Formulation And Characterization Of Mucoadhesive Tablets For Prolonged Drug Release

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Abstract
This study focuses on the formulation and evaluation of atenolol mucoadhesive tablets, aiming to enhance drug absorption and bioavailability. Hypertension, affecting a significant portion of the adult population, can lead to severe cardiovascular conditions. Atenolol, a beta-blocker, effectively manages hypertension and other heart-related issues. The study used mucoadhesive polymers like hydroxypropyl methylcellulose (HPMC), tamarind gum, and badam gum to prepare the tablets via direct compression. The formulation process included optimizing drug release kinetics and mucoadhesive strength. Pre-compression parameters such as angle of repose, bulk density, and compressibility index were evaluated. Post-compression evaluations covered organoleptic properties, hardness, friability, weight variation, and in-vitro dissolution. Stability studies followed ICH guidelines to ensure long-term efficacy and safety. Key findings include consistent drug content, adequate hardness, and desirable swelling behavior. The optimized formulation demonstrated prolonged drug release and significant mucoadhesive properties, confirming its potential for improved therapeutic applications. Statistical analyses validated the formulation's consistency and reliability.

Key Words: Hypertension, Mucoadhesion, Atenolol, Box-Behnken, Tamarind Gum

Introduction:
Hypertension is not a chronic disease, but it is independently associated with cardiovascular diseases in the elderly. Although it constitutes one of the most frequent factors for cerebrovascular diseases, it is an amendable to modifications factor. Hypertension, or elevated arterial blood pressure, is a substantial public health problem, affecting 25% of the adult population in industrialized societies. This disorder is a major risk factor for many common causes of morbidity and mortality including stroke, myocardial infarction, congestive heart failure, and end stage renal disease [1].
It is estimated that approximately 1% of patients with hypertension will at some point, develop a hypertensive crisis, and it has been estimated that hypertensive emergencies account for 25% of all patient visits to the medical section of an emergency department (ED), with hypertensive emergencies detected in one-third of these cases. Before the advent of antihypertensive therapy, this complication occurred in up to 7% of the hypertensive population. Men are affected twice as frequently as women. Among specific situations such as postoperative hypertensive crisis, the incidence varies depending on the population being reported; however, such a crisis is reported more frequently with immediate postoperative bypass surgical graft patients. Also, preclampsia (pregnancy-induced hypertension with significant proteinuria 300 mg/l or 500 mg/24-h) occurs in approximately 7% of all pregnancies, with most of them being null-gravidas [2].
Today many different terms have been applied to define acute severe elevations in BP, and the current terminology is somewhat confusing. The 2003 Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) defines “hypertensive crisis” as a systolic BP (SBP) 179 mmHg or a diastolic BP (DBP) 109 mmHg with or without acute target organ involvement, while it is important to define a true emergency from urgency [3]. Blood pressure must be tightly regulated to permit uninterrupted perfusion of all vital organs. For example, even transient interruption in blood flow to the brain will cause loss of consciousness, and longer interruptions will result in death of unperfused tissues. Conversely, higher pressures that deliver flow exceeding metabolic demand provide little or no metabolic gain but increase damage to blood vessels and organs. These consider actions dictate the normal ranges of blood pressure [4].
Atenolol is a medication primarily used to treat high blood pressure (hypertension) and certain heart conditions. It belongs to a class of drugs known as beta-blockers. Atenolol works by blocking the effects of the hormone epinephrine (adrenaline), which can lead to a reduction in heart rate and blood pressure. This, in turn, helps to decrease the workload on the heart and can be beneficial for individuals with various cardiovascular issues.
Some common uses of atenolol include:

- Hypertension (High Blood Pressure): Atenolol is often prescribed to lower blood pressure and help prevent complications associated with hypertension, such as heart attacks, stroke, and kidney problems.

- Angina (Chest Pain): It can be used to manage angina pectoris, a condition where the heart muscle doesn't receive enough blood and oxygen, causing chest pain.
- Arrhythmias: Atenolol may be used to manage certain irregular heart rhythms (arrhythmias) or to prevent them in people with conditions like atrial fibrillation.
- Preventing Migraines: In some cases, it is prescribed to reduce the frequency and severity of migraines.

A mucoadhesive tablet is a type of pharmaceutical formulation designed to adhere to the mucosal surfaces of the body, such as those found in the oral cavity, the gastrointestinal tract, the rectum, the eye, and the vaginal and nasal cavities. The primary goal of a mucoadhesive tablet is to prolong the contact time of the drug with the mucosal surface, thereby enhancing drug absorption, improving the bioavailability of the medication, and providing a more localized treatment.

The formulation of a mucoadhesive tablet involves selecting an appropriate active pharmaceutical ingredient (API) and mucoadhesive polymers like hydroxypropyl methylcellulose or carbopol, which ensure prolonged mucosal contact and enhanced drug absorption. Excipients such as plasticizers, fillers, and binders are added to optimize the tablet's physical properties. Techniques like direct compression are employed based on API and excipient characteristics. The tablet's effectiveness is confirmed through pre-formulation studies, swelling index measurements, and mucoadhesion strength tests. All these evaluation parameters ensure the safety, efficacy and adhesiveness, ensuring it meets therapeutic needs and patient comfort.

The materials utilized in this study encompassed various components crucial for the development of mucoadhesive tablets of atenolol. Atenolol, a beta-blocker drug renowned for its cardiovascular applications, was acquired with a confirmed purity level from a reputable source. To impart mucoadhesive properties to the tablets, a selection of mucoadhesive polymers including hydroxypropyl methylcellulose (HPMC), tamarind gum, and badam gum were procured, each with distinct molecular characteristics. Additionally, plasticizers such as polyethylene glycol (PEG) were obtained to enhance the flexibility and cohesiveness of the formulations. Complementary excipients like lactose, magnesium stearate, and talc were sourced to aid in the tablet manufacturing process.

The preparation of mucoadhesive tablets involved a systematic formulation design, where concentrations of atenolol, mucoadhesive polymers, and plasticizers were varied to optimize both drug release kinetics and mucoadhesive strength. Subsequently, tablets were compressed utilizing a direct compression method under controlled conditions of compression force and dwell time. The resultant tablets were subjected to rigorous characterization including assessment of drug content uniformity, mucoadhesive strength, swelling behaviour, and in vitro drug release profiles. Statistical analyses, employing appropriate experimental designs and software, were conducted to elucidate significant differences among formulations. Through this comprehensive approach, the study aimed to provide valuable insights into the formulation and evaluation of mucoadhesive tablets of atenolol for potential therapeutic applications[5-10].

Materials and Methods:

Materials: Atenolol was obtained as a gift sample from Vapi Care Pharma Limited, Vapi, Gujarat. HPMCK was obtained from the Coloron Asia Ltd. Goa, India. All other chemicals were of analytical reagent grade and were procured from local supplier.

Methods:

Extraction of Tamarind Gum:

extraction process of tamarind gum, also known as tamarind seed gum or tamarind kernel powder, begins with the collection of tamarind seeds from ripe tamarind pods. These seeds are then carefully cleaned to remove any adhering fruit pulp, dirt, or debris. Once cleaned, the seeds undergo a drying process to reduce their moisture content, typically through sun drying or mechanical drying at controlled temperatures. Following drying, the outer seed coat or husk is removed in a process called decortication, often achieved through mechanical methods like milling or grinding. The decorticated seeds are further processed into a fine powder known as tamarind kernel powder (TKP) or tamarind seed gum through milling or grinding.

Then 20g of powder is then subjected to extraction using solvents like water(200ml) or alcohol(200ml) to dissolve the gum present in the powder. Slurry was then poured into 800ml of boiling distilled water containing citric acid. The solution was boiled for 20 min with stirring in a water bath. The resulting solution undergoes filtration to remove insoluble impurities, yielding a clear gum solution. Depending on the desired purity level, the filtered gum solution may undergo additional purification steps such as centrifugation or precipitation to remove any remaining impurities. The purified gum solution is then dried to remove the solvent and obtain the tamarind gum in powdered form. Finally, the dried gum powder is sieved to achieve the desired particle size and quality [11].

Extraction of Badam Gum:

Badam gum, extracted from the bark of almond trees (Prunus amygdalus), is obtained through a simple but systematic process. Initially, incisions are made in the bark, causing the tree to exude a viscous fluid. This exudate is allowed to

harden into a gum-like substance over time. Once solidified, the gum is collected manually and then cleaned to remove impurities such as bark residues and dirt. The purified gum is dried thoroughly, ground into a fine powder, and stored in airtight containers to maintain its quality. This natural polymer is valued for its mucoadhesive and biocompatible properties in pharmaceutical applications.

Pre-Compression Parameters:

Angle of Repose: By measuring the resistance to movement between particles, the angle of repose can be used to evaluate the frictional forces inside loose powder. The funnel method is used to calculate this angle (θ). A funnel is set at a preset height above graph paper and granulate is poured until the conical pile formed touches the funnels tip.
The angle of repose is calculated using the formula:

Tan θ= h/r
where h is the height and
r is the radius of the conical pile

Bulk Density: Bulk density (ρb) is determined by pouring the granulate into a 10 ml graduated glass cylinder. The excess granulate shall be leveled out with a spatula, and the bulk density calculated by dividing the weight of the granulate into its volume.

Bulk density = weight of sample in gram/volume occupied by the sample

Tapped Density: A graduated glass cylinder holding a known weight of granulates is tapped for a predetermined amount of time to measure the tapped density (ρt). The weight of the granules is divided by the smallest volume of granules following tapping to get the taped density.
The tapped density is calculated using the formula:

Tapped Density= weight of sample in gram/ tapped volume

Compressibility index (CI) / Carr's index: In pharmaceutics, the Carr's index is often used to determine a powder's flowability. A Carr's index of 15 or below is thought to indicate good flowability, whereas one above 25 is thought to indicate poor flowability. The compressive strength of powder is measured by the Carr's index.
It's calculated by a formula:

% Carr's index = (Tapped Density – Bulk Density ÷ Tapped Density) × 100

Hausner's ratio: Hausner's ratio is a number that is correlated to the flow ability of a powder. It is measured by ratio of tapped density to bulk density.

Hausner's ratio = (Tapped density ÷ Bulk Density)

Melting Point: The melting point of a substance is defined as the temperature at which it transitions from a solid to a liquid state under atmospheric pressure. At this temperature, the solid and liquid phases of the substance exist in equilibrium. The melting point is a fundamental physical property and is unique to each pure substance. Atenolol was carefully positioned inside a capillary tube. One end of the capillary tube was sealed using a Bunsen burner. The sealed capillary tube was inserted securely into the heating block. Temperature was incrementally raised while observing changes. Initial and final melting points were noted during the observation. The apparatus was allowed to cool before any further steps. If needed, the process was repeated for accuracy. The average melting point was calculated and juxtaposed against known values for purity assessment[11-14].

Construction of standard calibration curve: Solutions of atenolol concentration ranging from 10-60 µg/ml is prepared with distilled water. The absorbance of these solution was measured at 275 nm in 1 cm cell against a reagent blank (distilled water) using Shimatzu UV/Visible Double Beam Spectrophotometer. And peak was measured at 265 nm[15].

Box-Behnken experimental design:
The Box-Behnken design is an independent quadratic design in that it does not contain an embedded factorial or fractional factorial design. In this design the treatment combinations are at the midpoints of edges of the process space and at the center. These systems are rotatable, or close to rotatable, and each factor requires three levels. Compared to central composite designs, the designs are limited in their ability to block orthogonal blocks.[16-17].

Table 1: Levels of variables for optimization

Factor	Name	Unit	Minimum	Maximum
A	Tamarind gum	mg	25	75
B	Badam gum	mg	25	75
C	HPMC K15	mg	12	50

Table 2: Composition of experimental batches of tablets

Std	Run	Tamarind gum	Badam gum	HPMC K50	Hardness (kg/cm^2)	Dissolution (%)	Swelling Index (%)
12	1	50	75	50	6.398	91.40	1.250
9	2	50	25	12	6.744	86.64	1.306
14	3	50	50	31	6.918	89.16	1.386
1	4	25	25	31	7.059	90.60	1.201
2	5	75	25	31	6.278	94.56	1.152
3	6	25	75	31	6.445	88.60	1.085
4	7	75	75	31	6.033	90.08	0.983
11	8	50	25	50	6.244	94.76	1.540
13	9	50	50	31	5.682	93.86	1.322
7	10	25	50	50	7.146	92.30	1.295
5	11	25	50	12	6.234	95.70	1.333
15	12	50	50	31	6.991	91.60	1.242
6	13	75	50	12	7.012	94.44	1.275
8	14	75	50	50	6.365	96.16	1.952
10	15	50	75	12	6.883	92.46	1.899

Preparation of Atenolol Mucoadhesive Tablet:

- Weigh drug, polymer, and excipients accurately according to the batch formula.
- Mix the drug thoroughly with mannitol using a stainless-steel spatula on butter paper.
- Combine all ingredients (except lubricant) in the order of ascending weights.
- Blend the mixture for 10 minutes in an inflated polyethylene pouch.
- Add Magnesium stearate as the lubricant.
- Mix the blend again for 2 minutes.
- Weigh 150 mg of the prepared blend for each formulation.
- Perform final compression at a pressure of 3.5 tons.
- Maintain the turret speed at 2 rpm to form bilayer tablets.

Post Compression Parameters:

Organoleptic characters: The colour, odour, and size of the tablet were determined by visual inspection, olfactory assessment, and physical measurement, respectively.

Procedure: 10 tablets were visually observed.

Thickness:

The thickness of the tablet was measured to determine the uniformity of size and shape by using Vernier calliper.

Hardness:

A Monsanto hardness tester was used to measure the tablets' hardness. On the testing platform, tablets were arranged one by one and compressed until they broke. The hardness value of each tablet was determined by measuring the force necessary to break it. This technique made it possible to measure the tablets' resistance to mechanical stress precisely.

Friability:

To determine tablet friability, first weigh a sample of tablets and record their initial mass. Place the tablets in a friabilator drum and rotate it at 25 rpm for 100 rotations. After rotation, remove and dedust the tablets to eliminate any loose particles.

Weigh the tablets again and record the final mass. Calculate the percentage weight loss using the initial and final weights. Tablets pass the friability test if the weight loss is less than 1%.

Weight variation:
Twenty tablets were weighed individually, and their average weight was determined. Each tablet's weight was then compared to this average. Compliance with the standards in Table 1 of the Indian Pharmacopoeia (IP) was necessary. According to these standards, no more than two tablets could deviate from the average weight by more than the specified percentage. Furthermore, no tablet could deviate by more than twice this percentage limit. This procedure ensured adherence to the IP guidelines for weight uniformity of tablets.

Table. 3: Uniformity of Weight and Percentage Deviation

S. No.	Average Weight of Tablet (mg)	Percentage Deviation (%)
1	80 or less	10%
2	80-250	7.5%
3	>250	5%

Wetting time and water absorption ratio:
A folded tissue paper was placed in a small petri dish with a diameter of 6.5cm, containing 6 ml of water. A pre-weighed tablet was positioned on the paper, and measurements were taken to determine the total wetness required. The time taken for the water to reach the upper surface of the tablet was recorded as the wetting time. The water absorption rate was calculated using the provided equation.

$$R = 100\frac{Wa - Wb}{Wb}$$

Where,
Wa - Weight of tablet before wetting.
Wb - Weight of tablet after wetting [18-21].

In- vitro dissolution test: The dissolution test was performed using a dissolution apparatus USP Type II with a paddle and 6.8 pH phosphate buffer solution (PBS) as the dissolution medium at 50 rpm and 37± 0.5°C. A 5 ml of the sample was withdrawn periodically as suitable time interval and the volume replaced with an equivalent amount of the same dissolution medium. The samples were analyzed spectrophotometrically at 265 nm.

Swelling studies: The extent of swelling was measured in terms of percentage weight gained by the tablet. One tablet from each formulation was weighed and kept in petri dish containing 15 ml of 0.1 N HCl. At the end of specified time intervals tablets were withdrawn from petri dish and excess buffer blotted with tissue paper and weighed. The percentage of weight gained by the tablet was calculated.

Stability Studies:
Conducting a stability study for atenolol mucoadhesive tablets involves rigorous assessment to ensure the medication maintains its quality over time. The study typically spans 6 months to 2 years and follows guidelines outlined by the International Conference on Harmonisation (ICH). Samples are prepared according to the finalized formulation and packaging protocol and subjected to various storage conditions, including long-term, accelerated, and intermediate testing. Throughout the study, parameters such as physical appearance, chemical composition, microbial content, mucoadhesive properties, and dissolution characteristics are monitored at predetermined intervals. Data collected from these analyses are meticulously recorded and analyzed to identify any significant changes over time. Findings are compiled into a comprehensive report that ensures compliance with regulatory requirements set forth by relevant authorities. This systematic approach guarantees the medication's stability and guides adjustments to formulation or storage conditions if needed, ensuring its efficacy and safety for patients [21-22].

Result and Discussion:
Organoleptic properties:

Table. 4: Organoleptic properties of Atenolol:

S. No.	Organoleptic Characteristics	Result
1	Colour	White to off-white Crystalline powder
2	Odour	Odourless
3	Taste	Slightly bitter
4	Nature	Crystalline powder

Table. 5: Physical Evaluation of Atenolol Mucoadhesive Tablets:

Formulation Code	Angle of Repose (θ)	Bulk Density (gm/ cm3)	Tapped Density (gm/ cm3)	Hausner's Ratio (HR)	Carr's Index (CI)
F1	27.3±0.5	0.453±0.13	0.53±0.02	1.16±0.01	14.40±0.26
F2	27.84±0.49	0.453±0.02	0.53±0.01	1.18±0.02	15.5±0.37
F3	29.17±0.18	0.50±0.05	0.56±0.02	1.13±0.04	13.31±0.19
F4	26.24±0.41	0.46±0.18	0.53±0.01	1.16±0.01	14.26±0.23
F5	28.31±0.92	0.48±0.11	0.56±0.02	1.16±0.02	14.29±0.16
F6	28.10±0.54	0.47±0.16	0.55±0.01	1.16±0.06	13.88±0.24
F7	25.57±0.89	0.49±0.06	0.57±0.01	1.15±0.05	13.43±0.15
F8	28.3±0.62	0.41±0.01	0.52±0.01	1.26±0.01	21.05±0.14
F9	24.11±0.43	0.41±0.02	0.51±0.02	1.25±0.02	20.69±0.16
F10	25.16±0.85	0.45±0.07	0.53±0.13	1.19±0.08	16.16±0.25
F11	25.16±0.54	0.43±0.12	0.53±0.16	1.22±0.04	18.58±0.34
F12	26.61±0.70	0.45±0.02	0.55±0.15	1.21±0.01	17.87±0.49
F13	28.14±0.22	0.50±0.14	0.57±0.02	1.15±0.02	13.28±0.27
F14	27.37±0.45	0.45±0.03	0.52±0.01	1.14±0.04	12.86±0.18
F15	28.32±0.64	0.45±0.12	0.52±0.02	1.16±0.01	14.47±0.52

Melting point of Atenolol: The melting point of atenolol is 147^0C determined through Melting point apparatus. This physical property is important for identifying and characterizing the compound, as well as for ensuring its purity and stability in pharmaceutical formulations.

Table. 6: Calibration Curve of Atenolol in Methanol:

S. No.	Concentration (µg/ml)	Absorbance (265 nm)
1	0	0
2	10	0.052
3	20	0.1
4	30	0.156
5	40	0.205
6	50	0.251
7	60	0.299

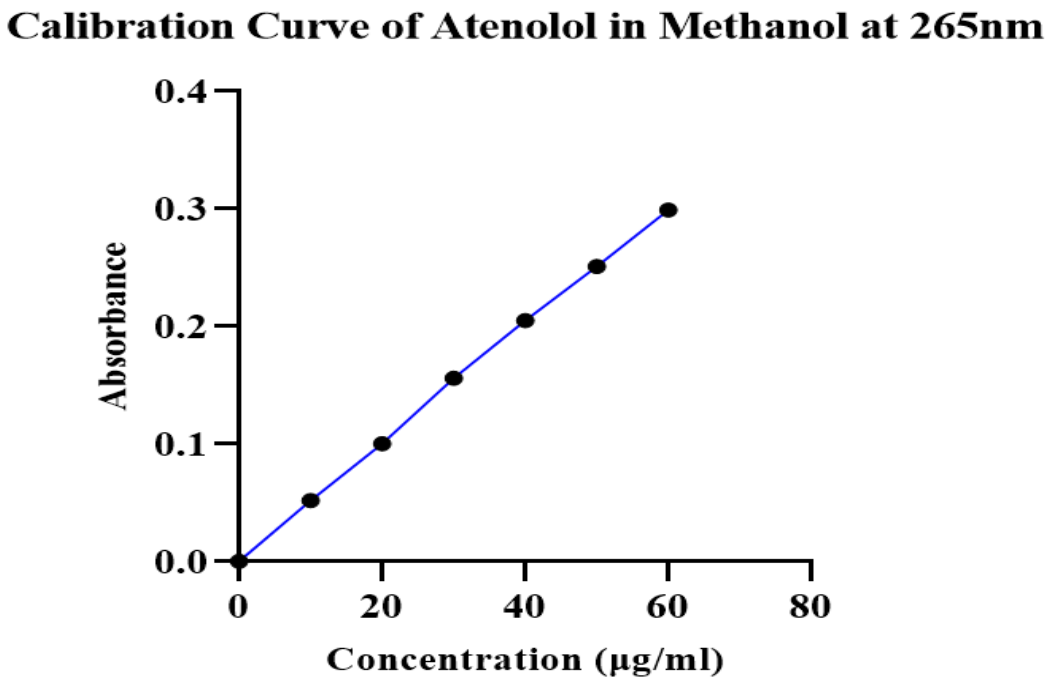

Fig. 1: Calibration Curve of Atenolol

Table. 7: Physical Evaluation of Atenolol Tablets:

Formulation Code	Weight Variation	Thickness (mm)	Hardness (Kg/Cm^2)	Swelling Index (%)	Dissolution (%)	Friability (%)
F1	149.5	3.11±0.03	6.398±0.33	1.250±2.3	91.40±	0.62±0.02
F2	151.2	3.12±0.01	6.744±0.25	1.306±1.8	86.64±	0.74±0.03
F3	150.9	3.11±0.04	6.918±0.64	1.386±2.6	89.16±	0.81±0.01
F4	148.3	3.10±0.06	7.059±0.30	1.201±2.5	90.60±	0.81±0.01
F5	148.8	3.13±0.02	6.278±0.28	1.152±2.8	94.56±	0.44±0.01
F6	150.2	3.11±0.01	6.445±0.35	1.085±3.5	88.60±	0.52±0.04
F7	153.1	3.10±0.03	6.033±0.40	0.983±4.4	90.08±	0.61±0.02
F8	158.7	3.20±0.05	6.244±0.46	1.540±3.0	94.76±	0.68±0.01
F9	149.7	3.10±0.04	5.682±0.24	1.322±2.5	93.86±	0.72±0.04
F10	150.3	3.11±0.01	7.146±0.36	1.295±1.5	92.30±	0.29±0.01
F11	148.6	3.17±0.01	6.234±0.55	1.333±2.0	95.70±	0.38±0.01
F12	152.6	3.12±0.04	6.991±0.64	1.242±2.5	91.60±	0.69±0.03
F13	153.3	3.14±0.06	7.012±0.30	1.275±1.0	94.44±	0.45±0.04
F14	150.6	3.11±0.02	6.365±0.28	1.952±3.5	96.16±	0.51±0.01
F15	150.4	3.17±0.01	6.883±0.35	1.899±2.6	92.46±	0.56±0.01

In vitro dissolution studies:

Table. 8: The in vitro drug release studies of Atenolol tablets

Formulation Code	2hrs	4hrs	6hrs	8hrs	12hrs	16hrs	18hrs	24hrs
F1	33.42	41.12	51.28	71.76	80.76	84.76	87.20	91.40
F2	24.81	43.21	53.71	64.55	74.55	80.55	83.16	86.64
F3	26.61	38.97	48.95	59.16	69.16	78.16	83.28	89.16
F4	24.19	32.11	57.27	68.56	77.56	82.56	85.96	90.60
F5	21.98	35.38	49.06	61.60	70.60	84.06	88.16	94.56
F6	18.64	29.26	42.28	54.08	65.28	78.28	82.48	88.60
F7	21.51	39.96	49.44	61.44	71.44	80.44	85.56	90.08
F8	19.82	35.72	47.32	58.28	69.28	82.28	87.00	94.76
F9	15.67	24.50	37.2	48.20	60.20	73.20	82.20	93.86
F10	20.87	32.72	48.86	61.00	72.00	86.00	90.00	92.30
F11	18.75	37.46	49.9	60.90	70.90	84.90	90.10	95.70
F12	24.46	38.65	51.3	62.30	71.30	85.03	88.90	91.60
F13	24.19	33.24	49.75	62.00	70.00	85.00	90.20	94.44
F14	23.75	36.51	49.16	61.16	71.16	85.02	89.12	96.16
F15	24.14	37.98	51.12	63.12	72.12	86.12	88.32	92.46

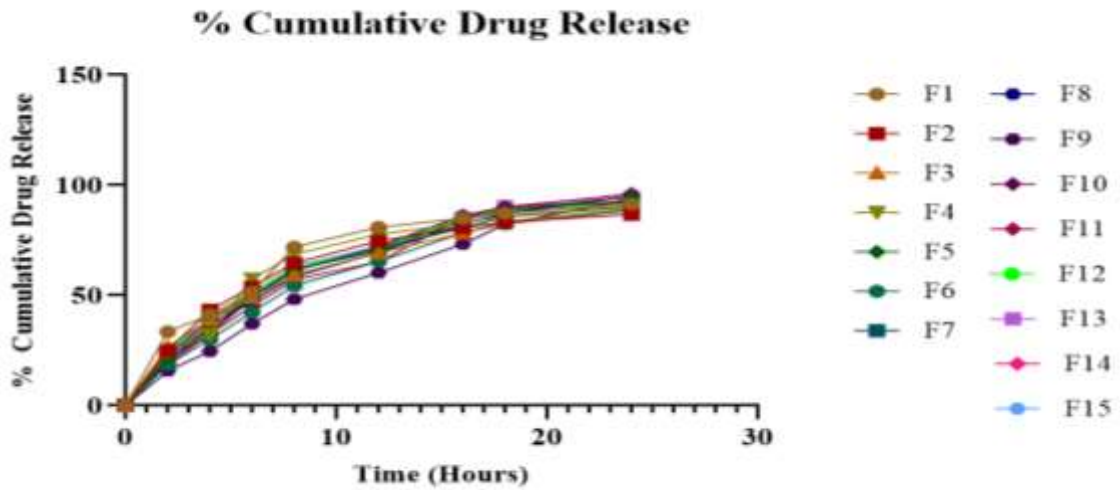

Fig. 2: Cumulative Percentage Drug release of Atenolol

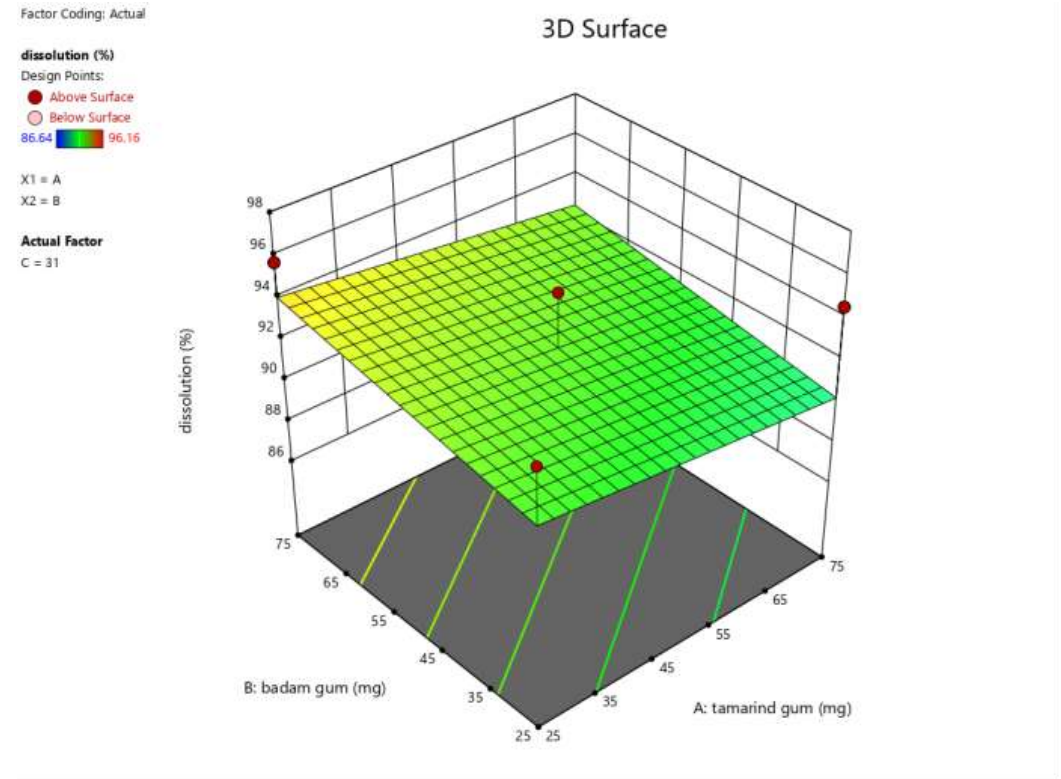

Fig. 3: The three-dimensional map shows how the total amounts of super-disintegrates (X1) and (X2) affect the Dissolution

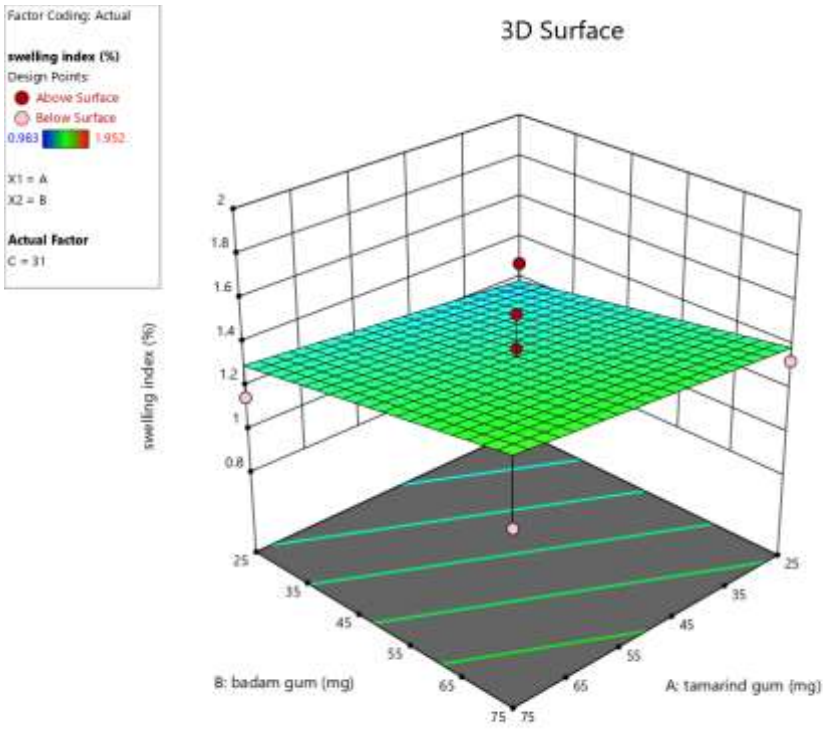

Fig. 4: The three-dimensional map shows how the total amounts of super-disintegrates (X1) and (X2) affect the Swelling Index

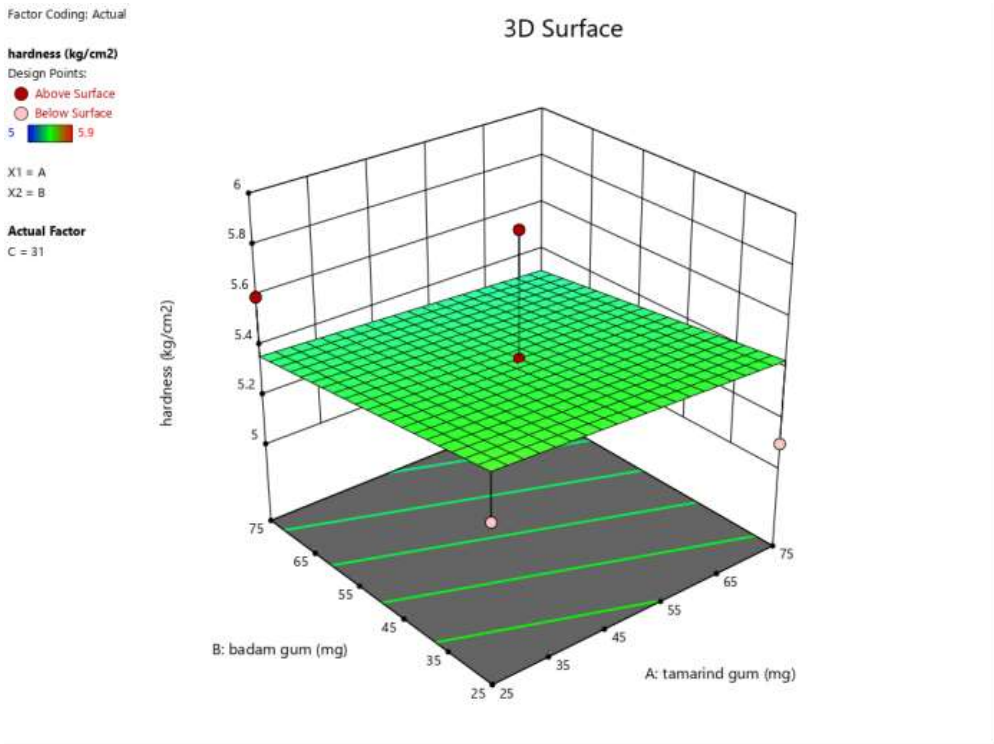

Fig. 5: The three-dimensional map shows how the total amounts of super-disintegrates (X1) and (X2) affect the Hardness

Conclusion

This study successfully formulated a mucoadhesive tablet of atenolol, demonstrating significant potential in enhancing bioavailability and providing sustained drug release. Various polymers were evaluated for their mucoadhesive properties, and the optimal formulation was identified based on adhesion strength, swelling index, and drug release profile. The in vitro dissolution studies revealed a controlled release pattern, maintaining therapeutic drug levels over an extended period. The application of Box-Behnken design successfully optimized the formulation of chewable tablets using direct compression. The optimized mucoadhesive tablet exhibited strong mucosal adhesion, ensuring prolonged retention at the site of absorption, which is expected to enhance patient compliance and therapeutic outcomes. These findings suggest that the mucoadhesive tablet formulation of atenolol could be a promising alternative to conventional dosage forms, offering improved bioavailability and consistent drug delivery**.**

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