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RESEARCH ARTICLE

Mucoadhesive Delivery of Alfuzosin HCl Using Hupu Gum: Insights from *In Silico* Docking and *Ex Vivo - In Vivo* Adhesion Studies

Rajeswari ALETI[*°], Monika NIJHAWAN[**], Pavan KUMAR THOTA[***], Bhavana JIDIGE[****]

Mucoadhesive Delivery of Alfuzosin HCl Using Hupu Gum: Insights from In silico Docking and Ex vivo - In Vivo Adhesion Studies

SUMMARY

Benign prostatic hyperplasia (BPH) is an age-associated disorder of enlargement of the prostate that leads to urinary obstruction. Alfuzosin HCl, a selective α1-adrenoceptor antagonist, is well absorbed in the duodenum and is more effective in extended-release formulations. This study investigates the formulation of mucoadhesive compression-coated tablets (MCCT) of alfuzosin HCl using hupu gum to enhance gastric retention and achieve a 24-hour extended drug release, addressing bioavailability issues that affect therapeutic efficacy. The investigation is further validated by in silico and ex vivo studies. Alfuzosin HCl, hupu gum, and lactose were used in this study. Initially an in silico study was conducted using software CB Dock 2 to know the interaction between hupu gum and mucin. Optimized Inner Core tablets (ICT) prepared with varying concentrations of hupu gum were then compression-coated with hupu gum. The tablets obtained were characterized and optimized on the basis of in vitro and ex vivo studies determining mucoadhesive and drug release parameters. Results of in silico studies confirmed multiple interactions between the hupu gum and mucin through conventional hydrogen bond, C-H bond, and van der Waals interactions. The presence of these bonds suggests that the formulation exhibits an extended gastric retention time on mucosal surfaces, thereby enhancing the efficacy of the mucoadhesive system. Formulation MCCT1 was optimized as the maximum amount of drug release of 98.2 % was observed over a period of 24 hours in gastric medium, and mucoadhesive strength was found to be 0.26 N. A study of gastric retention time using X-ray imaging indicates effective in vivo adhesion and prolonged gastric retention. The extended release of alfuzosin HCl was achieved by gastroretentive mucoadhesive tablets using a compression coating technique.

Keywords: *Alfuzosin hydrochloride, hupu gum, compression coating technique, mucoadhesive, in silico studies, ex vivo studies.*

Hupu Sakızı Kullanarak Alfuzosin HCl'nin Mukoadezif Taşınması: In Silico Docking ve Ex Vivo - In Vivo Adezyon Çalışmalarından Elde Edilen Bulgular

ÖZ

Benign prostat hiperplazisi (BPH), yaşa bağlı olarak ortaya çıkan ve prostatın büyümesiyle idrar yolu tıkanıklığına yol açan bir hastalıktır. Seçici bir α1-adrenoseptör antagonisti olan Alfuzosin HCl, duodenumda iyi emilir ve uzatılmış salım formülasyonlarında daha etkilidir. Bu çalışma, biyoyararlanımı etkileyerek tedavi etkinliğini azaltan sorunları ele almak amacıyla, hupu zamkı kullanılarak mide tutulumunu artırmayı ve 24 saatlik uzatılmış ilaç salımını sağlamayı hedefleyen alfuzosin HCl'nin mukoadezif kompresyon kaplı tabletlerinin (MCCT) formülasyonunu araştırmaktadır. Araştırma, in silico ve ex vivo çalışmalarla desteklenmiştir. Çalışmada Alfuzosin HCl, hupu zamkı ve laktoz kullanılmıştır. İlk olarak, hupu zamkı ile müsin arasındaki etkileşimi belirlemek amacıyla CB dock 2 yazılımı kullanılarak in silico çalışma gerçekleştirilmiştir. Daha sonra, farklı konsantrasyonlarda hupu sakızı ile hazırlanan optimize edilmiş iç çekirdek tabletleri (ICT), hupu sakızı ile sıkıştırma yöntemiyle kaplandı. Elde edilen tabletler, in vitro ve ex vivo çalışmalara dayanarak mukoadeziflik ve ilaç salım parametreleri açısından karakterize edilmiş ve optimize edilmiştir. In silico çalışmaların sonuçları, hupu zamkı ile müsin arasında geleneksel hidrojen bağları, C-H bağları ve van der Waals etkileşimleri yoluyla çoklu etkileşim olduğunu doğrulamıştır. Bu bağların varlığı, formülasyonun mukozal yüzeylerde uzamış mide tutunma süresi gösterdiğini ve böylece mukoadezif sistemin etkinliğini artırdığını göstermektedir. MCCT1 formülasyonu, mide ortamında 24 saat boyunca %98,2 oranında maksimum ilaç salımı sağladığı ve 0,26 N mukoadezif kuvvete sahip olduğu için optimize edilmiştir. X-ışını görüntüleme kullanılarak yapılan mide tutunma süresi çalışması, etkili in vivo adezyon ve uzatılmış mide tutulumunu göstermiştir. Alfuzosin HCl'nin uzatılmış salımı, kompresyon kaplama tekniği kullanılarak hazırlanan gastroretentif mukoadezif tabletlerle başarıyla gerçekleştirilmiştir.

Anahtar Kelimeler: *Alfuzosin hidroklorür, hupu zamkı, kompresyon kaplama tekniği, mukoadezif, in silico çalışmalar, ex vivo çalışmalar.*

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[*] ORCID: 0009-0001-8894-9063, Department of Pharmaceutics, Gland Institute of Pharmaceutical Sciences, Medak District, Telangana, India
[**] ORCID: 0000-0002-3564-0257, Department of Pharmaceutics, Professor, GokarajuRangaraju College of Pharmacy, Osmania University, Hyderabad, Telangana, India.
[***] ORCID: 0009-0009-5890-3636, Department of Pharmaceutics, GokarajuRangaraju College of Pharmacy, Osmania University, Hyderabad, Telangana, India.
[****] ORCID: 0009-0007-0819-1357, Department of Pharmaceutics, GokarajuRangaraju College of Pharmacy, Osmania University, Hyderabad, Telangana, India.

[°] Corresponding Author; Dr. Rajeswari Aleti,
Email: razi.pharma.87@gmail.com

INTRODUCTION

Age-related health issues are common, and Benign Prostatic Hyperplasia (BPH) is a notable example, characterized by an enlarged prostate gland that obstructs urine flow, resulting in symptoms such as increased urinary frequency, urgency, and a weak stream (Kim et al., 2016). Alfuzosin HCl, a selective α1-adrenoceptor antagonist, is widely used in the management of BPH. Although it is classified as a BCS Class I drug with good water solubility, its oral bioavailability is only 49% when taken with food and drops to 25% under fasting conditions (Pattnaik et al., 2009). This low bioavailability is attributed to extensive first-pass hepatic metabolism and a narrow absorption window, with peak absorption occurring primarily in the duodenum and jejunum, followed by a decline along the remaining intestinal tract (Maggi et al., 2000).

These pharmacokinetic limitations highlight the necessity of adopting gastroretentive drug delivery systems (GRDDS) to enhance systemic availability. Although immediate-release Alfuzosin tablets (2.5 mg) are commercially available and typically administered thrice daily, this frequent dosing regimen fails to maintain consistent plasma concentrations. Extended-release formulations are also available; however, due to the drug's narrow absorption window, short gastric retention time, and minimal absorption in the lower gastrointestinal tract, their efficiency remains suboptimal (Streubel et al., 2006).

Recent developments have explored chitosan-based sponges embedded with magnetite, which demonstrated excellent floating capacity and mucoadhesive properties, ensuring gastric retention for up to 5 hours (Abd El-Aziz et al., 2020). Nevertheless, floating systems depend on buoyancy in gastric fluids and require a minimum level of stomach content to remain effective. In contrast, mucoadhesive systems offer a distinct advantage by directly adhering to the gastric mucosa, allowing prolonged gastric residence regardless of the fed or fasting state.

This study highlights the development of a mucoadhesive gastroretentive formulation using mucoadhesive polymers that enable electrostatic interactions and hydrogen bonding between the dosage form and gastric mucin. In this investigation, a natural polymer, Hupu gum derived from *Sterculia urens*, was employed to achieve gastric retention and ensure controlled drug release over 24 hours. It is a hydrophilic polysaccharide abundant in galactomannans and is known for its high swelling index, making it suitable for localized and controlled drug delivery. However, there is limited literature on its pharmaceutical application, particularly in gastroretentive systems, adding novelty to this study (Aleti et al., 2025).

The aim of the present study is to investigate the gastric mucoadhesive property of hupu gum by *in silico* studies and the development of mucoadhesive compression-coated tablets (MCCT) of Alfuzosin HCl using a natural mucoadhesive polymer, hupu gum, to enhance bioavailability by achieving controlled release over 24 hours.

According to USP, Alfuzosin HCl extended-release tablets are required to exhibit a controlled dissolution profile, delivering 10–20% drug release within 1 hour, 40–55% within 6 hours, 65–85% within 12 hours, and not less than 85% by 20 hours (USP 47–NF 42, 2024). Hence, in the present study, the core tablets were developed with increasing concentration of hupu gum to function as a rate- controlling polymer and subjected to compression coating with a fixed concentration of hupu gum to function as the mucoadhesive polymer.

MATERIALS AND METHODS

Alfuzosin hydrochloride was obtained from MSN Labs, Telangana. Hupu gum was procured from the Girijan Cooperative Corporation, Visakhapatnam, Andhra Pradesh. Microcrystalline cellulose, magnesium stearate, lactose, and isopropyl alcohol were procured from Pioneer Chemical Industries, Hyderabad.

***In silico* studies**

Molecular docking is one of the most important computational methods to predict binding affinity between protein and ligand. In the present study, CB-Dock2 was used for molecular docking, and Discovery Studio for binding pose visualization and analysis.

Preparation of protein and ligands

The target protein structure, Mucin-2 (6RBF), was obtained in PDBQT format from the Protein Data Bank (RCSB-PDB). Water molecules and unwanted bonds were removed from the crystalline structure of the target protein using Discovery Studio to prepare it for docking studies. Polysaccharides of hupu gum (α-L-Rhamnose, Arabinose, α-D-Mannose, α- and β-Glucose, α- and β-Galactose, Glucuronic acid, and α- and β-Galacturonic acid) are selected as ligands and downloaded in SDF format from PubChem for the molecular docking. Before docking, the ligands were optimized through energy minimization to ensure accurate interaction predictions.

Molecular docking studies

The protein and ligands were uploaded in PDBQT and SDF formats, respectively, for the docking process, which was carried out using the software CB-Dock2. Using default parameters, CB-Dock2 automatically detected the binding cavity. The Vina score was used to rank the best poses. Following the docking process, the top-ranked pose was downloaded and uploaded into Discovery Studio to find out the binding sites and type of binding between the protein & ligand.

Drug-excipients compatibility studies

Samples were analysed using a Fourier transform infrared spectrophotometer by the KBr pellet method, and spectra were recorded over the wavenumber range between 4000–250 cm ^{1}. Compatibility between alfuzosin HCl and hupu gum was evaluated by comparing the spectra of alfuzosin HCl and the final formulation.

Precompression parameters

The precompression parameters of the powder blend were determined as mentioned. Using the funnel method, the angle of repose was determined by the equation tan θ = h/r, considering the height and radius of the pile formed by pouring the powder blend through the funnel. Bulk density (BD) was recorded by carefully adding the powder into a graduated glassware and calculating the weight-to-volume ratio. Tapped density (TD) was measured by introducing a specified amount of powder into a graduated glassware and subjecting it to 100 taps using a tapped density apparatus, continually reducing volume until no more reduction is seen. The ratio of tapped to BD refers to the Hausner ratio, while Carr's index (CI) was determined using the formula: (TD−BD)/TD x 100 (Aulton, 2002).

Formulation development of mucoadhesive compression-coated tablets (MCCT)

This formulation strategy was designed to enhance the stability of hygroscopic drugs like alfuzosin HCl by applying a compression coating that protects the tablet core from moisture and helps prevent dose dumping. The development of MCCT followed a two-step process. First, inner core tablets (ICT) were formulated and evaluated to study the drug release profile. These core tablets were then coated with a mucoadhesive polymer, such as hupu gum, to extend the drug release and enhance gastric retention. The final MCCT formulation was optimized by focusing on key parameters of mucoadhesive gastroretentive drug delivery. The best-performing tablet, based on achieving maximum drug release over 24 hours, was selected for further *ex vivo* evaluation.

Preparation of ICT

The ICT was formulated using the direct compression method. The required quantities of alfuzosin HCl, hupu gum, and microcrystalline cellulose (MCC) were sieved and weighed accurately as per the composition mentioned in (Table 1.). The contents were transferred to a mortar and pestle and mixed thoroughly to ensure a uniform blend. Further lubricants were incorporated into the blend and triturated to achieve consistency. The resulting mixture was subjected to direct compression using a 6 mm punch.

Table 1. Formulation of core tablets of alfuzosin HCl

Ingredients (mg)	ICT1	ICT2	ICT3	ICT4	ICT5
Alfuzosin HCl	10	10	10	10	10
Hupu gum (%)	10	20	30	40	50
MCC	76	56	36	26	16
Mg. Stearate	2	2	2	2	2
Talc	2	2	2	2	2
Total weight (mg)	100	100	100	100	100

Evaluation of ICT characteristics

The ICT was characterized for different tableting parameters. The thickness of six ICT from each batch was determined using a Vernier calliper. Hardness was tested on six randomly selected tablets per batch using a hardness tester (Monsanto). Ten tablets from each batch were subjected to a friability test using a friabalator as per the Indian Pharmacopoeia, Section 2.5.5. For uniformity of weight, the individual weights of ICT were accurately measured, and the mean value along with % deviation was calculated as per the Indian Pharmacopoeia, Section 2.5.3. Drug content was analysed spectrophotometrically at 244 nm by randomly selecting twenty ICT from each batch (Sanki & Mandal, 2012).

Dissolution performance of ICT

A USP-type I dissolution apparatus was used at 100 rpm, 0.01 N HCl (pH 1.2), and 37 °C. Fresh medium was replaced after each sample (5 ml) was collected and analysed spectrophotometrically at 244 nm, to determine cumulative percentage drug release.

Preparation of coating granules

Coating granules with 10 % hupu gum were prepared by wet granulation using a 70:30 ratio of isopropyl alcohol and water as the granulating agent. The wet granules were screened through a BSS#30 sieve after passing through a BSS#22 sieve and drying for 1 hour at 40°C. Finally, they were lubricated, then mixed for 3 minutes to ensure uniform distribution.

Compression coating of ICT

The mucoadhesion of ICT is augmented by compression coating using a mucoadhesive polymer sufficient to coat evenly on all sides. In preliminary studies, it was determined that 150 mg of coating granules exhibited 1mm coat thickness on all sides. In the coating process, half of the required granules (75 mg) were first placed evenly in the die cavity, then ICT was positioned at the center of the powder bed, followed by the addition of the remaining granules to the die cavity. The entire contents were compacted using an 8-mm tablet punch to form the coated tablets (Aleti & Murthy, 2023).

Tableting properties of MCCT

MCCT tablets were tested for tableting properties following the same procedures outlined earlier for the evaluation of the ICT.

Dissolution performance of MCCT

The study was conducted in accordance with the specified dissolution conditions. At time points 1, 6, 12, 20, and 24 hours, samples withdrawn were subjected to quantitative analysis spectrophotometrically to determine the % release of the drug in all formulations. The optimized formulation % drug release is compared with the marketed product (ALFUNIL-10 ER).

***Ex vivo* studies**

Ex vivo experiments of mucoadhesive strength and mucoadhesive retention time determination were performed in triplicate (n = 3), and results were expressed as mean ± standard deviation.

Determination of mucoadhesive strength

Mucoadhesive strength is a critical parameter that reflects a formulation's ability to bond with the mucosal surface, directly influencing both the mucoadhesive retention time and drug release profile. The mucoadhesive strength was measured using a modified simple balance method. Goat stomach mucosal tissue was obtained from a local slaughterhouse, thoroughly rinsed with 0.01 N HCl, secured to a glass slide, and placed in a petri dish as shown in (Figure 1.). The petri dish was then filled with 0.01 N HCl buffer until the tissue was sufficiently moistened. Tablets from various formulations were affixed to the underside of the left pan using adhesive tape, allowing them to make contact with the mucus membrane. On the opposite pan, water was gradually added dropwise from a burette. As the weight of the water increased, it gradually caused the tablet to separate from the tissue. The total weight of water on the right pan at the point of separation represented the mucoadhesive strength, measured in grams (Park & Robinson, 1984). The method was validated through consistent repeatability across trials.

For each formulation, three trials were conducted, and the mean value was recorded and determined using the following equation.

$$N = W * g / 1000$$

Let N = Mucoadhesive force, W = Weight (g) sufficient to detach the tablet from tissue, and g = Acceleration due to gravity 9.81 m/s^2.

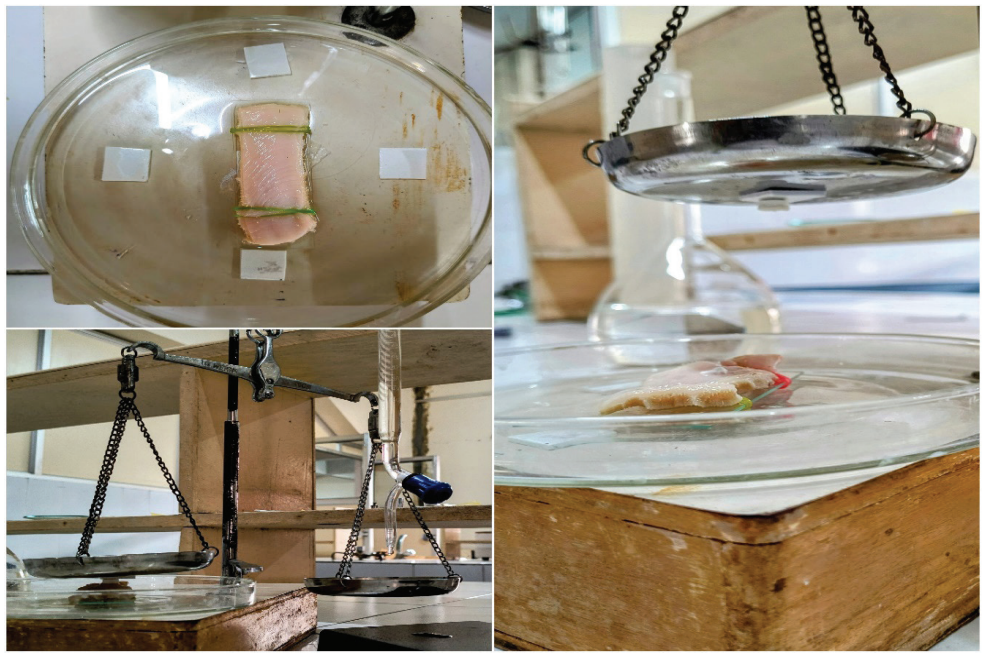

Figure 1. *Ex vivo* evaluation of mucoadhesive strength of MCCT using modified balance method

Determination of mucoadhesive retention time

The duration of mucoadhesive time is a crucial factor that reflects the formulation's ability to remain adhered to the mucosal surface, ensuring extended drug release and effective treatment. The *ex vivo* retention time, measured using a USP Type II apparatus, demonstrated consistent adherence across samples. Fresh goat stomach mucosal tissue was collected from a local slaughterhouse, cleaned with distilled water, and pH 1.2 buffer (0.01 N HCl). The mucosal tissue was then attached to a glass slide and adhered to the paddle of the dissolution apparatus, as shown in (Figure 2.). The tablet was placed in contact with the tissue for 30 seconds after hydrating one side of the tablet with 0.01 N HCl. The setup was then immersed in the dissolution medium at 37±0.5 °C, rotating at 100 rpm.

Tablet detachment time from the mucosal surface was recorded (Sankar & Jain, 2013; Kumar et al., 2020; Panda et al., 2022).

Each formulation was evaluated in triplicate (n = 3), and results were reported as mean ± s.d. Statistical comparisons were performed using appropriate post hoc tests.

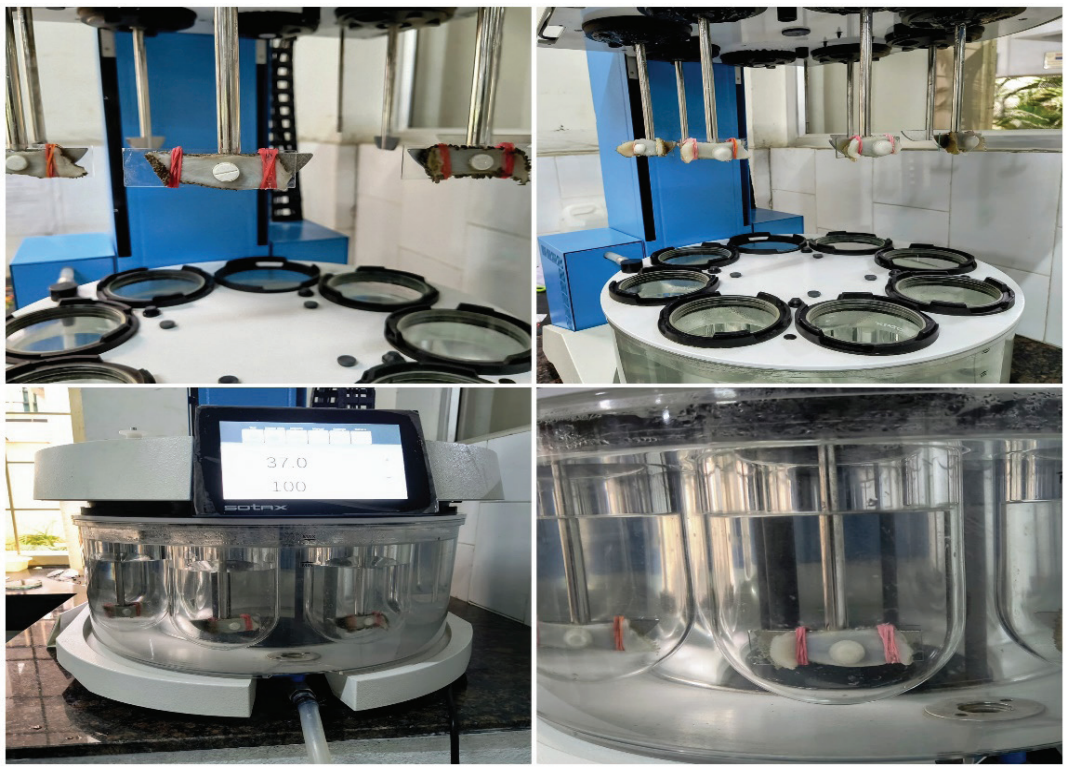

Figure 2. *Ex vivo* evaluation of mucoadhesive retention time using goat gastric mucosa

***In vivo* gastric retention time**

Visual evidence of retention time was validated through radiographic imaging (Ige & Gattani, 2013). The study was conducted with a single animal (n = 1) for preliminary confirmation of gastric retention behavior. Results were interpreted qualitatively based on radiographic visibility and positional consistency. All experimental procedures were performed in compliance with the ethical standards set by the Institutional Animal Ethics Committee (IAEC), Gokaraju Rangaraju College of Pharmacy. The study protocol was reviewed and approved under protocol no. GRCP/CEU/005/2024.

The optimized MCCT1 formulation was downsized to the appropriate animal dose. A healthy rabbit of approximately 2.5 Kg was selected as the subject and fasted overnight. The optimized formulation was administered the following morning along with 25 mL of water.

X-ray images were taken at intervals of 12 and 24 hours to monitor the tablet's position within the gastric region. After 5 hours of tablet administration, the rabbit was fed to assess the impact of food on gastric retention.

Stability profile of optimized formulation

Stability testing for the final optimized formulation (MCCT1) was conducted as per ICH Guidelines, 2018. Two sets of MCCT1 samples were sealed in hermetically sealed bottles and stored under controlled conditions: long-term (30°C/70% RH) and accelerated (40°C ± 2°C/75% ± 5% RH), as specified in the ICH

Guidelines for Zone IV and WHO standards (2021). Samples were evaluated at 3 and 6 months, for physicochemical properties, *in vitro* dissolution behaviour, and mucoadhesive performance.

RESULTS AND DISCUSSION

In silico studies

The docking analysis conducted using CB-Dock2 indicated that hupu gum exhibits strong binding affinity with the mucin protein. The interaction is evident from Vina scores ranging from -5.5 kcal/mol to -6.3 kcal/mol binding affinity in the order of Arabinose > α-D-Glucose > β-D-Glucose > α-L-Rhamnose > α-D-Mannose > D-Glucuronic acid > α-D-Galactose > β-D-galactose > β-D-Galacturonic acid > α-D-Galacturonic acid. Visualization by Discovery Studio indicates interactions between ligands and the amino acid residues located in the active site, as represented in (Figure 3.).

α-D-Galacturonic acid achieved the highest binding affinity among the ligands, with a Vina score of -6.3 kcal/mol. It formed four conventional hydrogen bonds with GLN B 956, ARG B 1112, ARG B 973, and SER B 1093, in addition to a carbon-hydrogen bond with GLU B 1089. β-D-Galacturonic acid showed a Vina score of -6.2 kcal/mol, forming hydrogen bonds with GLY B 955, GLU B 1176, and CYS B 1163, with additional van der Waals interactions involving TYR B 1124 and a carbon-hydrogen bond with VAL B 954. β-D-Galactose exhibited a Vina score of -6.2 kcal/mol, with conventional hydrogen bonds formed with ARG B 1140, ARG B 952, PHE B 1142, and ASN B 1154, as well as four van der Waals interactions with SER B 1153, VAL B 1157, TYR B 1164, and VAL B 954. α-D-Galactose showed a vina score of -6.1 kcal/mol, engaging in hydrogen bonds with ARG B 1112, GLN B 956, ARG B 973, and SER B 1093, along with carbon-hydrogen bonding with GLU B 1161, ALA B 1096, and ASP B 971, and one van der Waals interaction with GLU B 1089.

D-glucuronic acid displayed a Vina score of -6.0 kcal/mol, forming hydrogen bonds with ARG C 973, GLN C 956, PRO A 1114, and PRO C 118, along with a carbon-hydrogen bond with CYS C 1117. α-D-Mannose demonstrated a binding affinity of -5.8 kcal/mol, forming hydrogen bonds with ARG B 1112, GLN 956, and SER 1093, as well as two carbon-hydrogen bonds with GLU B 1089 and ARG B 973. Additionally, two van der Waals interactions were detected with ALA B 1096 and ASP B 971.

α-L-Rhamnose, with a Vina score of -5.7 kcal/mol, formed hydrogen bonds with ARG B 1112, GLN B 956, PRO B 1118, and ARG B 973, alongside a carbon-hydrogen bond with ASP B 1115. β-D-glucose had a binding affinity of -5.7 kcal/mol, forming hydrogen bonds with TYR A 1134, PRO C 1127, and GLU C 1129. α-D-Glucose exhibited a Vina score of -5.7 kcal/mol, with conventional hydrogen bonds observed between the ligand and the receptor amino acids GLN 956, ARG 973, PRO 1114, and ARG B 1112. Arabinose displayed a Vina score of -5.5 kcal/mol, interacting through conventional hydrogen bonds with ASP 971, SER B 1093, ARG B 973, and GLN B 956.

The presence of hydrogen bonding, C-H bond, and van der Waals interactions suggests a strong and stable binding affinity between the receptor and the ligand**.** These interactions suggest strong adhesion, as the hydrogen bonds enhance stability while the C-H bonds and van der Waals interactions facilitate additional molecular interactions (Peppas & Buri, 1985). The existence of these bonds suggests that the formulation exhibits an extended retention time on mucosal surfaces, thereby enhancing the efficacy of the mucoadhesive system (Andrews et al., 2009). This finding suggests that hupu gum could serve as an effective polymer in mucoadhesive delivery of alfuzosin HCl, thereby improving drug retention and release characteristics.

These docking studies provide a foundation for further investigation into mucoadhesive properties and drug release behaviour through *in vitro* and *ex vivo* experiments.

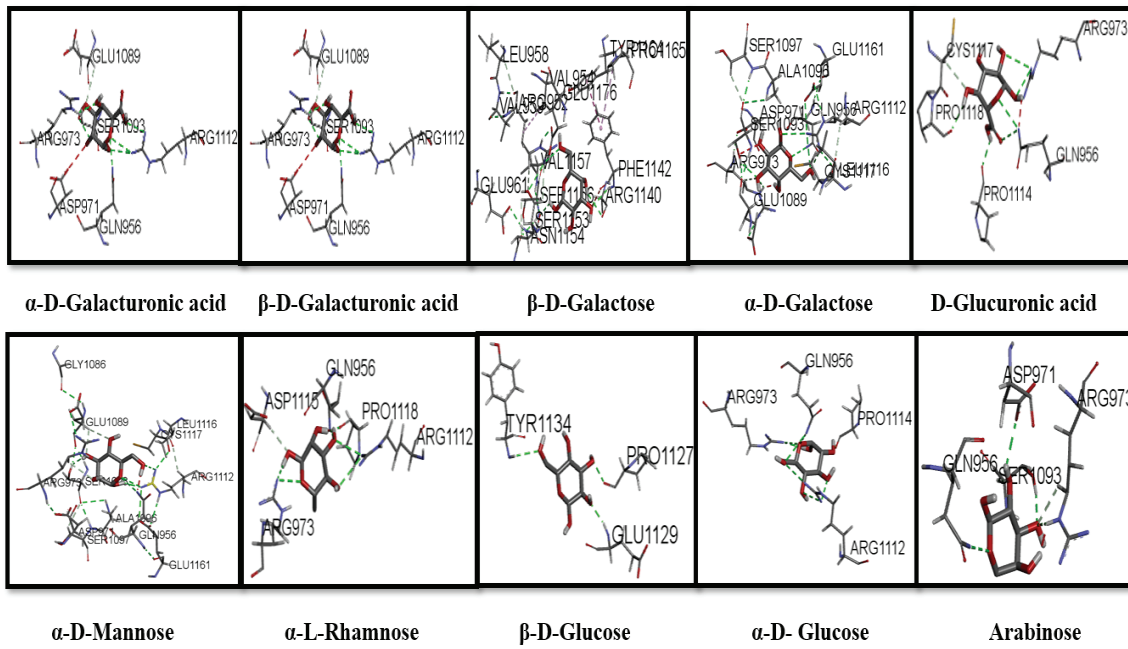

Figure 3. Protein-ligand interaction sites of hupu gum and mucin

Drug-excipients compatibility studies

The FTIR spectra for pure alfuzosin HCl and optimised formulation MCCT1 are compared (Vaishali et al., 2013) in Figure 4. The FTIR spectrum of pure alfuzosin HCl exhibited characteristic absorption bands at 1654.93 cm^{-1} (C=O stretching), 1240.23 cm^{-1} (C–O–C stretching), and 2843.08 cm^{-1} (C–H stretching), while the MCCT1 formulation showed corresponding peaks at 1656.86 cm^{-1}, 1240.23 cm^{-1}, and 2850.79 cm^{-1}. The absence of significant shifts in these characteristic peaks in the formulation blend suggests that no major interactions occurred between the drug and excipients. The functional groups remained unchanged, indicating that alfuzosin HCl did not undergo chemical degradation or form new compounds during the formulation process. This confirms the compatibility of alfuzosin HCl with Hupu gum.

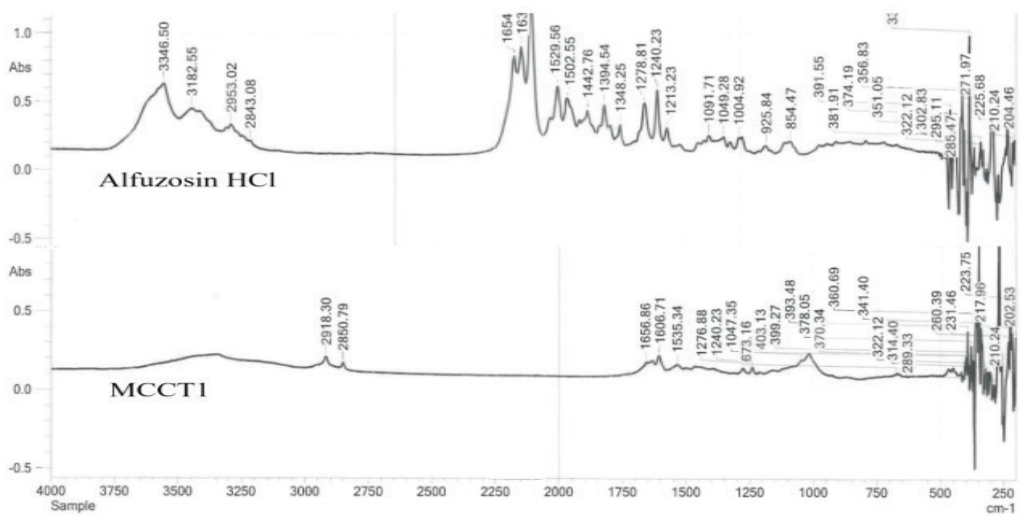

Figure 4. FTIR spectrum of alfuzosin HCl and optimized formulation MCCT1

Precompression parameters

The flow properties of the powder blend for various formulations, as shown in (Table 2.), demonstrated that all precompression parameters were within acceptable limits. Overall, the powder blend exhibited good flow and compaction characteristics suitable for tablet formulation.

Table 2. Results of precompression parameters of core tablets

Formulations	Angle of repose (°)	BD (gm/cm³)	TD (gm/cm³)	CI (%)	Hausner's ratio
ICT1	29.11.14	0.460.18	0.530.04	12	1.090.11
ICT2	30.18.53	0.420.07	0.490.26	16	1.060.03
ICT3	31.13.65	0.430.09	0.570.45	15	1.110.04
ICT4	32.04.31	0.450.11	0.510.19	13	1.150.08
ICT5	33.12.14	0.440.15	0.550.14	15	1.160.12

mean±s.d., n=3

Evaluation of ICT characteristics

The characteristics of the formulated ICT, summarized in (Table 3.), showed a hardness of 5.1-5.6 kg/cm², indicating sufficient mechanical strength, and a friability of less than 0.5%, confirming their suitability for compression coating. The tablet's thickness ranged from 4.2 to 4.5 mm, with consistent weight uniformity across the batch. The drug content was 99.91±0.02%, confirming uniform drug distribution within the tablets.

Table 3. Tableting characteristics of core tablets

Formulations	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Weight variation (mg)	Drug content (%)
ICT1	3.20.14	5.1.2	0.350.11	100±0.1	99.910.02
ICT2	3.40.21	5.40.16	0.420.06	100±0.3	99.970.18
ICT3	3.40.16	5.20.12	0.320.03	100±0.2	99.650.07
ICT4	3.30.18	5.60.16	0.290.05	100±0.5	99.950.25
ICT5	3.50.11	5.30.14	0.280.10	100±0.9	98.320.32

mean±s.d., n=3

Dissolution performance of ICT

The percentage drug release of all ICT formulations, represented graphically in Figure 5, indicates that among all formulations, ICT1 demonstrated maximum drug release within 12 hours, while ICT2, ICT3, and ICT4 extended the release to 15, 16, and 18 hours, respectively. ICT5, which had the highest polymer concentration, achieved drug release up to 20 hours due to the formation of a dense, highly viscous gel layer that restricted drug diffusion (Ford, 2014; Siepmann & Peppas, 2012).

As the formulation strategy focused on extending the drug release profile not by further increasing polymer concentration in the core, which could negatively affect tablet performance, but by applying an external mucoadhesive compression coating, as mucoadhesion is a surface-dependent phenomenon (Smart, 2005). Accordingly, all the core tablets were subjected to compression coating.

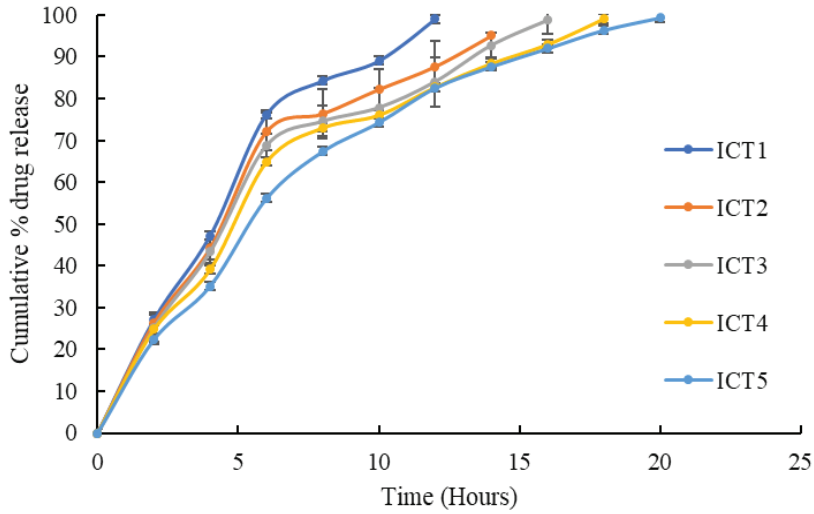

Figure 5. *In-vitro* drug release profiles of ICT1–ICT5 core tablets (n = 3, mean ± SD) in USP apparatus II, 900 mL phosphate buffer pH 6.8, 37 ± 0.5 °C, 50 rpm.

Tableting characterization of MCCT

The tableting characteristics of the formulated MCCT were assessed, and the results are represented in (Table 4.). The evaluated parameters indicate that all the formulations are as per the USP specified limits. The drug content ranged from 98.28 ± 0.30 % - 99.96±0.19 %, ensuring precise dosing. The tablet thickness was between 5.1 and 5.6 mm, while the hardness ranged from 5.1 to 5.7 kg/cm², confirming adequate mechanical strength. The friability values range between 0.24 - 0.38 %, indicating good resistance to abrasion. All tablets exhibited consistent uniformity of weight, demonstrating the reliability of the compression-coating process in producing uniform and high-quality tablets.

Table 4. Tableting characteristics of MCCT

Formulations	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Weight variation (mg)	Drug content (%)
MCCT1	5.10.17	5.1±0.32	0.37±0.02	250±0.5	99.94±0.16
MCCT2	5.30.12	5.1±0.21	0.38±0.03	250±0.6	99.96±0.19
MCCT3	5.10.16	5.3±0.18	0.35±0.01	250±0.8	98.60±0.04
MCCT4	5.70.18	5.5±0.42	0.27±0.05	250±0.4	99.90±0.24
MCCT5	5.60.15	5.6±0.12	0.24±0.03	250±0.1	98.28±0.30

mean±s.d., n=3

Dissolution performance of MCCT

The cumulative % release of formulations MCCT1-MCCT5 were represented in (Figure 6.). Dissolution profile of the MCCT1 formulation closely matched with that of the USP monograph for alfuzosin HCl, with maximum drug release observed in 24 hours. However, the remaining formulations MCCT2, MCCT3, and MCCT4 did not meet the USP standard release criteria. The difference in dissolution profile among the formulations is likely due to the higher concentration of polymer in the core tablet which resulted in excessive swelling of the tablet, which in turn reduced the porosity in the swollen polymer matrix, causing delayed drug release.

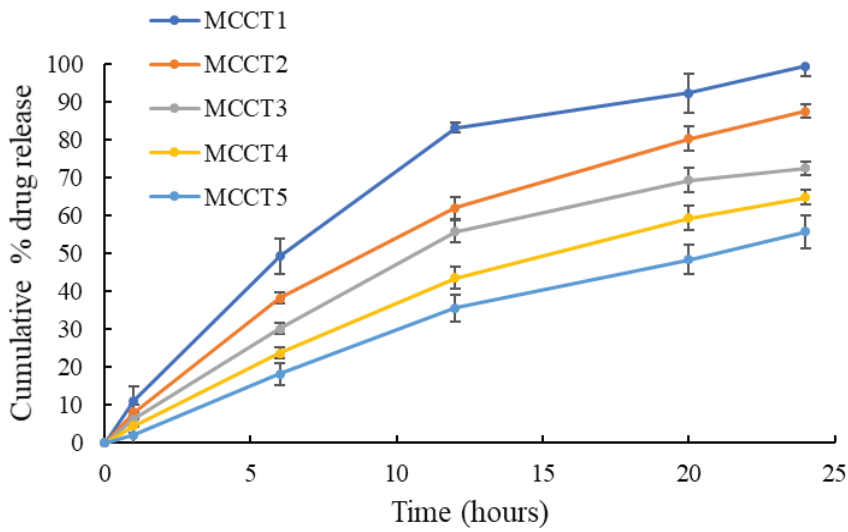

Figure 6. *In-vitro* drug release profiles of MCCT1–MCCT5 tablets (n = 3, mean ± SD) in USP apparatus II, 900 mL phosphate buffer pH 6.8, 37 ± 0.5 °C, 50 rpm.

The ratio of 1:1 hupu gum in the core and coat layer effectively extends drug release up to 24 hours while maintaining prompt initial drug availability and improved gastric retention. To support this selection, drug release kinetics of all formulations were fitted into various mathematical models and the results are represented in (Table 5.) (Korsmeyer et al., 1983).

Table 5: Mathematical modelling of mucoadhesive compression-coated tablets

Formulation	Zero-order (R^2)	Higuchi (R^2)	Peppas (R^2)	Peppas n	Mechanism
MCCT1	0.983	0.991	0.994	0.62	Non-Fickian diffusion
MCCT2	0.961	0.987	0.993	0.68	Anomalous transport
MCCT3	0.957	0.984	0.991	0.74	Anomalous transport
MCCT4	0.942	0.976	0.982	0.81	Case-II transport
MCCT5	0.936	0.972	0.980	0.84	Case-II transport

Among the developed mucoadhesive compression-coated tablet formulations, MCCT1 emerged as the optimized gastroretentive system capable of sustaining drug release over 24 hours**.** MCCT1 exhibited the highest correlation with the Korsmeyer–Peppas model (R^2 = 0.994), along with strong agreement with the Higuchi (R^2 = 0.991) and zero-order (R^2 = 0.983) models, indicating a well-controlled and predictable release pattern.

The Peppas release exponent (n = 0.62) confirms a non-Fickian diffusion mechanism**,** demonstrating a balanced contribution of drug diffusion and polymer relaxation. This dual mechanism enabled uniform hydration, stable gel formation, and sustained matrix integrity, which are critical for effective mucoadhesion and prolonged gastric residence (Peppas & Buri, 1983).

Compared with higher-polymer formulations (MCCT2–MCCT5), MCCT1 avoided excessive matrix rigidity and over-retardation, ensuring complete and continuous drug release throughout the 24-hour period. The optimized polymer content in MCCT1 thus provided an ideal balance between mucoadhesive strength, gastroretentive behavior, and controlled drug release, making it the most suitable formulation for once-daily mucoadhesive gastroretentive delivery.

Comparison of drug release profiles

The comparative dissolution profiles of the optimized formulation (MCCT1) and the marketed product are represented in (Figure 7.). The marketed product exhibited a complete drug release within 8 hours, whereas the optimized formulation (MCCT1) demonstrated an extended-release profile, achieving 100% drug release over 24 hours. This indicates that the optimized formulation provides a more controlled and prolonged release compared to the marketed product, potentially enhancing therapeutic efficacy and patient compliance.

A quantitative assessment was carried out using the similarity factor (f_2), which yielded a value of 42.6, indicating dissimilarity between the MCCT1 and the marketed product.

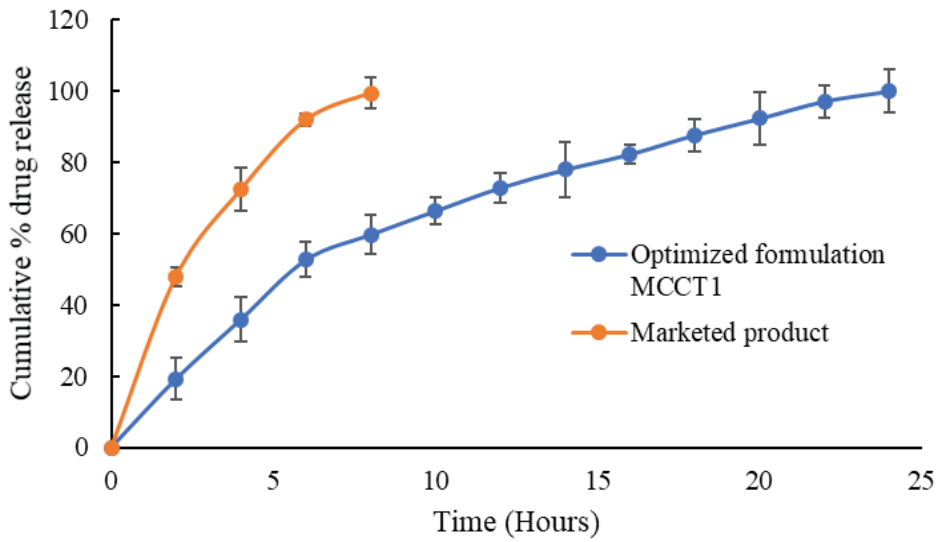

Figure 7. Comparative dissolution profiles of MCCT1 and marketed formulation (n = 3, mean ± s.d.,)

***Ex vivo* mucoadhesion strength**

Mucoadhesive strength testing was conducted on all ICT and MCCT formulations, as presented in Figure 8. The results revealed that the compression-coated formulations (MCCT1–MCCT5) consistently exhibited higher mucoadhesive strength compared to the core ICT tablets. Effective mucoadhesion of Hupu gum depends on adequate surface hydration and subsequent chain entanglement with mucin present on the gastrointestinal mucosa. Emphasizes that internal polymer does not significantly contribute to mucoadhesion. Earlier studies emphasizes that internal polymer does not significantly contribute to mucoadhesion (Khutoryanskiy, 2011). Compression coating offers a distinct advantage by localizing the mucoadhesive polymer on the tablet surface, thereby maximizing polymer exposure to the mucosal tissue This configuration promotes stronger and more sustained mucoadhesive interactions compared to matrix-based systems.

An incremental rise in mucoadhesive strength was observed with increasing polymer content in the ICT. To determine the statistical significance of the observed differences in mucoadhesive strength, one-way ANOVA was conducted among all formulations. The results showed a statistically significant difference (p

< 0.05), validating the role of polymer concentration and coating architecture in enhancing mucoadhesion.

To support these observations, *ex vivo* mucoadhesive retention time was evaluated for all MCCT formulations. This additional analysis provided further evidence of the strong and prolonged adhesion properties of the coated tablets, reinforcing the impact of the coating strategy on mucoadhesion.

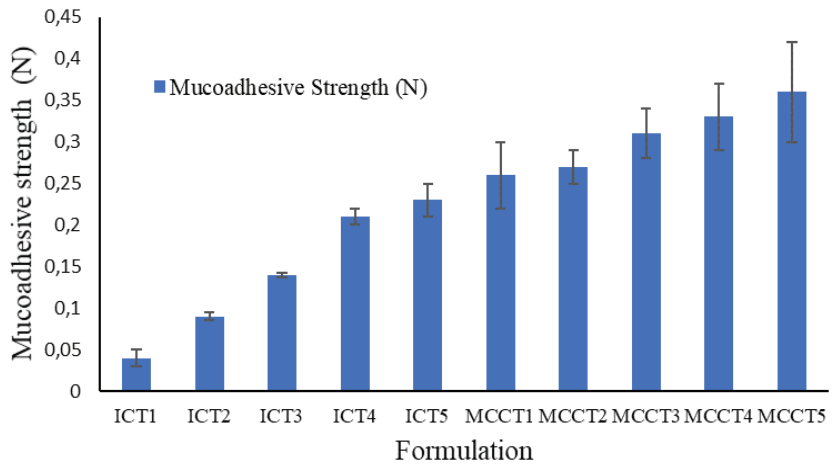

Figure 8. Mucoadhesive strength of all formulations (mean ± s.d., n = 3; $p < 0.05$, ANOVA with Tukey's test)

***Ex vivo* mucoadhesive retention time**

Mucoadhesive retention time of all MCCT formulations was tested and represented in (Figure 9.) All MCCT formulations exhibited retention times exceeding 24 hours, with MCCT1 exhibiting mucoadhesion over a 24-hour duration, while MCCT5 demonstrated the longest retention, nearly up to 29 hours. These findings confirm the strong and sustained mucoadhesive property of hupu gum. This prolonged adhesion supports the formulation's potential to deliver the drug over an extended period, enhancing its therapeutic efficacy. However, compression-coated mucoadhesive systems were optimized based on superior release control, enhanced mucoadhesive efficiency, and lower polymer load compared to the high-polymer matrix system.

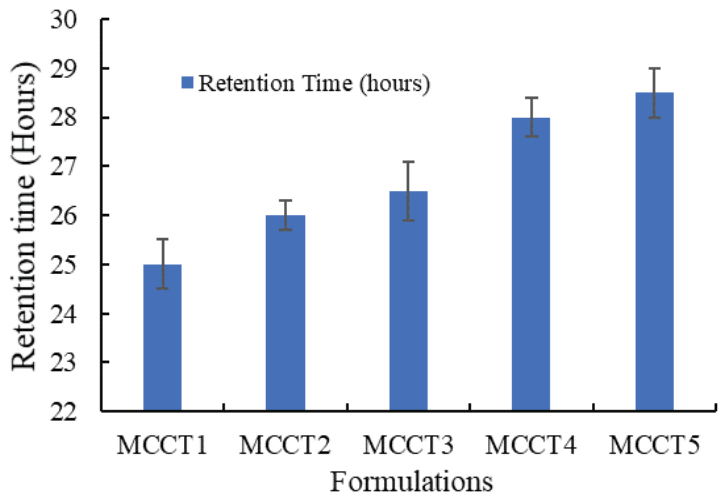

Figure 9. Mucoadhesive retention time of MCCT formulations (mean ± s.d., n = 3)

Among the evaluated formulations, MCCT1 demonstrated a gastric retention time of approximately 25 hours, which was adequate to maintain the dosage form intact within the gastric environment until complete drug release. This outcome successfully met the study objective of achieving prolonged gastric residence, thereby enabling sustained and complete drug delivery over 24 hours. Consequently, MCCT1 was identified as the most suitable formulation, offering an optimal balance between gastric retention efficiency, structural integrity, and controlled drug release within the intended therapeutic timeframe.

***In vivo* gastric retention time**

X-ray images of a rabbit after drug administration demonstrated that the alfuzosin HCl compression-coated tablet adhered to the gastric mucosa effectively over 24 hours. X-ray images taken at intervals of 12 and 24 hours were represented in (Figure 8.). This finding confirmed the tablet's retention in the stomach without significant displacement. At the 12-hour mark, the tablet remained positioned firmly in the gastric region, and by 24 hours, it showed consistent adherence, indicating strong mucoadhesive properties. These findings validate the formulation's potential for prolonged gastric retention, aligning with the stipulated extended drug delivery profile. This strong retention correlates well with *ex vivo* mucoadhesive data, supporting the *in vivo* relevance of the formulation's design. The persistent gastric localization is particularly advantageous for drugs like alfuzosin HCl that benefit from localized release and improved bioavailability in upper GI tract conditions.

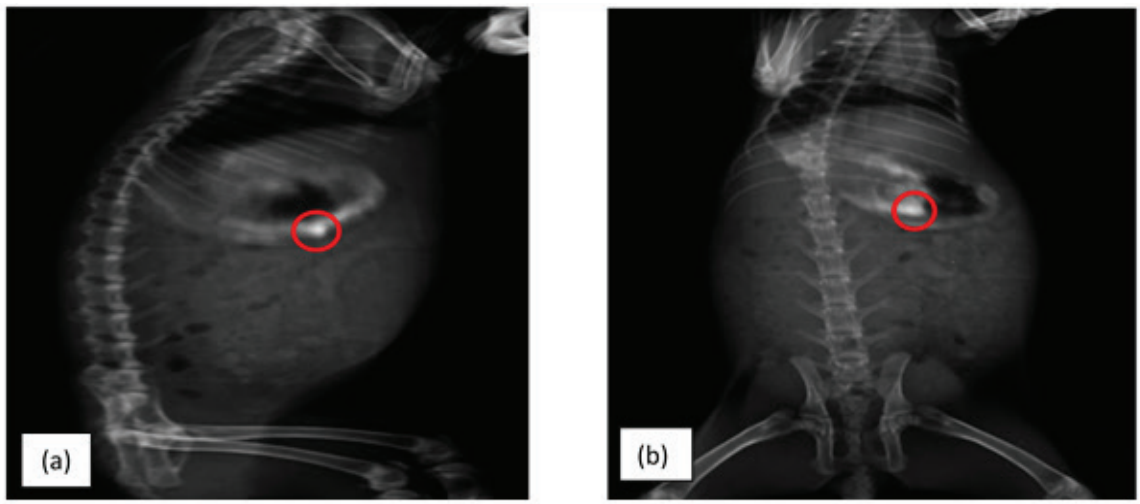

Figure 8. X-ray images of MCCT1 mucoadhesive gastric retention in a rabbit at (a)12 hours (b) 24 hours

Optimized formulation: stability profile

The stability study results in (Table 5.) showed no visible or physical changes in the product stored under both long-term and accelerated conditions. As shown in Table 9, drug release remained consistent before and after storage, with similarity factor (f2) values of 91.25 for long-term and 87.41 for accelerated conditions. These findings confirm that the coating thickness and polymers used in the formulation effectively protected the drug from environmental factors, with no changes in drug content or mucoadhesive properties, demonstrating the product's stability in line with ICH guidelines.

Table 5. Stability studies of optimized formulation MCCT1

Test	Fresh samples	Storage condition			
		Acelerated		Longterm	
		3 months	6 months	3 months	6 months
Thickness[a] (mm)	5.1±0.17	5.1±0.15	5.1±0.13	5.1±0.16	5.1±0.14
Hardness[a] (Kg/cm^2)	5.1±0.32	5.1±0.29	5.1±0.28	5.1±0.30	5.1±0.31
Weight variation[b] (mg)	250±0.5	250±0.4	250±0.3	250±0.7	250±0.6
Drug content[c] (%)	99.94±0.16	99.94±0.13	99.94±0.14	99.94±0.18	99.94±0.15
Mucoadhesive strength	0.26 ± 0.04	0.26 ± 0.07	0.25 ± 0.03	0.25 ± 0.06	0.25 ± 0.05
Mucoadhesive retention time	24±0.5	24±0.3	24±0.2	24±0.4	24±0.3

n=3

CONCLUSION

The study successfully established a mucoadhesive gastroretentive drug delivery system capable of sustaining the release of alfuzosin HCl for a full 24-hour period. Among all the developed formulations, MCCT1 demonstrated superior performance, exhibiting a gastric residence time of approximately 25 hours while retaining its structural integrity in the gastric environment until complete drug release. This confirmed the achievement of the primary objective of prolonged gastric retention.

The enhanced performance of MCCT1 was primarily attributed to efficient polymer utilization and improved mucoadhesive behaviour achieved through the compression-coated design. By localizing the mucoadhesive polymer on the tablet surface, the formulation maximized interaction with the gastric mucosa while limiting the overall polymer load. This approach resulted in more predictable drug release, better formulation reproducibility, and improved patient acceptability.

Molecular docking studies further reinforced the mucoadhesive potential of the system, revealing the involvement of hydrogen bonding, C–H interactions, and van der Waals forces. The presence of these interactions indicates strong and stable binding between the polymer and mucosal components, which is likely to enhance mucosal adhesion and prolong retention at the site of action, thereby supporting sustained drug release.

The findings clearly identify Hupu gum as an effective mucoadhesive polymer for the gastroretentive delivery of alfuzosin HCl. Overall, MCCT1, formulated with a 1:1 ratio of Hupu gum in the core and coating layers, emerged as the most suitable and optimized formulation for once-daily mucoadhesive gastroretentive therapy. In addition, the docking results provide a scientific foundation for further *in vitro* and *ex vivo* investigations into mucoadhesive performance and drug release behavior.

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AUTHOR CONTRIBUTION STATEMENT

RA, PKT, MN, BJ contributed to this article. RA contributed to conceptualisation, supervision. RA, PKT contributed to the literature search, data acquisition and calculations and writing of the preliminary draft of the manuscript. MN and BJ edited the manuscript and made critical revisions. All authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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