

Formulation And Evaluation Of Sustained Release Tablets Using Natural Polymer

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ABSTRACT

Utilizing isolated biocompatible Tamarind gum (TG) as a binder, a sustained-release (SR) tablet of Aprepitant was formulated. The pre-compression properties of the wet granulated granules were found to be within the official standard range, indicative of their free-flowing nature. The tablets of Aprepitant with extended release were made using wet granulation. Following compression, the generated tablets were examined for quality control tests and the outcomes fell within the authorized official range. Given that the FT-IR spectra showed no additional peaks, it demonstrated that the drug and TG did not interact chemically. Following an in-vitro release investigation, formulation AF4 was determined to be the optimal formulation. The stability studies verified that the produced tablet formulation maintained its original form indicating the tablet's stability.

Keywords: Sustained-release tablet, Granules, free-flowing, drug release

1. INTRODUCTION

When making a sustained-release oral formulation, hydrophilic matrices are a viable alternative. Due to their physical characteristics, these matrices can regulate the release of drugs [1]. Since polysaccharides are non-toxic and approved by regulatory bodies, they are the preferred material among the hydrophilic polymers employed [2]. Guar gum [6], locust bean gum [5], xanthan gum [4], and cellulose ethers [3] are some of the several polysaccharides used in drug delivery applications. Different types of natural polymers produced from the seed kernel of *Tamarindus indica* are known for their unique properties, such as high viscosity, a wide pH tolerance range, non-carcinogenic, mucoadhesive, and biocompatible. Approximately 65% of the components of tamarind seeds are made up of the polysaccharides found in them [10]. The most straightforward method for forming a sustained-release system is to use matrix tablets, which are made of a drug and a polymer to delay release. Because it's natural, simple, convenient, and safer, the oral route of drug delivery has drawn the utmost interest for continuous release systems. Different concentrations of the resulting TG powder were used as a binder to make the Aprepitant sustained-release tablets [11].

2. MATERIALS AND METHODS

Materials

From Chhaya Industries in Barshi, Maharashtra, India, tamarind kernel powder was sent as a gift sample. MSN Laboratories in Hyderabad provided a complimentary sample of aprepitant. Goa, India's Colorcon Asia Pvt Ltd was the supplier of Hydroxy Propyl Methyl Cellulose (HPMC). Anshul Agencies in Mumbai, India is where we acquired the polyvinylpyrrolidone (PVP-K-30). From S.D. Fine Chemical Ltd. in Mumbai, India, we acquired magnesium stearate, microcrystalline cellulose, and dicalcium phosphate. From Merck Ltd. in India, absolute ethanol was acquired. A.R. grade chemicals used were all that were used.

Extraction and modification of tamarind gum (TG)

TG was isolated from commercially available tamarind kernel powder (TKP). A mixture of 50 grams of defatted powder and 200 milliliters of cold water was made into a slurry [12]. The 54,162 grams of dried product were ground, screened, and kept. Furthermore, tamarind seeds were used to isolate TG. A record of the yield percentage was kept.

Characterization of TG

Organoleptic evaluation of TG: We 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 °C 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 checked by a pH meter.

Determination of Swelling: A precisely measured one milligram of powder was used to make measurements of 25 millilitres. 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].

ATR-FTIR study of TG:

The ATR-FTIR spectrophotometer (IR Affinity, Shimadzu, Japan) was used to record the infrared spectrum. The ATR was used to hold the sample while the spectra were recorded from 600-4000 cm⁻¹.

Thermal analysis of TG: A thermogravimetric analyzer (TGA/DSC1, Mettler-Toledo, Switzerland) recorded the TGA and DSC of TG. The sample was subjected to a nitrogen environment and heated at a rate of 10°C/min from 30°C to 500°C. ¹⁸⁻¹⁹..

X-ray powder diffraction (X-RD): The scanning speed of the X-ray diffractometer was 2°C/min, the scanning angle varied from 0 to 90° (2θ), the voltage was 30 kV, and the target was copper. The X-ray diffractometer (PW1729, Philips) was used to record the XRD pattern of the TG ^[20].

Formulation Design (Fig -1)

Table 1: Ingredients chosen for formulation

Drug/Excipient	Function
Aprepitant	Active Pharmaceutical ingredient
Microcrystalline cellulose	Fillers
Dicalcium phosphate	Fillers
Magnesium Stearate	Lubricating agent
Talc	Glidant
Bentonite	Adsorbent
Tamarind Seed Extract	Binding agent
Starch paste	Binding agent

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 ^[21].

Tapped density (Td): Obtaining the tapped density from a container holding the powder sample by mechanical tapping is

the standard procedure ^[22].

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 an elevation of 2.5 cm onto a rigid surface at 2-second intervals, allowing it to fall under its own weight. The tapping was kept up until the volume did not alter any further .

Compressibility Index (C.I): From bulk densities, Carr established an indirect way to measure powder flow. With a low Carr's index, the primary packing arrangement is good and there are fewer voids in the volume. Powder flow reduces when these indices' values rise

Hausner's Factor: The relative significance of inter-particulate interactions can be evaluated using Hausner's ratio, which assesses the powder's capacity to settle .

Design of Experiment (DOE):

Full Factorial Design: Investigators also employed a full factorial design with 3 levels to determine how different drug doses and TG affected the percentage drop in blood glucose level. Nine trials were carried out, simultaneously altering both variables, using the model (Table 2) ^[26].

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			
% Drug release at 1 hour (Q1)	Maximize		
% 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 ^[27].

Preparation of Aprepitant tablets using Tamarind seed extract: Wet granulation was used to generate 17 distinct formulations (AF1–AF17) with varying proportions of tricalcium phosphate, dicalcium phosphate (DCP), and microcrystalline cellulose (MCC). Before mixing with Aprepitant and MCC, the TG powder was individually sieved through sieve no. 22. After adding enough distilled water, the mixture was granulated. The granules In a tray drier set at 40°C, the grains were evaporated [28,29]. The granules were lubricated by passing them through filter no. 20, subsequently by the addition of talc and magnesium stearate (1:1). With the help of appropriate punches, the granules were compressed using a 10-station tablet compression machine. To find out how each independent variable affected each dependent variable, researchers used a 3²-way full factorial design.

Post Compression Analysis:

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

Thickness: A digital vernier caliper was used to evaluate the tablet's thickness and diameter. Five tablets of the mixture were selected arbitrarily and measured one by one

Hardness: This was determined using the Pfizer hardness tester. Five tablets are used for each batch.

Friability (F): After weighing twenty tablets, the device was spun at 25 rpm for four minutes in the Roche friability tester. After being powdered, the pills were weighed once again.

Where, W = Original weight of tablets; W_t = Weight of tablets after rotation.

Drug content: Weigh 150 mg of Aprepitant 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 make up the final volume. The absorbance at 278 nm is used to calculate the drug's concentration.

Weight variation test: We took 20 tablets at random from the batch, weighed them separately, and averaged their weights. Each tablet's weight was associated with the mean weight, and the % variation was determined.

Disintegration test: The disintegration test apparatus contains six tubes in the basket, containing one tablet. The basket, which had a stainless-steel screen (mesh no. 10) on the bottom, was submerged in water at $37 \pm 2^\circ\text{C}$. The duration desirable for the tablet to fully pass through the sieve was noted.

In-vitro dissolution studies: Employing 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. $37 \pm 0.5^\circ\text{C}$ was maintained as the medium's temperature; 50 rpm was set. 5 milliliters of the sample were removed at intervals of 1 to 10 hours according to the protocol, and a similar volume of fresh medium was added at each interval. The samples were tested on a UV spectrophotometer at 278 nm.

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

3. RESULTS & DISCUSSION

Pre-formulation tests

Melting point (M.P): The drug's M.P was determined to be close to 253.33°C , which agrees with the results of the DSC and the literature ($251\text{--}255^\circ\text{C}$).

Extraction of TG(table 3): Using TKP for extraction resulted in a TG yield of more than 50% (58.46 ± 3.75). Screened the obtained TG via sieve no. 80 and then placed it in a desiccator for storage.

Table 3: 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

Shape of TG particles

The TG particles had a rough surface and an uneven shape. The form of the particles was mostly rectangular. The development of a thread-like structure during extraction might account for this.

Identification tests: The TG powder was found to contain carbohydrates, according to the identification tests. The presence of carbohydrates was established 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 4).

Table 4: Phytochemical identification tests for TG extract

Phytochemical Test	Present (+) /Absent (-)
Carbohydrate	+
Hexose sugar	+
Monosaccharides	-
Alkaloid	-
Tannins	-

Fats and oils	-
Proteins	-
Amino acids	-
Mucilage	-

Determination of solubility: It was determined that the TG sample had a cold-water solubility of 1.85 ± 0.27 mg/ml. When the sample is heated, the swelling of TG in the water causes a thick solution to form. It demonstrates how well TG gels. The TG powder was insoluble in acetone, ethanol, methanol, benzene, or ether.

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 drug 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. .

Drug-Excipient Compatibility:

FTIR Results show that O-H, N-H, C-H, C=O, C-O, and 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 2).

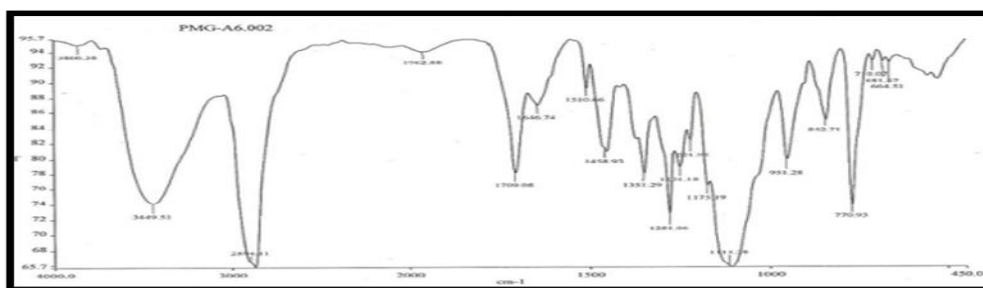


Figure 1: FTIR spectrum of pure drug (Aprepitant)

Aprepitant showed multiple clear and observable peaks. Secondary alcohols were the source of the O-H bond stretching at 3305 cm^{-1} and the C-O bond stretching vibrations at 1120 cm^{-1} . The C=N stretching, the symmetric C-H stretching of the methylene group, and the asymmetric C-H stretching of the methyl group may be indicated by the peaks at 2967, 2856, and 1707 cm^{-1} , respectively. Since all of the drug's distinctive peaks were present in the optimized formulation, there was no interaction between the drug and the polymer (Figure 2)

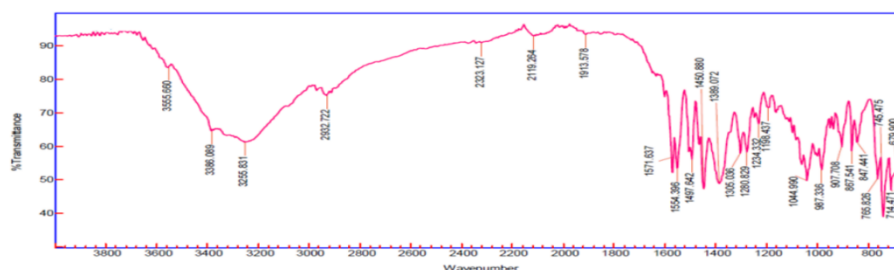


Figure 2: FTIR spectrum of the optimized formulation

Using powdered X-RD & DSC, the polymorphic forms of Aprepitant API were characterized. The aprepitant powder's crystallinity was assessed with a Bruker D8 Advance XRD equipped with a copper target Figure 3-6 .

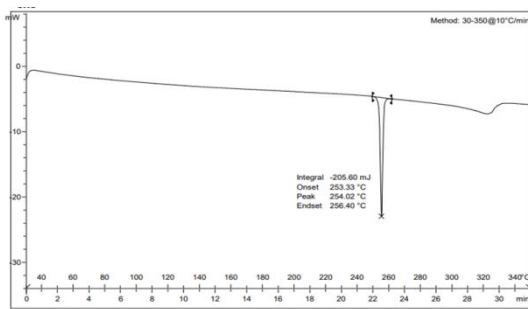


Figure 3: DSC of Aprepitant

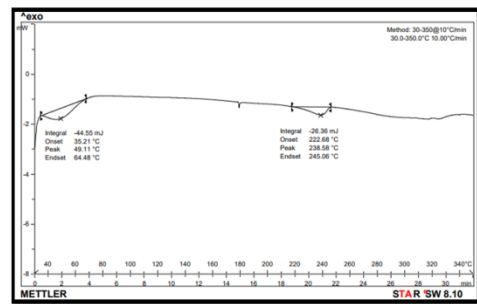


Figure 4: DSC of Optimized Formulation

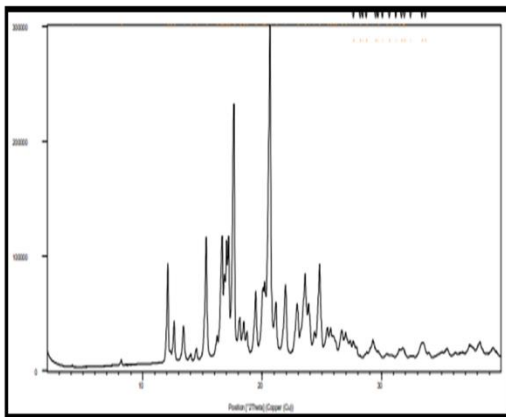


Figure 5: XRD of Pure Drug (Aprepitant)

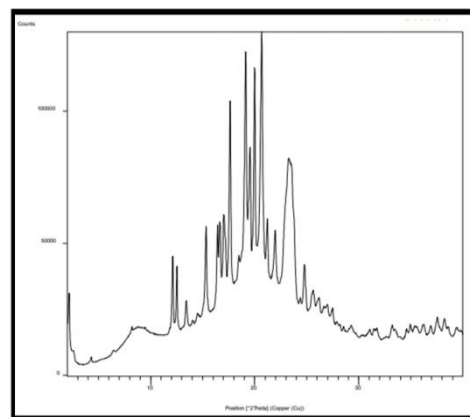


Figure 6: XRD improved formulation

Pre-compression Constraints

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 5)

Table 5: 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: (Fig-7)

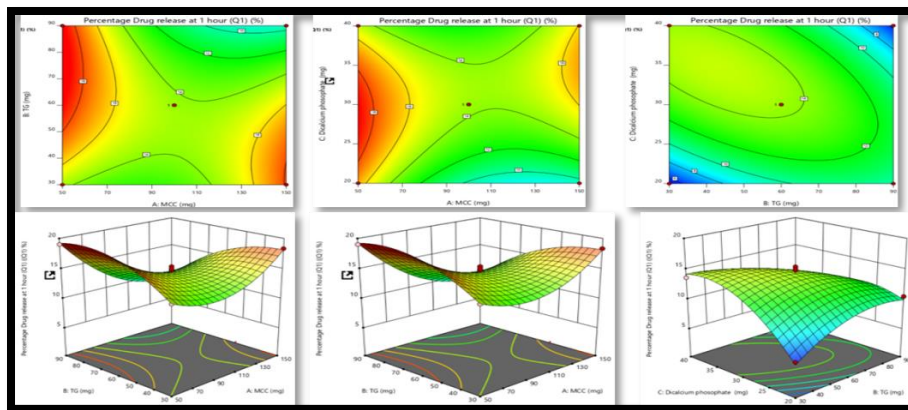


Figure 7: Effect of independent variables on dependent variables of Percentage Drug Release at 1 hour (Q1)

A significant model is indicated by an F-value of 23.59. The likelihood of a noise-induced F-value this large is a mere 0.02%. Significant model terms are indicated by p-values that are <0.0500. Here, all terms are important model terms. Lack of fit has an F-value of 0.50, which means it is not statistically significant when associated with pure error.

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(Fig 8):

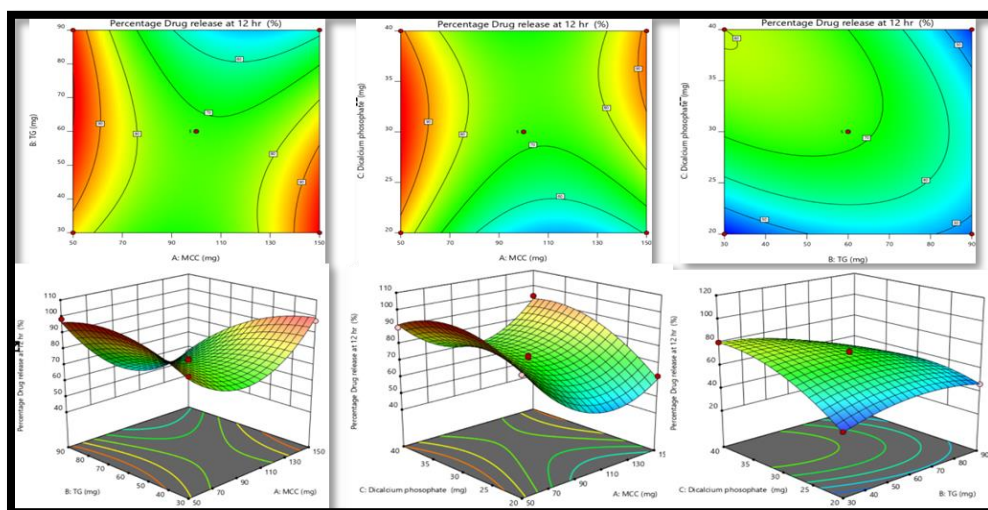


Figure 8: Effect of independent variables on dependent variables of Percentage Drug release at 12 h

An F-value of 110.12 indicates a significant model. An F-value with this high of a likelihood could only occur by chance. Model terms that are considered significant are denoted by p-values less than 0.0500. Key terms in this model are A, B, C, AB, AC, BC, and A², B², and C². The F-value of 2.25 indicates that there is no discernible difference between it and the pure error.

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)(Fig-9)

The model has a statistically significant F-value of 57.69. Only by coincidence could there be an F-value with this high of a likelihood. Model terms with p-values less than 0.0500 are regarded as important. This model's key terms are A, B, C, AB, AC, BC, as well as A², B², and C². When the values are higher than 0.1000, the model terms are considered to be unimportant. Reducing the number of superfluous model terms (apart from those needed to preserve hierarchy) will improve the performance of your model.

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

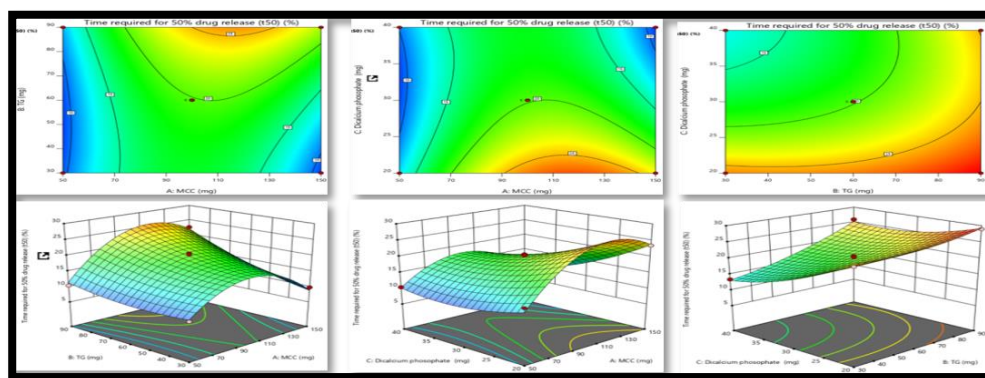


Figure 9: Effect of independent variables on dependent variables of Time required for 50% drug release (t₅₀)

Evaluation Tests

Color, smell, and shape were among the several physiochemical qualities tested for in each of the seventeen formulations (AF1–AF17). The outcomes displayed that all the formulations were round, flat, and odorless, with a cream color. As shown in Table 6, the results were tabulated.

Table No 6: Aprepitant post-compression analysis

Formulation codes	Weight variation(mg)	Hardness (kg/cm ²)	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
AF6	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(Fig-10): First, it was done in 0.1N HCl for 2 hours. For the subsequent twenty-four hours, the medium was substituted with 6.8 pH simulated intestinal fluid. 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 drug was released 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 augmented, the drug release from the preparations diminished. The optimized formulation table reveals that the drug 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.

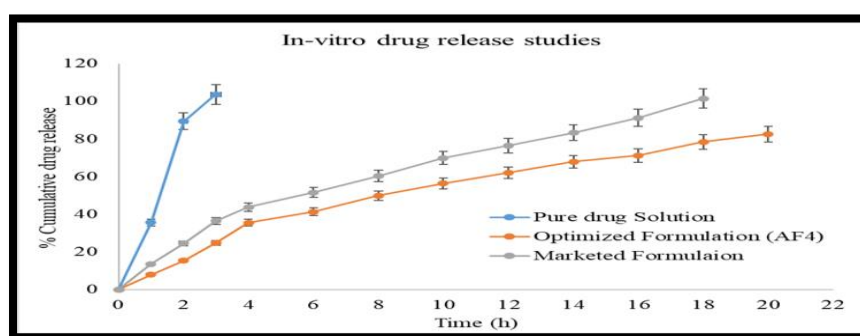


Figure 10: Comparison of in-vitro drug release profile

4. 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. A new effort to extract gum from plants, specifically tamarind seed, is detailed in this research. The Aprepitant SR tablets were made using the obtained TG powder as a binder in varying concentrations. The post-compression specifications were within the permissible official bounds. AF4 was chosen as the best formulation after an in-vitro release study. The stability investigations confirmed that the formed tablet formulation remained unchanged, thereby confirming that the tablet was stable.

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