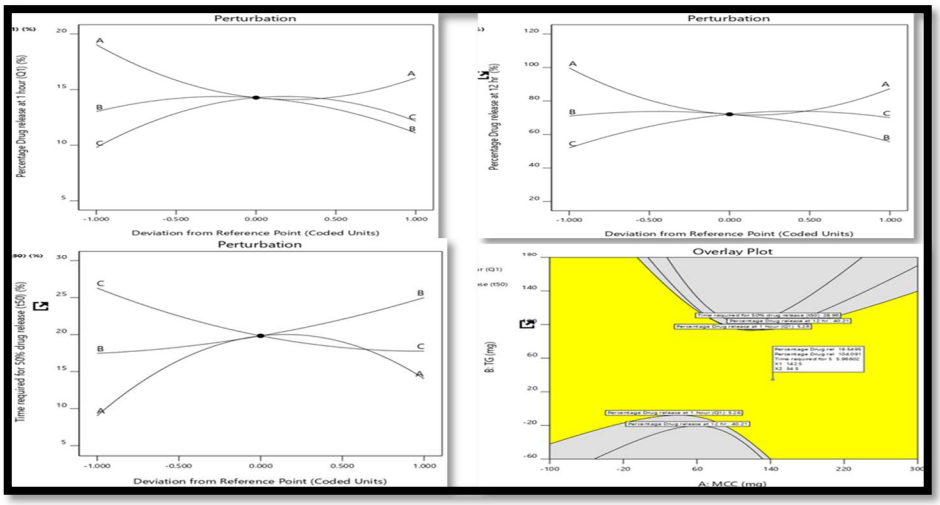

Figure 18: Perturbation plots of dependent variables and overlay plot of optimized formulation

Evaluation Tests

The results showed that all of the formulations were round, flat, and odorless, with a cream color.

Table No 11: Aprepitant post-compression parameters

Formulation codes	Weight variation(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
AF1	498.56±2.19	4.5±0.23	0.50±0.02	6.8±0.13	99.76±0.02
AF2	468.79±3.42	4.5±0.14	0.51±0.04	6.9±0.24	97.45±0.13
AF3	485.29±4.15	4.4±0.25	0.51±0.03	4.9±0.16	99.34±0.29
AF4	501.42±2.61	4.6±0.36	0.55±0.09	6.9±0.35	99.88±0.14

AF5	479.86±3.02	4.2±0.13	0.56±0.04	6.7±0.15	96.14±0.17
0AF6	480.31±1.28	4.5±0.42	0.45±0.05	6.5±0.12	98.56±0.28
AF7	495.16±1.27	4.1±0.28	0.51±0.04	6.4±0.16	98.42±0.32
AF8	488.26±2.64	4.3±0.13	0.49±0.03	6.7±0.11	99.65±0.16
AF9	493.21±2.41	4.3±0.11	0.55±0.09	6.6±0.14	95.12±0.17
AF10	501.64±0.12	4.1±0.28	0.51±0.05	6.9±0.31	98.42±0.31
AF11	497.85±0.24	4.3±0.13	0.51±0.04	6.7±0.14	99.65±0.19
AF12	491.52±0.61	4.3±0.11	0.51±0.08	6.5±0.13	94.12±0.14
AF13	486.53±0.84	4.4±0.25	0.55±0.06	6.4±0.14	99.45±0.18
AF14	497.28±0.24	4.6±0.36	0.56±0.08	6.7±0.14	96.34±0.27
AF15	492.53±0.42	4.2±0.13	0.51±0.01	6.6±0.135	98.88±0.19
AF16	496.58±0.68	4.5±0.42	0.49±0.06	6.4±0.18	97.14±0.13
AF17	498.12±0.95	4.4±0.25	0.55±0.04	6.7±0.15	99.45±0.16

In-vitro drug release:

First, the in-vitro release research was conducted in 0.1N HCl (an acidic buffer with a pH of 1.2) for two hours. Then, for the following twenty-four hours, the medium was substituted with simulated intestinal fluid (a phosphate buffer with a pH of 6.8). After 2 hours, the amounts of drug released by the marketable formulation in 0.1N HCl, the optimized tablet, and the pure drug solution were 24.59%, 15.36%, and 89.35%, respectively. Because retardant TG is not present in the pure drug solution formulation, the majority of the medication releases after 2 hours. Optimal sustained release tablets release 39% of the medicine after 12 hours, while the commercial version releases 62.59% after 12 hours. The results demonstrated that when the concentration of TG increased in each formulation, the drug release from the formulations reduced. The optimised formulation table reveals that the medication release is slower than any other formulations. Formulation AF4, which releases 92.35% of the drug after 24 hours, was deemed the optimal formulation according to the drug release profile.

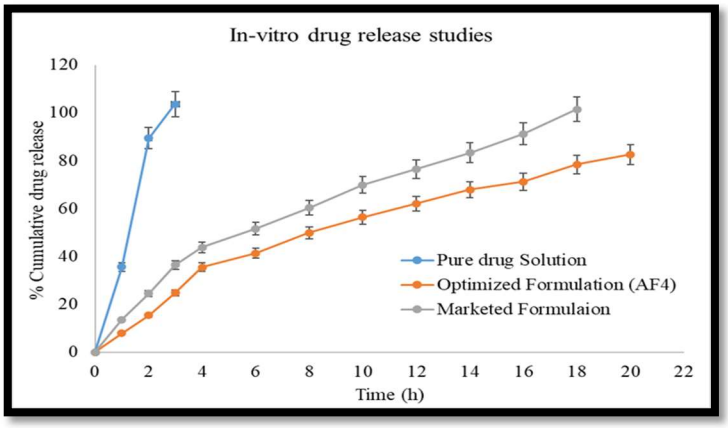

Figure 19: Comparision of in-vitro drug release profile

Stability studies

For this product's AF4 batch, stability experiments are conducted in a stability chamber at 40 ℃/75%RH for

approximately three months, according to ICH requirements. A three-month stability investigation was carried out on the AF4 formulations at 40 ℃/75%RH. Prepared tablets were determined to be stable during the study time due to the lack of change in case of physical appearance, as well as no significant alterations in hardness, drug content, and dissolving study.

Table 12: Stability studies of Optimized sustained-release tablets (AF4)

Days	Evaluation parameters			% Cumulative drug release
	Color	Hardness	Drug content	
0	Cream	4.6±0.36	99.88±0.14	92.35±0.12
30	Cream	4.59±0.21	99.85±0.01	90.53±0.31
60	Cream	4.56±0.31	99.64±0.11	89.65±0.25
90	Cream	4.51±0.15	99.05±0.12	88.07±0.14

Summary & Conclusion

As an alternative to traditional drug delivery systems, sustained-release dosage forms offer the advantage of a continuous release of the active ingredient over an extended period. The Aprepitant sustained-release tablets were made using the obtained TG powder as a binder in varying concentrations. The produced tablets were tested for hardness, friability, weight fluctuation, disintegration time, and drug content after compression. The results were found to be within the permitted official limits. The FT-IR spectrum did not show the presence of any additional peaks for new functional groups indicating no chemical interaction between the drug and TG. The cumulative proportion of drug release was shown to be much lower as the concentration of natural TG increased. Formulation AF4 was chosen as the best formulation after an in-vitro release research, and it was tested for stability for 90 days. The stability investigations confirmed that the created tablet formulation remained unchanged in terms of its physical appearance, drug content, and in-vitro drug release properties, thereby confirming that the tablet was stable.

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