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Original Article

Development and Evaluation of Gastroretentive Bioadhesive Tablet of Atenolol Using a Naturally Occurring Biodegradable Polymer

Soji Soman[1], Aysha Padinhar Basheer[2], Geethu Mol[2], Luthfa Ahamed Muneer[2], Mariyammath Rafeeqa Khazi Abdul Rahiman[2], Gasper Fernandes[1], Srinivas Mutalik[1,*]

[1]Department of Pharmaceutics, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, Karnataka, INDIA.
[2]Department of Pharmaceutics, Malik Deenar College of Pharmacy, Kasaragod, Kerala, INDIA.

ABSTRACT

Aim: Using atenolol as a model active pharmaceutical and galactomannan from the seeds of Trigonella foenumgraecum as a mucoadhesive polymer, an effort was made to develop a gastroretentive bioadhesive floating delivery system to improve the residence time in the stomach. **Materials and Methods:** Different formulations were made with Hydroxypropyl Methyl Cellulose (HPMC) and galactomannan. Galactomannan was chosen because of its exceptional swelling properties in aqueous environments. In this investigation, citric acid and sodium bicarbonate were utilized as gas-producing components. Pre- and postcompression evaluations were performed on the manufactured tablets. The floating properties as well as the atenolol release pattern were investigated. **Results:** The extracted polymer was characterized using various techniques and found to be similar to literature. The results from GC analysis showed a residual acetone content of 0.127 ppm, indicating that the extracted polymer is safer to use in the formulation of gastroretentive tablets. The physicochemical properties of the manufactured tablets were satisfactory in terms of swelling index, release characteristics, and buoyancy pattern. All of the manufactured batches had adequate *in vitro* buoyancy. The gastroretentive tablet exhibited axial and radial swelling throughout the *in vitro* buoyancy test. According to the testing, the formulation remained buoyant for approximately 8 to 12 hr. **Conclusion:** According to the results of the evaluation, the manufactured tablet has a pleasing look, is heat stable, and is therapeutically efficient. F3 was determined to be the optimal formulation based on the data collected.

Keywords: Atenolol, Galactomannan, Gastroretentive floating bioadhesive tablets, HPMC, Natural polymer.

Correspondence:
Dr. Srinivas Mutalik
Principal and Professor, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Research, Manipal-576104, Karnataka, INDIA.
Email: ss.mutalik@manipal.edu

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INTRODUCTION

The most accepted drug delivery technique is oral administration since it is simple to use and well tolerated by patients. The two ideal characteristics that an ideal drug delivery system should process are as follows: it must release the medication precisely at the target site, and the system should only require a single or less repeated dose over the course of therapy. Over time, oral drug administration methods have advanced from instantaneous to target-specific drug delivery.[1,2] The property of a Floating Drug Delivery System (FDDS) of less density compared to gastric fluid allows the system to float on the surface of the gastric fluid, which can cause enhanced delivery of medication to the stomach. The mucoadhesive nature of particular polymers makes them an agent for bioadhesive drug delivery for long-term site-specific drug targeting.[3]

The primary drawback of the floating system is that it works best when the stomach is completely filled with gastric fluid. The mucous produced by the mucosal lining can cause the detachment of the system from the stomach wall, which results in stomach emptying together with its components. This drawback can be overcome by designing Floating Bioadhesive Systems (FBSs), which can closely attach to the mucous lining in the stomach wall.[4] Hence, FBSs have the benefit of increasing medication gastroresidence time over standard FDDS. The gastroresidence period of medications is greatly extended by gastroretentive FBS systems since they stay in the gastric area for several hours. Reduced drug loss and improved solubility for medications that are less soluble under high pH environments are among

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the benefits of prolonged stomach retention. Moreover, it can be used for local administration of medication to the proximal small intestine and stomach. With novel treatment options and significant patient advantages, gastroretention contributes to the greater accessibility of new drugs. It is possible to accomplish the regulated gastric residence of tablets by mucoadhesion, floating, expansion, or by simultaneously administering drugs that interrupt stomach emptying.[5,6] FBSs may be created by combining bioadhesive polymers with standard FDDSs.[7] The prolonged holding time of Floating Bioadhesive Systems (FBSs) in the gastric area significantly increases the retention time of drugs in the gastric region, which results in the enhanced bioavailability of the formulation.[8]

Hydrocolloids exhibiting enhanced swellability and gel-forming capacity are commonly utilized in floating delivery systems. To accomplish the desired swelling as well as drug release characteristics, a variety of polymers (HPMC) are utilized. After being exposed to an aqueous solution, these polymers take up water and form a gel that mediates drug release.[9] The number of methoxy groups is directly proportional to the viscosity of the mass formed during gel formation.[10]

Natural polymers such as chitosan, guar gum and pectin are employed as mucoadhesive polymers because they are inexpensive, safe, stable, and gel-forming in nature. Galactomannans have a variety of novel and economically valuable characteristics. This biomaterial is the second most abundant type of storage polysaccharide in plants, and it has been discovered in the endosperm cell wall in the seeds of different plants. Galactomannans are also employed in various forms for human consumption.[11,12] They are versatile materials with several uses due to their various physicochemical characteristics. They are good viscosity modifiers and thickeners in simple aqueous systems, as well as brilliant emulsion stabilizers. Since they are nonhazardous, they can be utilized in the pharmaceutical, biomedical, and food sectors.[13] Several studies over the last decade have proven the benefits of galactomannan in the production of solid dosage forms in traditional as well as controlled formulations, notably tablets and capsules.[14,15] The galactomannan mucoadhesive polymer isolated from *Trigonella foenum-gracum L.* seeds has a high mucilage content. It is employed in the pharmaceutical industry as a binding, dissolving, and mucoadhesive gelling agent.[16]

Antihypertensive medicines are a group of pharmaceuticals used to treat hypertension. Atenolol is a beta-adrenergic receptor blocker[17-19] commonly employed for the therapy of hypertension as well as angina pectoris. It is employed for the therapy of hypertension alone or in conjunction with other antihypertensive medications, such as thiazide diuretics. Due to inadequate jejunal permeability and absorption levels in humans, atenolol shows only 50% oral bioavailability and the rest is eliminated intact in stool. As atenolol exhibits a short elimination half-life of 3-4 hr and little to no hepatic first-pass metabolism, the development of gastroretentive tablets to increase its oral bioavailability is encouraged.[18] Atenolol's absorption site is the stomach; making the drug retain within the stomach for a longer period improves the medication efficiency and reduces dosage requirements.[20]

Xanthan gum, guar gum, and chitosan polymers are generally used as natural polymers for the formulation of FBSs. Many studies have shown that the physiochemical properties, morphology, release behaviour, dosage form shape, and particle size of natural polymers frequently affect the pattern of drug release. Natural polymers have a benefit in that they have been shown to be safe and biocompatible. However, there are no reports available on using mucilage from *Trigonella foenum graecum* seed as a mucoadhesive agent in the development of FBSs with atenolol as the active ingredient. The aim of this study was to fabricate FBS with a specific blend of flotation along with bioadhesion to extend the duration of gastric residence with atenolol as a model medicine and galactomannan polymer from Trigonella foenumgraecum seeds as a mucoadhesive biopolymer.

MATERIALS AND METHODS

Trigonella foenum graecum seeds were acquired from Kasaragod, Kerala State, India. Atenolol was given as a gift sample from Sangrose Laboratories, Alapuzha, India. Yarrow chem., Mumbai, provided HPMC K-4 M, lactose, citric acid, and sodium bicarbonate. The chemicals utilized in this experiment were all of analytical grade.

Separation of Galactomannan from *Trigonella foenum-graecum* L. Seeds

Trigonella foenum-graecum L. seeds (200 g) were soaked in 1.5 L of water for 24 hr, and then the mixture was boiled until slurry formed. The formed slurry was then cooled and kept aside for 24 hr to settle any remaining undissolved particles. The upper clear part of the solution was decanted and heated at 60°C in a water bath and made up to one-third of the actual volume. It was then cooled to room temperature. The polymer concentrate was added to a threefold amount of acetone with vigorous stirring. The resulting product was rinsed three more times using acetone for one day. The extracted polymer was sieved through a number 80 sieve before being kept in a desiccator to prevent the polymer from being exposed to moisture. The storage area was kept clean and free from dust and other contaminants.[16]

Characterization of the Polymer

The colour and odour of the dry powdered material were examined qualitatively by manual methods. The polymer's solubility in water, ethanol, acetone, and chloroform was tested. The prepared polymer was checked for its pH, angle of repose, bulk and tapped density, Carr index and Hausner's ratio.

The isolated biopolymer was characterized with respect to various techniques. The important functional groups of the isolated galactomannan were identified with FTIR (Alpha II-Bruker, Germany). 10 mg of the sample was taken, and the spectra were recorded in a wavelength region of 4000-400 cm^{-1}.

For Thermogravimetric Analysis (TGA), the galactomannan biopolymer was pyrolyzed and burned using a DTA-TG device (DTG-60H, Shimadzu Co. Japan). A platinum crucible containing 10 mg of the isolated polymer was heated from 25 to 1000°C at a heating rate of 10°C/min.

Differential Scanning Calorimetry (DSC) was utilized to evaluate the thermal features of galactomannan with a DSC60 plus (Shimadzu, Japan). The dried galactomannan sample of approximately 7 mg was put into an aluminium pan, which was sealed and subjected to analysis. DSC spectra were obtained under a nitrogen flow rate of 40 mL/min and a temperature range of 20 to 400°C at 10°C/min.

SEM and EDS Analysis of Galactomannan

Energy Dispersive Spectroscopy (EDS) analysis (X-act, Oxford, Japan) was performed, and a Scanning Electron Microscope (EVO MA18, Zeiss) was used to characterize the sample microstructure. Together, SEM and EDS can be used to provide a detailed characterization of galactomannan polymers. SEM can provide information about the surface morphology and structure of the biopolymer, while EDS can provide information about its elemental composition.

For NMR analysis, the samples ^{1}H NMR spectra were captured in an NMR spectrometer (Bruker, Bremen, Germany). Tetramethylsilane was used as the internal standard. The chemical shift was recorded in ppm after 100 mg of material had been dissolved in D_2O. Using D_2O as the solvent, an NMR spectrum of the biopolymer was generated at a base frequency of 400 MHz, with a delay time of 1.5 s. In terms of the TMS resonance, the chemical changes were represented in ppm.

For the determination of the swelling index, a glass stoppered cylinder containing one gram of the sample was graded across 120-130 mm in 0.5 divisions. After adding 25 mL of water, it was vigorously shaken again every 10 min. After an hour of shaking at the designated intervals, the sample was kept aside for 24 hr. How much space the galactomannan occupied was measured, and the mean of three readings was calculated.

For drug identification and to assess drug-polymer interactions, the drug and physical mixtures of drugs and polymers were subjected to FTIR (Bruker, Alpha-II, Germany) analysis. The compatibility was determined based on spectral changes in the combination.

Since acetone was used to extract the galactomannan polymer, it is important to identify any traces of solvent that remain in the polymer that has been collected. Gas chromatography is an appropriate option as a method for determining residual solvent since organic solvents frequently have low boiling temperatures and are thermally stable.[21] The residual solvent content of the extracted polymer was determined using gas chromatography with headspace chromatography (HS-20, Shimadzu, Japan). The calibration curve was made by preparing different concentrations of acetone standard stock solutions in water. One gram of polymer was dissolved in two milliliters of water to make the sample solution. A volume of 1 mL of standard and sample solution was injected into the GC injection port. The temperature of the injection port was maintained at 170°C at a split ratio of 1:10, with nitrogen as a carrier gas.

Formulation of Atenolol Floating Bioadhesive Drug Delivery System

The method of direct compression was followed for the manufacturing of mucoadhesive tablets. Atenolol, HPMC K4M, galactomannan, sodium bicarbonate, and lactose were weighed, passed via a 40 number sieve and combined to produce a homogeneous mass. Sifted talc, citric acid, and magnesium stearate were incorporated into the blend and mixed well. Using 8 mm round-flat punches (Shakthi single punch tablet press, SSTP-12, India), the powder mixture was made into tablets. The overall weight of each tablet was approximately 200 mg. Table 1 shows the components of the various formulations.

Table 1: Composition of developed formulations.

Ingredients (mg)	Formulation code		
	F1	F2	F3
Atenolol	25	25	25
Galactomannan	40	50	60
HPMC K4M	40	40	40
Lactose	64	54	44
Citric Acid	10	10	10
Sodium bi carbonate	15	15	15
Talc	4	4	4
Magnesium stearate	2	2	2

Evaluation of the Floating Bioadhesive Drug Delivery System of Atenolol

Physicochemical Evaluations

The prepared tablets were visually examined for pinholes, fractures, and other flaws. Using a Monsanto apparatus, the tablets' hardness was evaluated and expressed in kg/cm^2 of surface area. The thickness of the tablets was determined with screw gauze.[22]

The tablet friability was assessed with a Roche friabilator (Electrolab, EF2, India). The weight variation evaluation was conducted by weighing 10 mucoadhesive tablets from every batch. The mean of the weights and % deviation of the data obtained from the tablets were calculated.[23]

The assay (%drug content) of the prepared mucoadhesive tablets was measured by taking six tablets, which were pulverized, and weighing out powder corresponding to the mean weight of one tablet. The powder was then dissolved in 100 mL of simulated gastric fluid (0.1 N HCl, pH 1.2) in a volumetric flask. The well-mixed solution was then filtered, and a UV spectrophotometer was used to analyse the sample.

The swelling index was determined by weighing one tablet from each batch and keeping it in a petri dish with 25 mL of acidic buffer (pH 1.2). The tablet was taken from the plate after every 1 h interval, cleaned with filter paper, and weighed for up to 6 hr. The given formula was employed to determine the swelling index.[24]

$$\text{Swelling index} = (W2 - W1) \times 100 / W2,$$

Where, W_1 is the initial weight and W_2 is the weight of the hydrated tablet.

Buoyancy: Floating Time and Lag Time

The floating efficacy of the gastroretentive tablet was measured with type II dissolution equipment filled with simulated gastric fluid (900 mL) at 75 rpm. The time it took the gastroretentive tablet to come to the top of the flask from the underside is called the floating lag time, and the time it remained on the plane of the buffer is termed the floating time, both of which are measured in minutes.

Measurement of Bioadhesion Time

The formulated tablets were placed in a newly sliced chicken pouch to measure the *ex vivo* mucoadhesion time. The fresh chicken pouch was glued onto a glass slide followed by wetting the tablet with a single drop of simulated gastric fluid prior to adhesion to the buccal mucosa with a fingertip for 30 sec. The glass slide with the tablet was placed in an 800 mL beaker with phosphate buffer and held at 37±0.5°C. The mucoadhesion time was calculated by measuring the time it took for the tablet to disengage from the buccal mucosa.[25]

Dissolution Study

The atenolol release from the mucoadhesive tablet was examined in simulated stomach fluid devoid of enzymes at pH 1.2 using a type II dissolution apparatus (900 mL) (Labindia, DS8000, India). The temperature was maintained at 37±0.5°C, and the spinning speed was 50 rpm. At predefined intervals, 5 mL aliquots were taken, and the dissolution medium was kept constant by the addition of an equal amount of fresh buffer. At 224 nm, the absorbance of the removed samples was determined. The results from drug release investigations were applied to the kinetic models to investigate the atenolol release pattern along with the release rate kinetics of the prepared FBS using zero order, first order, Higuchi's model and Korsmeyer-Peppas equation.[26]

Stability Study

The stability study information is used to determine appropriate storage requirements, retesting duration, and shelf-lives. A group of optimized tablets were maintained at ambient temperature for 30 days, while the others were stored in a stability chamber (Thermolab TH 500) maintained at 40°C±2°C and 75%±5% RH. Both formulations were taken after 30 days and tested for the specified parameters to see if the values were well within the limit.[27]

RESULTS AND DISCUSSION

Isolation of Gum

Galactomannan was chosen because of its exceptional swelling properties in aqueous environments. This property enables it to build a long-lasting and cohesive gel matrix, which, when combined with our formulation, aids in controlled drug release and long-term buoyancy. As a result, the final dosage form has the distinct advantage of retaining its integrity and floating ability in the stomach, which is crucial for gastroretentive drug delivery systems. The polymer from *Trigonella foenum-graecum* L. seeds was isolated using a suitable extraction method (Figure 1). Galactomannan extraction and purification using the reported approach was very successful. Following purifying procedures, a brownish galactomannan in the form of a gummy substance was obtained, where identical features of the biopolymer are reported in the literature. From a yield perspective, the technique for extracting galactomannan biopolymers was highly successful. A total of 8.2 g of galactomannan was produced per 100 g of fenugreek seeds, indicating a yield of 8.2%. According to the literature, the yield of mucilage collected from plants is fairly low and may be influenced by the method employed to extract biopolymers[28] The gum was water soluble but was not soluble in ethanol, acetone, and chloroform.

Characterization of the Gum

The gum was evaluated for angle of repose, bulk and tapped density, Carr's index and Hausner's ratio. The results indicated

Table 2: Characterization of polymer.

Sl. No.	Parameters		Result
1	Macroscopic features	Colour	Brown
		Odour	Odourless
2	Solubility characteristics	Water	Soluble
		Ethanol	Insoluble
		Acetone	Insoluble
		Chloroform	Insoluble
3	pH		6.80
4	Angle of repose (^{0})		28.01
5	Tapped density (g/cc)		0.69
6	Bulk density (g/cc)		0.43
7	Carr's index		17.35
8	Hausner's ratio		1.17

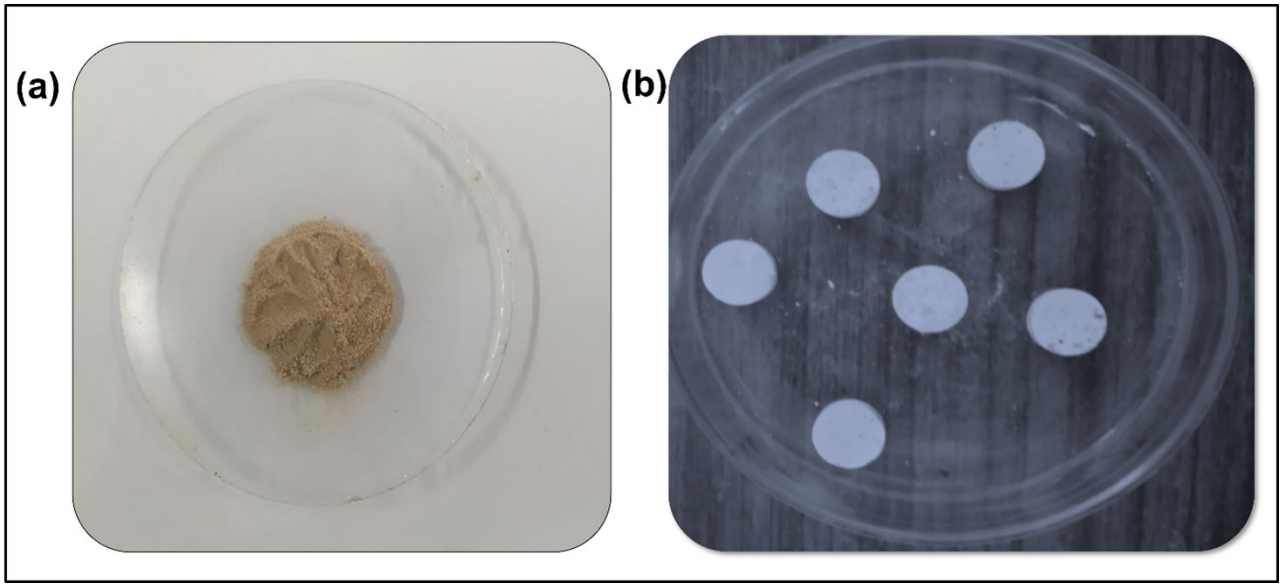

Figure 1: (a) Isolated galactomannan polymer (b) Gastroretentive tablet of atenolol.

the desirable flow of the gum powder. The results are depicted in Table 2. The isolated polymer showed excellent flow properties that can be depicted from the powder characteristics. The angle of repose of the extracted polymer corresponds to the excellent flow characteristics of the powder. In addition, the Carr index and Hausner's ratio showed fair flow characteristics. The 1% solution of extracted polymer in water showed a pH of 6.80, almost neutral and near the acidic side. This demonstrates that the galactomannan polymer would cause no pH-dependent irritation to mucous membrane and can be utilized for the design of gastroretentive drug delivery systems.

FTIR Study

FTIR analysis is an important tool for the primary characterization of biopolymers from different sources. The obtained spectra showed different bands stretching in the range between 3328.50 cm^{-1} and 519.84 cm^{-1} (Figure 2(a)). A stretching in the wavenumber range of 3000-3500 cm^{-1} indicates the OH^- of the carbohydrate group and a trace amount of moisture. The peak at 2889.96 cm^{-1} represents the C-H stretch; the C-O bond of the alcohol group was confirmed by a peak at 1011.13 cm^{-1}. The carbohydrate nature of the synthesized biopolymer could be confirmed with the abovementioned peaks. The stretching in the range of 1000-1200 cm^{-1} is a representation of C-O functional groups, and the peak at 2889.96 cm^{-1} proved the presence of the C-O-C group. The presence of protein in the moieties of the galactomannan biopolymer is represented by a stretching peak at a wavenumber of 1618.74 cm^{-1}. The peaks at 866.64 and 768.01 cm^{-1} represent the glycosidic linkage of the β-D-mannopyranose unit and the anomeric configurations of the α-D-galactopyranose units.[25-27] The FTIR spectra of atenolol along with the polymer and excipients are given in Figure 2(b), (c), and (d). As per these results, the peaks at 2965.02 cm^{-1}, 1639 cm^{-1}, 1514.81 cm^{-1}, and

1242.90 cm^{-1} correspond to C-H stretching, C=N stretching, N-H bending, and C-O stretching, respectively. The spectra of atenolol with galactomannan or HPMC K4M indicated that the drug's distinctive peak remained unaffected with no interaction, no compatibility issues, and no peak shift. As a result, the IR analysis demonstrates that the pharmaceuticals were in their free form in the formulation, with no drug-excipient interactions. Therefore, the isolated biopolymer can be utilized in the gastroretentive delivery of atenolol.

Thermal Characteristics of the Polymer

TGA study was employed to analyse the thermal features of the galactomannan biopolymer under optimal conditions. TGA is a quick and reliable method that may be used to examine the thermal stability along with the degradation characteristics of biopolymers. The thermogram analysis of the extracted polymer was performed by plotting weight loss (%) against the temperature (°C), as shown in Figure 3(a). The polymer showed a degradation temperature of 315.70°C in the TGA curve. Between 27 and 180°C, a first weight loss of approximately 14% was noticed, which may have been caused by the loss of moisture present in the galactomannan biopolymer as free water. Furthermore, this weight loss indicates the presence of more carboxyl groups in the biopolymer structure and its hydrophilic nature.[28] The next weight loss detected at 20°C could be due to the hydrocolloidal thermal degradation of the polymer, which was higher than that of other mucilage isolated from Zapota (178.60°C) and the Lanzan seed polymer (170.40°C).[29] The degradation temperature of the polymer was found to be 315.70°C and is higher than that of other biopolymers, such as LBG (278.46°C) and xanthan gum (282.65°C).[25]

The thermal transition properties of the prepared galactomannan biopolymer while heating in an inert atmosphere were investigated using DSC analysis (Figure 3(b)). The DSC curve of the polymer consisted of two major regions: i) the first peak region was in the temperature range of 25.90 to 130.13°C at a peak of 85.77°C with an enthalpy change of -537.80 J/g. This peak represents moisture outflow from the biopolymer structure during heating, and ii) the second region is positioned in a range of 331.88°C to 393.65°C, having a peak at 346.19°C and showing an enthalpy change of -80.22 J/g. The other peak demonstrates that the galactomannan isolated can hold water even at higher temperatures. Furthermore, a similar trend has been observed in many other polymers, such as melanoxylon seed polymer (DSC peaks at 70.10°C and 324.70°C)[30-32] and galactomannan polymer from *Mimosa scabrella*, which showed temperature peaks at 100 and 331°C.[33] The DSC results indicated that the galactomannan polymer can be used in various industrial and pharmaceutical applications, such as microencapsulation.

SEM and EDS Analysis of Galactomannan

Many researchers in the area of hydrocolloids have reported SEM as a method of choice for the surface morphology characterization of biopolymers.[34] The SEM results of the isolated galactomannan

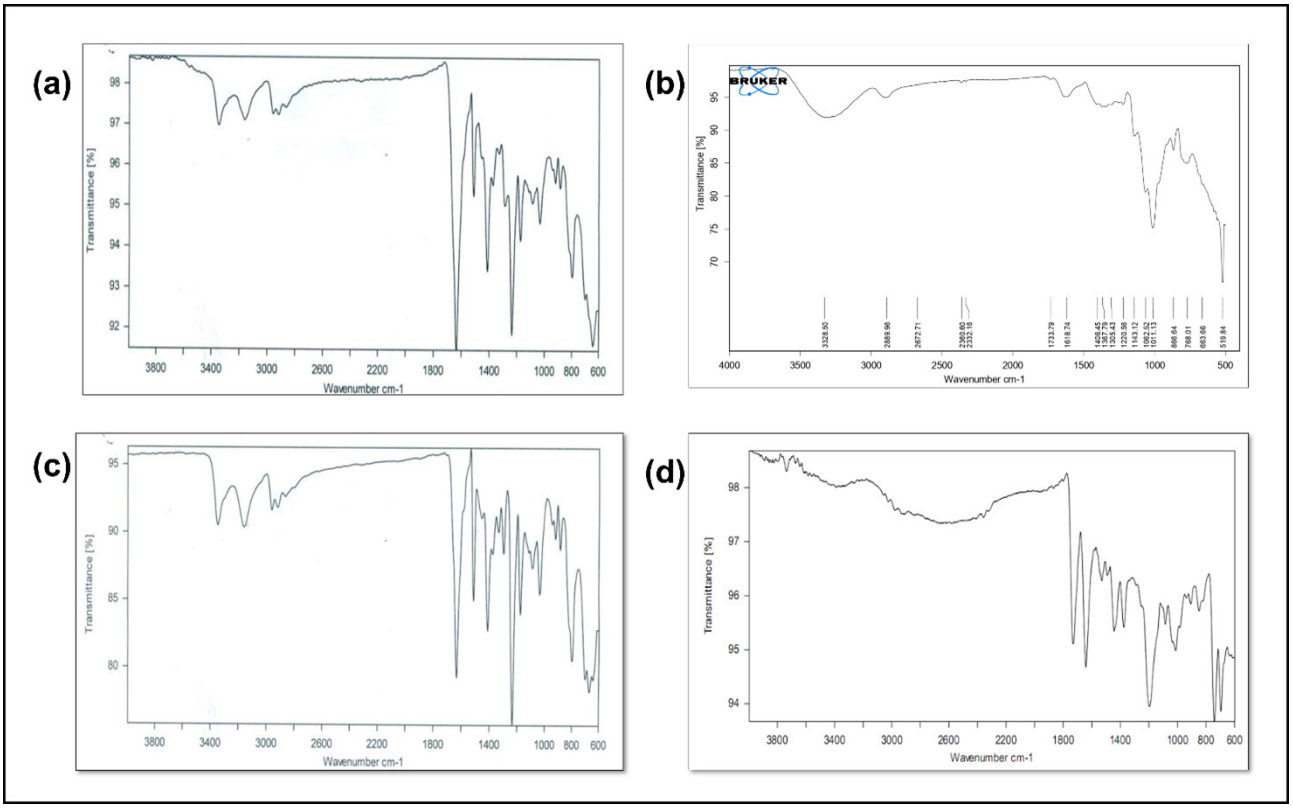

Figure 2: FT-IR spectrum of (a) Pure Atenolol (b) Galactomannan biopolymer (c) polymer (d) Atenolol+HPMC K4M polymer.

Table 3: Evaluation of Physical Parameters of atenolol mucoadhesive floating Tablet.

Sl. No.	Formulations	Average Weight. (mean±S.D.) (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)
1	F1	200.14±0.43	2.87±0.04	6.20±0.12	0.69
2	F2	200.34±0.05	2.84±0.03	6.21±0.32	0.42
3	F3	200.30±0.85	2.91±0.02	6.27±0.41	0.28

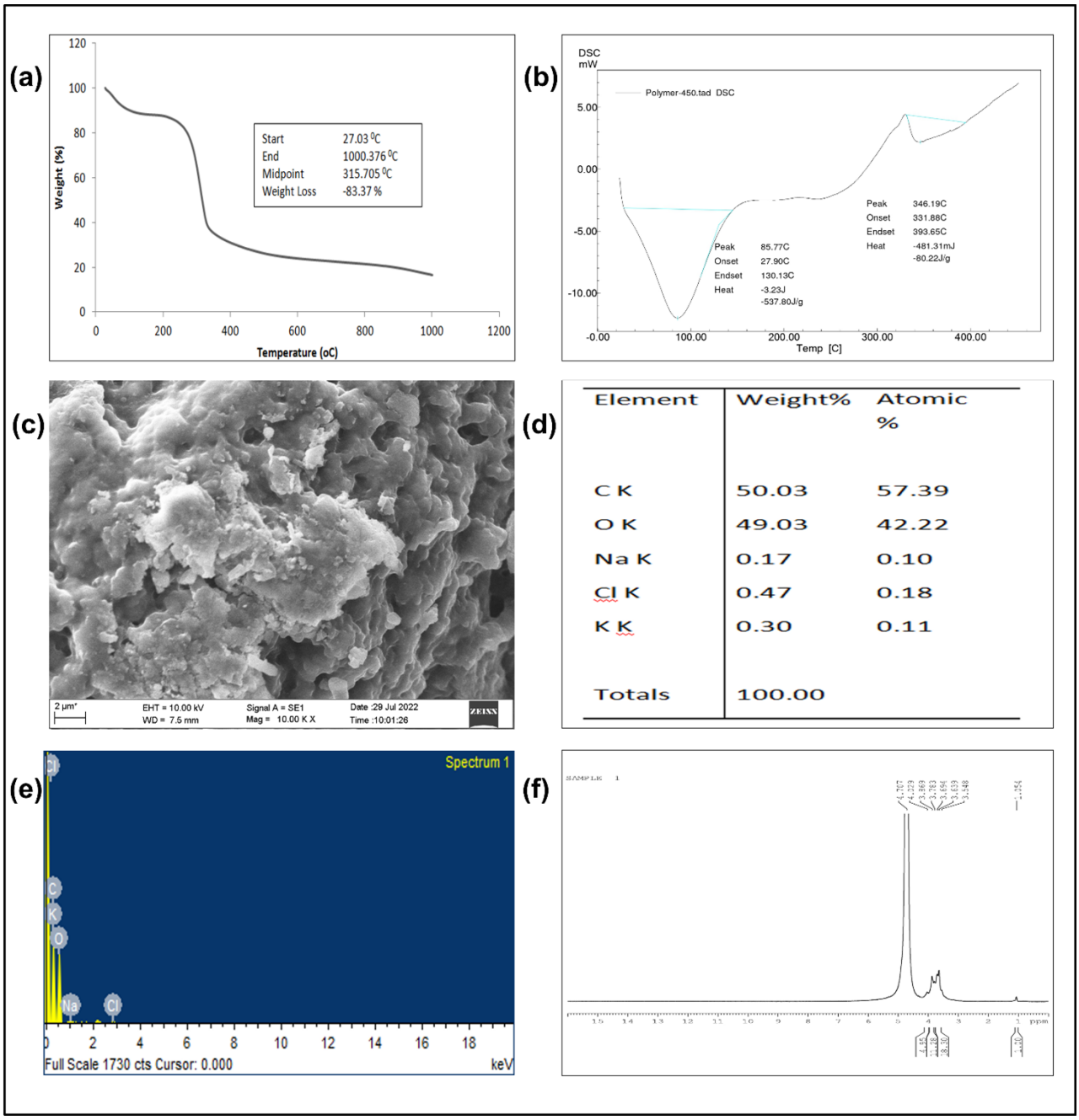

Figure 3: Characterization of galactomannan polymer (a) Thermogravimetry (b) Differential Scanning Colourimetry (c) SEM and (d) EDS measurements (e) EDS spectrum of galactomannan (f) ^{1}H NMR spectrum of Galactomannan biopolymer.

polymer are illustrated in Figure 3(c). The SEM image shows the smooth, sparkling surface of the galactomannan biopolymer, which indicates the structural integrity of the biopolymer.[29] Galactomannan is a suitable choice for both film-forming and biopolymer-mediated drug release systems because of its smooth surface and structural integrity. Elements in biopolymers were evaluated using EDS spectra and are shown in Figure 3(d) and 3(e).

NMR Study

NMR spectroscopy is the most effective technique for polysaccharide analysis. It aids in creating a relationship between various bondages and the number of carbon and hydrogen atoms, assisting in the prediction of structures while taking the findings from IR spectra and other relevant spectroscopic approaches into consideration. The ^{1}H NMR study results provided a complete and consistent idea of ^{1}H signals, as shown in Figure 3(f). The chemical shift in the ^{1}H spectrum of the galactomannan biopolymer shows δ values for galactose at 3.78, 3.86, and 4.02. The anomeric proton (H-1) of the D-mannopyranosyl units, which naturally have the β-D configuration, is clearly seen in the spectrum at 4.8 ppm. The H-1 of the galactopyranosyl units is assigned a second signal at 5.0 ppm, indicating that they have the anticipated α-D configuration.[35]

Swelling Index

The swelling property of the polymer is a significant determinant of the tablet's bioadhesion. The bond strength will increase with increasing hydration up to a point at which excessive hydration causes the glue quality to abruptly decline due to unfolding at the polymer/tissue interface. When compared to commercially available guar gum (42%),[36] fenugreek gum showed an enhanced swelling index of 86%. It was observed that as the mucilage concentration rose, the swelling index also increased.

Residual Solvent Analysis

Residual solvents in pharmaceuticals are defined as organic volatile compounds employed or produced during the synthesis of drug ingredients or excipients or in the preparation of drug products for pharmacopeial reasons. Because residual solvents have no therapeutic value, they should be eliminated to the greatest extent practicable to meet ingredient and product specifications, good

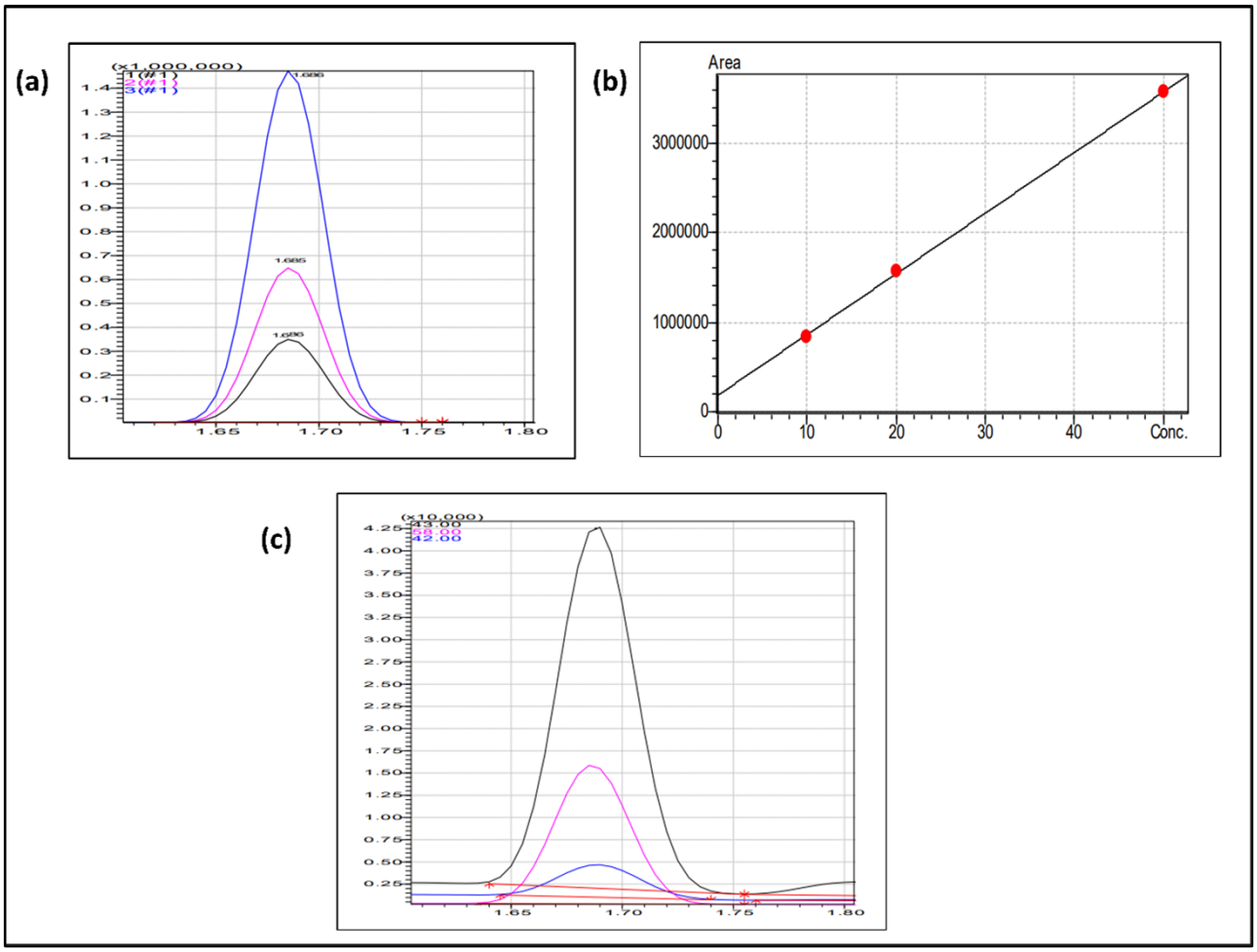

Figure 4: Residual solvent analysis by headspace gas chromatography (a) Standard chromatogram of acetone for 3 levels (b) Calibration curve (c) Sample chromatogram.

Table 4: Regressional analysis of the *in vitro* release results of Atenolol tablet as per different release kinetic models.

Formulation code	Zero order	First order	Higuchi	Korsemeyer-Peppas	
	R^2	R^2	R^2	R^2	N
F1	0.9895	0.9114	0.9145	0.9855	0.9322
F2	0.9865	0.9716	0.9558	0.9487	0.9336
F3	0.9947	0.9402	0.9389	0.9900	0.8322

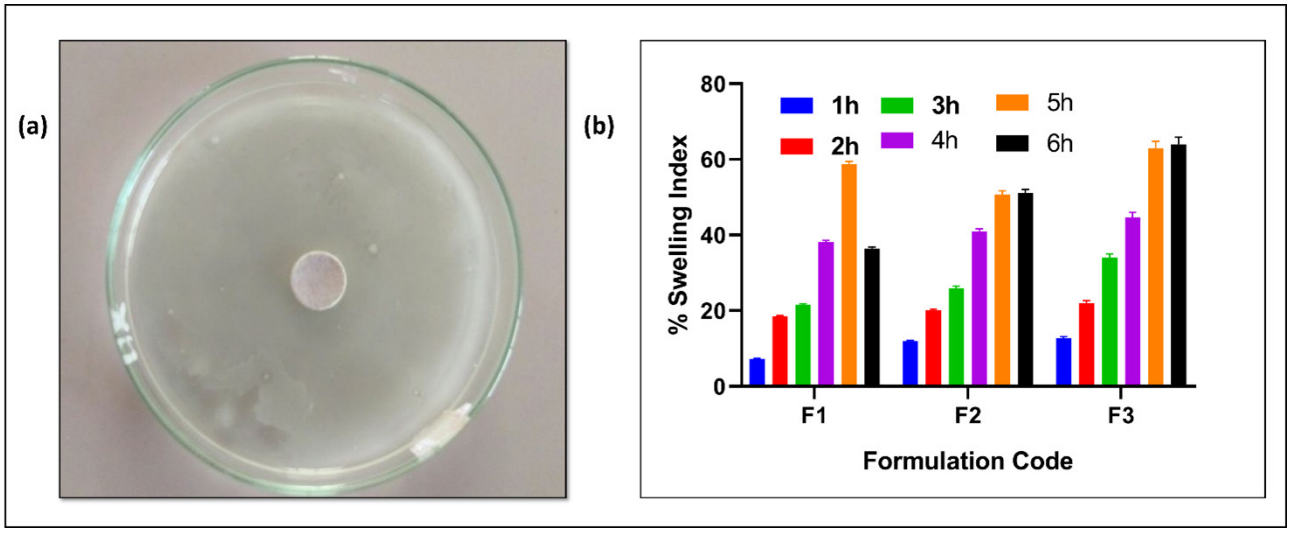

Figure 5: (a) Swelling index study (b) Swelling index data.

manufacturing practices, or other quality-based requirements. Formulations should contain no higher levels of residual solvents than can be supported by safety data. Acetone is a class 3 residual solvent that may be regarded as less toxic and of lower risk to human health than Class 1 and Class 2 residual solvents. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the residual solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies.

Gas chromatography was employed to detect the residual solvent level in the extracted polymer. The developed gas chromatographic method showed a retention time of 1.68 minutes. The linearity of the method was determined by making injections of standard acetone solutions of different concentrations. The regression coefficient (R^2) of the developed method was found to be near unity, and the calibration curve was linear within this range (Figure 4). The residual acetone concentration of the galactomannan polymer was found to be 0.127 ppm. Class 3 residual solvents are limited to not more than 50 mg per day, corresponding to 5000 ppm or 0.5%. The results show that the extracted polymer is safer to use in the formulation of gastroretentive tablets.

Evaluation of the Gastroretentive Drug Delivery System of Atenolol

Physicochemical Evaluations

All the prepared tablets were inspected visually. No tablets showed general flaws, including chipping, lamination, or capping. All the tablets were spherical in shape with a diameter of 8 mm (Figure 1(b)).

Table 3 summarizes the findings of thickness, hardness, and friability. The hardness of the gastroretentive tablets ranged between 6.20±0.12 and 6.27±0.41 kg/cm^2. A difference in formulation hardness indicates a difference in tablet density and porosity, which are hypothesized to create different drug release patterns by affecting the pace at which the dissolving fluid penetrates the product surface and the creation of gel barriers. Tablets with higher hardness will have a compact polymer mass with comparatively fewer pores, which will slow the release. The values demonstrate excellent tablet strength as per the USP requirements.[37,38]

The thickness of the tablets was measured in Micrometres (µm). The die fill was consistent, as evidenced by the uniform thickness of the tablets. The major parameters affecting tablet thickness are size of the punches (8 mm) and tablet weight (200 mg). In Table 3, the average weight of each formulation is reported. The thickness values varied from 2.87±0.04 to 2.91±0.02 mm. The tablet strength depends on the extent of friability. Table 3 demonstrates the

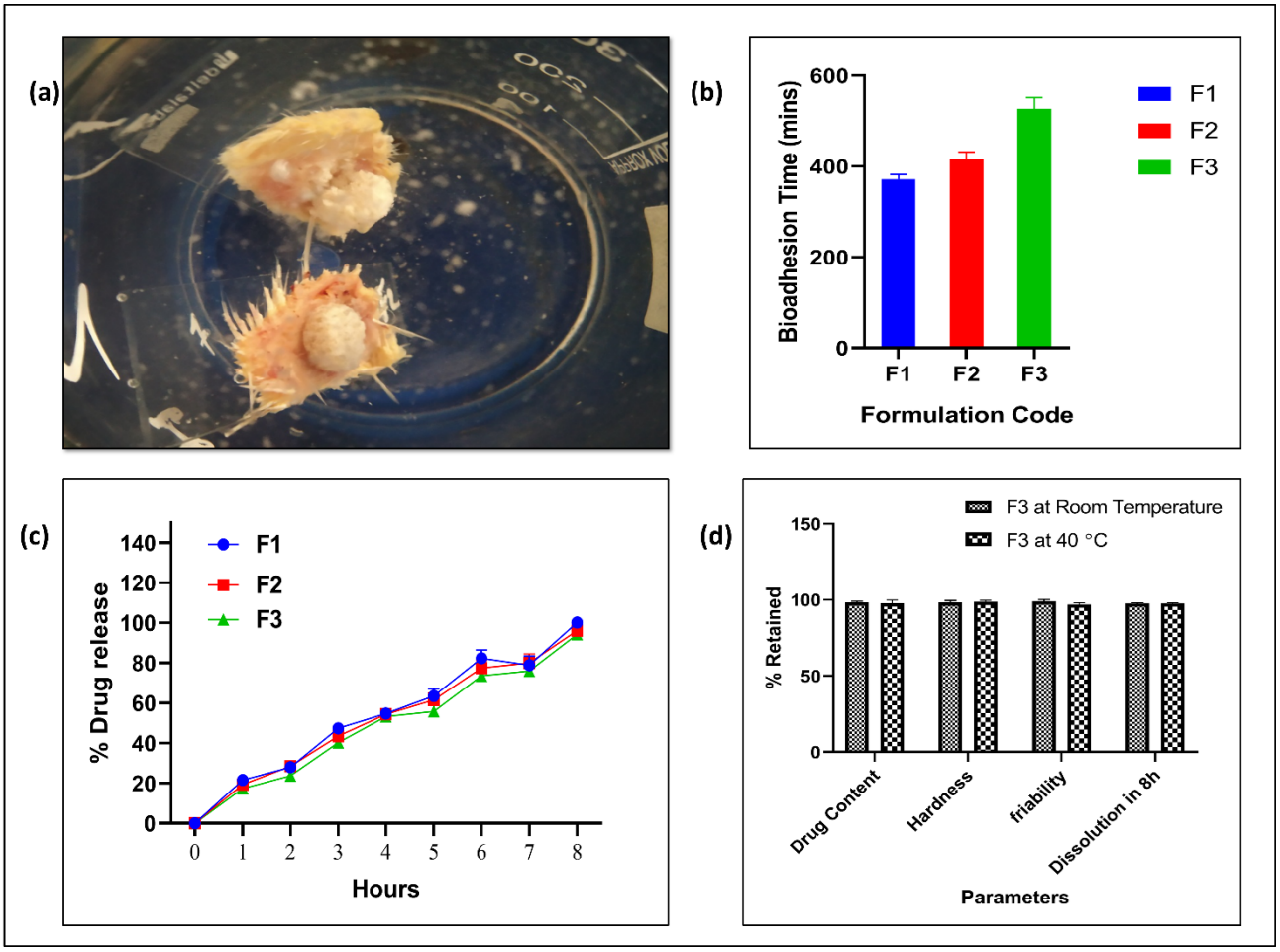

Figure 6: Performance evaluation of prepared tablet (a) Bioadhesion time study (b) Bioadhesion time data (c) *in vitro* drug release data (d) Stability study data.

results of the friability test. All of the formulations had a friability of less than 1%, which is the acceptable value for conventional tablets. The results suggested that the tablet had acceptable mechanical strength. The friability value varied from 0.28 to 0.69. Table 3 lists the results of the weight variation test. The results were nearly homogeneous, with values ranging from 200.14±0.43 to 200.34±0.05 mg. The percent weight difference was within the acceptable limits of Pharmacopoeia's guidelines of ±7.5% of the weight; hence, all the mucoadhesive tablets passed the friability test. The atenolol content of all the batches was confirmed to be in the acceptable range. Atenolol's percentage drug content values for F1, F2 and F3 were 94.89±0.886%, 95.08±0.43%, and 97.89±1.009%, respectively.

The absorption of a liquid causes the tablet to expand, which brings about an increase in the weight and volume of the tablet, which enables atenolol release from the tablet. For all batches, the swelling index was calculated. Over time, the swelling of all of the tablets increases because the hydrophilicity of the polymer causes it to progressively absorb water. As the outermost hydrophilic polymer layer gradually dissolves or disperses, the swelling process continues toward newly exposed surfaces, maintaining the integrity of the dosage form. It was shown that the polysaccharide concentration significantly affects medication release. The tablet exhibited an increased swelling index with an increase in galactomannan gum concentration from 40 to 60 mg, while keeping other ingredients constant (Figure 5). This could be due to the enhanced hydration characteristics of the galactomannan polymer with increasing polymer concentration. After 5 hr of maximum swelling, the polymers began to erode slowly in the provided medium. The maximum swelling index was shown by F3 (62.63%), and the minimum was 50.55% by F2. The formulated bioadhesive tablet showed similar swelling index values compared to reported polymers isolated from jackfruit (62.78%)[39] and bioadhesive polymers from *Manilakara zapota* (68.65%).[40] The results demonstrated that formulation F3 showed greater swelling than F1 and F2, which is linked with the concentration-mediated water absorption by the hydrophilic polymer (galactomannan polymer).

Assessment of Buoyancy in Terms of Floating Time and Lag Time

To achieve efficient *in vitro* floating of the formulated tablets, an effervescent strategy was used. After coming into contact with stomach fluid, the system should begin to float within a few minutes; hence, the gas-generating agent was crucial for optimal floating. As a gas-generating agent, sodium bicarbonate was included; it serves as a crucial variable in the floating tablets. As per previous studies, the optimum sodium bicarbonate concentration for efficient floating was observed to be between 5 and 15%. The reported results evidently demonstrated that as the sodium bicarbonate concentration increased, the floating lag time decreased. Therefore, the concentration at 5-15% sodium bicarbonate provides the best buoyancy; thereafter, increasing the concentration of sodium bicarbonate does not significantly alter the floating and lag time values. Thus, here, we used 10% w/w sodium bicarbonate. The prepared tablet on exposure with the simulated gastric fluid of 0.1 HCl caused the production of CO_2 bubbles and floated above the fluid.[41] All of the formulations floated for more than 8 hr on average, with floating lag times ranging from 20 to 103 sec. When comparing batches with high polymer content to batches with medium polymer concentration, there was a considerable difference in lag period. The formulation containing a higher concentration of galactomannan gum (F3) showed a longer floating lag time of more than 8 hr. The formulation with a lower concentration of gum (F1) showed a shorter lag time of 20 sec with appreciable floating time (>8 hr). Bioadhesive tablets with intermediate polymer concentrations showed a floating lag time of approximately 30 sec. These results suggest the influence of galactomannan gum on the *in vitro* buoyancy of the prepared gastroretentive tablets. This could be a result of polymers' limited gelation properties at lower concentrations.[42]

Measurement of bioadhesion time

The *ex vivo* bioadhesion performance of the formulated gastroretentive tablets was determined for all formulations, and the results are given in Figure 6(a) and (b). The study was performed in gastric pH (0.1 N HCl). Bioadhesion was highest for F3 (8 hr 50 min) and lowest for F1 in regard to atenolol tablets (6 hr 15 min). We observed a steady increase in the bioadhesion time in formulations from F1 (increased polymer) to F3 (less polymer). This could be due to the increase in the concentration of galactomannan gum, which improved the bioadhesive characteristics of the tablets.

Dissolution Study

Gastroretentive delivery systems can enhance the gastroretention time and thereby enhance the bioavailability of drugs. The addition of different concentrations of natural gum showed a notable effect on the *in vitro* release of atenolol. Figure 6c shows the *in vitro* atenolol release characteristics of the formulations. The bioadhesive tablet F1 showed approximately 100% atenolol release in 8 hr, where 22% of atenolol was released in the first hour and then controlled release for 8 hr. Formulas F2 and F3 showed an atenolol release of 95.17% and 93.37%, respectively, at 8 hr. These results evidently show that the galactomannan gum concentration has an inhibitory effect on atenolol release; this could be due to gel barrier formation on the gastroretentive tablet. Drug diffusion via the gel barrier requires greater time as its thickness increases, which is evidenced by the higher swelling index shown by the formulation with a higher galactomannan gum concentration. Ideal drug delivery systems should release the medicine in a specified way to increase patient compliance, as well as the safety and effectiveness of the medications. The outcomes demonstrated that galactomannan gum might be utilized to create gastroretentive delivery systems.

To assess the drug release mechanism, different kinetic models were employed. The values were calculated using kinetic analysis, and the best fitting model was chosen. Table 4 shows the findings of the study utilized to evaluate the release mechanism as well as the regression analysis. The *in vitro* release result was kinetically treated to determine the release mechanism. When R^2 values from zero-order, first-order, and Higuchi kinetic models were compared, *in vitro* drug release zero-order kinetic equations were near unity. This result suggests the zero-order release of atenolol from the prepared tablets and thus indicates that the atenolol release rate was independent of the residual concentration of the drug. The drug release mechanism from the prepared tablets was further checked with the Korsmeyer-Peppas model. The obtained 'n' values in Koresmeyer's equation were >0.5, indicating non-Fickian diffusion of atenolol release.[38] This result indicates that diffusion and polymer swelling mediated atenolol release from the tablet formulations.

Stability Study

According to the evaluation, formulation F3 demonstrated controlled release of atenolol with outstanding matrix integrity, desirable floating time with good swelling index, and less floating time than other batches. The formulation batch F3 was discovered to be the best optimum among the other batches in this series. As a result, formulation F3 was selected for the stability investigation. There was no significant difference between the parameters tested before and after stability testing, and all were found to be within acceptable ranges. At 40°C, the tablets displayed satisfactory physical stability in terms of colour, surface texture, hardness, friability, drug content, and dissolution (Figure 6d).

CONCLUSION

This work was a successful attempt to develop a mucoadhesive drug delivery system for Atenolol, an orally administered antihypertensive medication, with the goal of increasing its oral bioavailability and providing long-term drug release. It may be deduced from the experimental data that without capping or chipping, all of the manufactured tablets were reported to be satisfactory with respect to swelling index, buoyancy features and release pattern. According to the findings of this investigation, the swelling index rises as the galactomannan concentration rises. The F3 tablet was found to be the optimized formulation. This investigation demonstrated that it is safe, stable, and capable of sustaining drug release via mucosa to create new mucoadhesive floating tablets utilizing natural mucoadhesive hydrophilic polymers. Therefore, these tablets may be particularly effective in preventing and treating hypertension.

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CONFLICT OF INTEREST

The authors declare that there isno conflict of interest.

ABBREVIATIONS

DSC: Differential scanning calorimetry; **EDS:** Energy dispersive spectroscopy; **FBS:** Floating Bioadhesive System; **FDDS:** Floating drug delivery system; **FTIR:** Fourier Transform Infrared Spectroscopy; **HPMC:** Hydroxypropyl methyl cellulose; **NMR:** Nuclear Magnetic Resonance; **TGA:** Thermogravimetric analysis; **USP:** United States Pharmacopeia.

SUMMARY

- A gastroretentive bioadhesive tablet was manufactured with hydroxypropyl methyl cellulose (HPMC) and galactomannan.
- GC analysis revealed a residual acetone content of 0.127 ppm in galactomannan polymer, indicating safe use in gastroretentive tablet formulations.
- The prepared tablets exhibited satisfactory physicochemical properties, including swelling index, release characteristics, and buoyancy pattern. All batches demonstrated adequate in vitro buoyancy.
- The gastroretentive tablets showed both axial and radial swelling during in vitro buoyancy tests. The formulation remained buoyant for about 8 to 12 hours.
- The release study demonstrated that atenolol release from the tablet formulations is mediated by diffusion and polymer swelling.

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